16. APPENDICES

APPENDIX 16.1: STUDY INFORMATION

APPENDIX 16.1.1: PROTOCOL AND PROTOCOL AMENDMENTS

Protocol FIS-001-2020

Administrative Letter – CRP addition to safety labs on D1, D2, and D4

Date: 25 January 2021

It is well recognized that C-reactive protein (CRP) and interleukin-6 (IL-6) are biomarkers that are important in the evaluation of the inflammatory response to the Sars-CoV-2 virus. Fulcrum therefore requests that these two biomarkers be added to the chemistry safety labs that are already being drawn on treatment Days 1, 2, and 4 (seen in the table below as D1, D2, and D4). As chemistry safety laboratory assessments are already being collected on these days per the protocol table below, no additional blood draws would be required for the study subjects. Please note that all other assessments remain as written in the protocol and that it is extremely important that all lab draws for safety labs (performed at the local lab) and biomarkers (performed at the central lab) be done on time as listed in the protocol.

These changes to the Schedule of Assessment will be reflected in the next protocol amendment.

Fulcrum Therapeutics
Protocol FIS-001-2020

Losmapimod

Assessment[1] \ Time point	SCR -3d to -1d	Treatment Period D1 (baseline)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	FU[14] D21 (± 3d)	FU[14] D28 (± 3d)	ET
Oxygenation and FiO_2[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments:															
Physical examination	X														X
Weight/height[9]	X												X		X
Hematology, chemistry safety labs[6]	X	X	X		X			X		X		X	X		X
CRP[5]	X	X	X		X										
Urinalysis[10]	X							X							
Urine or serum β-hCG (female subjects only)	X[11]												X		X
ECG[12]	X							X							
HR, BP, RR, temperature[3]	X	X	X	X	X	X	X	X	X	X	X	X			X
(S)AEs[13]	X														X
Concomitant medications (including SOC)	X														X

AE = adverse event; BP = blood pressure; COVID-19 = novel coronavirus; HR = heart rate; P = pre dose; PAO_2 = partial pressure of oxygen; PR – pre-randomization; RR = respiratory rate; sent = sentinel; SOC = standard of care; SCR = screening.
Note: All screening assessments are to be performed before dosing. If procedures required at any time point have already been performed as part of routine clinical care, these assessments do not need to be repeated, and information will be collected and entered on the eCRF from the subject's medical records. Unscheduled visits can take place at any time at the discretion of the site to check for new AEs/SAEs or to repeat key missed assessments or for other reasons.
[1] The order of assessments can be performed at the discretion of the investigator once informed consent is obtained.
[2] COVID-19 diagnosis to be confirmed by local testing (PCR) before randomization and first dosing. Saliva, swab, or sputum testing may be used based on local standard of care.
[3] To be performed while hospitalized based on standard-of-care local assessment. Evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
[4] PK assessments will be performed as a substudy in all sentinel subjects. For those subjects requiring dialysis, a single pre- and post-dialysis PK should be obtained for review by the DMC to decide if dose adjustment is needed. PK should be measured weekly for 2 weeks at C_{max} (4-5 hours post dose) for subjects with renal insufficiency when possible.
[5] Assessments for biomarkers post randomization have a window of ±2 days. Biomarker samples to be collected in all subjects at the specified time points when possible.
[6] Assessments for clinical/respiratory status, progression, and safety serum chemistry and hematology tests to be performed and samples to be collected while hospitalized based on standard-of-care local laboratory assessments and after discharge from the hospital by home visit or outpatient clinic visit or telemedicine call. For subjects who are discharged to home or other outpatient setting after initial hospitalization, the assessments and laboratory samples can be obtained less often but not less than at least once weekly. CRP result required to determine eligibility are based on local laboratory results at screening.
[7] Viral load testing will be collected daily for the first 4 days using central testing in the first 10 enrolled subjects as part of the sentinel safety assessment at select sites. For all subjects, including the sentinel subjects, swabs, saliva, or other sample collection (as specified in the Study Manual) for central viral load testing will be collected on D1 pretreatment and on D7 or earlier if being discharged from the hospital prior to D7.

[redacted]MD
Medical Director, LOSVID Trial
Fulcrum Therapeutics, Inc.

Protocol FIS-001-2020

Clarification Memo – Eligibility Screening Labs

Date: 05 January 2021

The labs used to determine eligibility at screening should ideally be drawn after the informed consent form (ICF) has been signed and within 3 days of baseline on D1. This is to assure that the patient's current clinical status is known at screening. However, if patients are hospitalized and have had labs drawn prior to formal screening and the signing of the ICF and the Principal Investigator believes that they are representative of the patient's current clinical status, those labs can be used for screening purposes as long as they were obtained no more than 72 hours prior to D1. The labs need to have been drawn at the facility where the patient has been hospitalized continuously since the labs were drawn. This accommodation is intended to avoid unnecessary procedures on vulnerable patients while also minimizing interactions with hospital staff in an attempt to avoid the spread of infection.

[redacted], MD
Medical Director, LOSVID Trial
Fulcrum Therapeutics, Inc.

Summary of Changes to the Protocol

Protocol History	
Version and Date of Protocol	**Comments**
Version 3.0, 21 October 2020	Inclusion criteria were updated as follows: • The age in inclusion criterion 3 was changed from ≥50 years old to ≥40 years old based on clinical site feedback regarding recruitment challenges, while maintaining older age as an important risk factor for progression of COVID-19. • Baseline oxygen requirements in inclusion criterion 7 were changed based on clinical site feedback to oxygen saturation ≥ 92%, which can be either on room air or on oxygen supplementation if using ≤10L/min by nasal canula or close-fitting face mask. • The "note" for inclusion criterion 8 was combined into the main criterion 8 for optimal readability. Exclusion criteria were updated as follows: • The definition of critical disease in exclusion criterion 2 was updated to remove "anticipated need for intubation" and "severe pulmonary involvement" based on clinical site feedback; ARDS and immediate need for intubation or mechanical ventilation were retained in the definition of critical COVID-19 disease. Evidence of pulmonary involvement remains in inclusion criterion 8. • Exclusion criterion 5 was updated to note that the exclusion is for poorly controlled HIV and to allow for the inclusion of subjects with HIV if their CD4 counts are normal and they have been on a stable antiviral regimen and are anticipated to remain on that regimen for the duration of the study. The changes above were also applied where applicable in the descriptions of the study design and procedures. Minor administrative/operational and typographical clarifications were made.

Version 2.1, 10 July 2020	Minor administrative/operational and typographical clarifications were made, including the following:
	• IND number was removed on title page to be more broadly applicable to worldwide sites
	• Clarification made to secondary endpoints that these are measured "by Day 28" for alignment with other secondary objective wording and clarity
	• Note was added to inclusion criterion 1 to clarify that patient's LAR may give consent, in alignment with LAR language in Section 9.1.3 of version 2.0 of the protocol.
	  ○ It was further clarified in inclusion 1 and Section 9.1.3 that the patient should provide assent in this scenario.
	  ○ In addition, it was clarified in Section 7.1.1 that the LAR may report AEs when appropriate
	• Inclusion criterion 10 units of measurements were clarified for ease of site determination of eligibility

	• It was clarified that the methods of birth control should follow local/country guidelines and regulations as applicable for sites out the US, for more broad applicability to worldwide sites • Exclusion 9 wording was clarified for ease of site determination of eligibility • Wording in statistical analyses sections was clarified to note that the adjustment for CRP is for baseline CRP. • For change in clinical status endpoint, it was clarified that the model using regression analyses would be adjusted for stratification factors, sex, and baseline CRP, similarly to the primary analysis • For total number of study days free of oxygen supplementation/in ICU/ of hospitalization/ free of respiratory failure / alive, it was clarified that the model using regression analyses would be adjusted for stratification factors, sex, baseline CRP and number of days on study. • Sample collection language for confirmation of diagnosis was clarified, including clarification that saliva or sputum collection may be used in addition to swab • Sample collection language for viral load/viral presence testing in sentinel subjects was clarified for alignment with vendor procedures and with viral load assessments during the rest of the trial (changed to central testing, not local) • Oxygenation and FiO_2 at Days 21 and 28 were added to the Schedule of Assessments to align with methodology and analyses as specified in version 2.0 of the protocol • It was clarified that PK assessments in patients with renal insufficiency should be measured weekly for 2 weeks at C_{max}, when possible (overall duration of this weekly assessment added) • Benefit-risk section was added to consolidate benefit-risk information found in protocol version 2.0 into a single location in the protocol for convenience • Reporting of pregnancy section 7.2.2 was updated to clarify that the Sponsor's designee, [redacted] will collect this information; the name of the form was updated to match the designee's procedures • Other general editorial/typographical updates

Version 2.0, 29 June 2020	• Updated statistical methods based on feedback from the United States Food and Drug Administration (FDA):
	  • Comparisons for primary and secondary endpoints (clinical status, percentage of subjects discharged from hospital, all-cause mortality, clearance of quantifiable viral RNA) will use adjusted risk difference obtained from a regression model (with sex, CRP, and stratification factors as covariates) rather than stratified Cochran-Mantel-Haenszel testing
	  • A section was added to specify type I error control for selected key study endpoints
	• Operational clarification was made in Visit and Assessment Schedule to align with COVID history will being a separate CRF page from medical history (both were to be collected per the main text in the original protocol)

	• The reasons for study treatment discontinuation were clarified based on feedback from the FDA • The reasons for study discontinuation were clarified based on feedback from the FDA • Subjects may only discontinue from the study due to withdrawal of consent or loss to follow-up; subjects should be encouraged to complete all follow-up visits if they discontinue study drug • Operational clarification was made that some of the laboratory assessments are done at a central laboratory and some at a local laboratory (details are available in the Study Manual) • For optimal clarity, Section 7.1.1, Recording of adverse events, was added to incorporate timing of AE/SAE recording that was in the Visit and Assessment schedule in the original protocol • The name of the CRO was updated to [redacted], and contact information was updated in Reporting of serious adverse events section • Other general editorial/typographical updates
Version 1.0, 29 May 2020	• Original Version

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

Short Title:	Losmapimod safety and efficacy in COVID-19 (LOSVID Study)
Version:	3.0.
Date:	21-Oct-2020
Study number:	FIS-001-2020
Sponsor:	Fulcrum Therapeutics 26 Landsdowne St., 5th floor Cambridge, MA 02139 USA
Sponsor signatory:	[redacted], MD

Information described herein is confidential and may be disclosed only with the express written permission of the sponsor.

CONTACT DETAILS

SPONSOR	Fulcrum Therapeutics 26 Landsdowne Street, 5th floor Cambridge, Massachusetts 02139 USA
Clinical Trial Leader	[redacted] MD Telephone: [redacted] e-mail: [redacted]
Drug Safety Physician	[redacted] MD Telephone: [redacted] e-mail: [redacted]

SIGNATURE PAGE - INVESTIGATOR

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I have read the protocol and agree to conduct the study as described herein.

Investigator Name
Title

DocuSigned by:
[redacted]
10/22/2020
Signer Name: [redacted]
Signature Reason: I approve this document
Signing Time: 10/22/2020 | 4:33:24 AM PDT
85FB9C773FFC42828A9CADA38A079032

Signature Date (dd Mmm yyyy)

SIGNATURE PAGE - SPONSOR

Fulcrum Therapeutics

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I approve this protocol on behalf of the sponsor.

[redacted]
Chief Scientific Officer

DocuSigned by:
[redacted] 10/22/2020
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10/22/2020 | 7:05:31 AM EDT
7AF6AE0D5E284E2AB0742E0CCCF2ABD3

Signature Date (dd Mmm yyyy)

[redacted], MD
Senior Vice President
Head, Clinical Development

DocuSigned by:
[redacted] 10/21/2020
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10/21/2020 | 11:59:05 AM EDT
B30B7B0252674261A13E7A9D9B141A67

Signature Date (dd Mmm yyyy)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
BID	*bis in diem* / twice per day
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	Maximum concentration
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	disease caused by novel coronavirus
CRP	C-reactive protein
CXCL13	chemokine ligand 13
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
ET-1	endothelin
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSGS	focal segmental glomerulosclerosis
FSHD	facioscapulohumeral muscular dystrophy
GCP	Good Clinical Practice
[redacted]	[redacted]
GSK	GlaxoSmithKline
H5N1	highly pathogenic Asian avian influenza A, subtype H5N1
HIV	human immunodeficiency virus
HMGB-1	high mobility group box protein-1
hsCRP	high-sensitivity C-reactive protein
HSV-1	herpes simplex virus-1
IA	interim analysis

ICAM-1	intercellular adhesion molecule-1
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	independent ethics committee
IL-6	interleukin-6
IND	investigational new drug application
IRB	institutional review board
IxRS	interactive/web voice response system
JAK	Janus kinase
[redacted]	[redacted]
LLQ	lower limit of quantitation
LS	least square
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusions
MCAR	missing-completely-at-random
MedDRA	Medical Dictionary for Regulatory Activities
OAT	organic anion transporter
PAO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PH	proportional hazards
PK	pharmacokinetics
PO	*per os* / orally
PPS	per protocol set
QTcB	QT corrected interval using Bazett's formula
QTcF	QT corrected interval using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SE	standard error
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID Study)

Short Title

Losmapimod safety and efficacy in COVID-19 (LOSVID Study)

Background & Rationale

Poor prognosis for many COVID-19 patients has been attributed to an exaggerated inflammatory response following SARS-CoV-2 infection. This hyperactivated immune response is associated with pulmonary edema, acute respiratory distress syndrome (ARDS), and cardiomyopathy that may lead to increased mortality in the sickest patients.

p38 mitogen-activated protein kinase (MAPK) is an important mediator of inflammation, and extensive nonclinical data have linked p38 to the hyper-inflammatory response to viral infections.

Losmapimod is a potent and selective p38α/β MAPK inhibitor that is currently in Phase 2 clinical trials for the treatment of facioscapulohumeral dystrophy and has previously been administered to more than 3600 adult healthy volunteers and subjects including participants in a Phase 3 trial. Many of these trials were for chronic inflammatory indications for which the compound exhibited a favorable safety profile not significantly different from placebo. These trials have also indicated that losmapimod has good exposure after oral dosing, robust target engagement, and acutely reduces inflammatory biomarkers that have been associated with poor prognosis in COVID-19, including C-reactive protein (CRP) and interleukin-6 (IL-6). Additionally, a clinical study recently concluded that losmapimod restored the normal immune response of older subjects (median 69 years, range: 65, 77 years) following a viral challenge. Further information is available in the losmapimod Investigator Brochure.

Losmapimod is attractive as a potential therapeutic option for COVID-19:

- p38 inhibition improves survival in mouse SARS-CoV-1 models and other nonclinical viral models, suppressing the exaggerated immune response to acute infection.
- Losmapimod acutely has reduced exaggerated inflammatory responses in human trials for multiple inflammatory diseases, including IL-6 and CRP, and has normalized immune response to viral or other acute inflammatory challenges in older subjects.
- Losmapimod is a clinical-stage, potent, and selective p38 inhibitor with extensive human experience and extensive evidence of safety and tolerability, including in a Phase 3 clinical trial in acute myocardial infarction.
- p38 inhibition has the potential to reduce hypothesized deleterious effects of increased angiotensin II in COVID-19, such as vasoconstriction, increased inflammation, cardiac arrhythmias, and organ failure.

Objectives and Endpoints:

All study objectives will be evaluated in subjects diagnosed with COVID-19:

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale: • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation by Day 28 Total number of study days in ICU by Day 28 Total number of study days hospitalized by Day 28 Total number of respiratory failure-free study days by Day 28 Percentage of subjects discharged from the hospital by Day 28
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive by Day 28

Objectives	Endpoints
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

Design

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥40 years old who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or ARDS or immediate need for intubation or mechanical ventilation per the judgment of the investigator.

Subjects who sign informed consent and meet all entry criteria (listed below) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg orally (PO) twice daily (BID); OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (approximately 5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any

additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter.

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site.

Investigational drug

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Comparative drug

Matching placebo tablets will be provided for oral administration.

Inclusion criteria

1. Able and willing to provide written informed consent.
    a. Note: Subject's legally authorized representative may provide informed consent as applicable based on local guidelines and regulations. If consent is obtained from a legally authorized representative, then assent should be obtained from the subject.
2. Willing and able to comply with all study procedures.
3. Age ≥40 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. Oxygen saturation ≥92% at the baseline visit, which can be either on room air or on oxygen supplementation if using ≤ 10LPM by nasal prong or close-fitting mask.
8. Evidence of pulmonary involvement consistent with COVID-19 by either clinical examination or radiographic examination (whichever is per local standard of care), per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator
10. CRP at screening >15 mg/L (which is equivalent to >1.5 mg/dL) on local laboratory testing.

11. Agrees to practice an approved method of birth control as follows (as applicable to local [country] guidelines and regulations for sites outside the United States):
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock, or ARDS) or immediate need for intubation or mechanical ventilation per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or poorly controlled HIV infection. (Subjects with HIV infection who have normal CD4 counts may participate if they have been on a stable antiviral regimen for the 30 days prior to screening and are anticipated to remain on the regimen throughout the duration of the study.)
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Has been treated with immunomodulators or immunosuppressants including, but not limited to, interleukin (IL)-6 inhibitors, tumor necrosis factor (TNF) inhibitors, anti-IL-1 agents, and Janus kinase inhibitors, within 5 half-lives or 30 days, whichever is longer, prior to randomization, or plan to receive these agents any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.

11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

Sample size justification

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an interim analysis (IA) will be conducted after approximately 206 subjects (103 in each of the losmapimod and placebo arms) have completed the Day 28 visit, to assess futility.

Statistical methodology

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the IA. The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% confidence intervals.

Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

Primary endpoint

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from a regression model, adjusted for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP. An interim analysis to assess futility analysis—and potential sample size re estimation—will be conducted. All results will be summarized descriptively by treatment arm and expressed as

proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p values.

Secondary endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and post-baseline will be modelled using regression models appropriate for ordinal data, adjusting for stratification factors, sex, and baseline CRP. Details will be provided in the SAP.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Total number of study days by Day 28: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, adjusting for stratification factors, sex, baseline CRP and number of days on study (as applicable). Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital by Day 28: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Table 1: Visit and Assessment Schedule

	SCR	Treatment Period											FU[14]		ET
Time point / Assessment[1]	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Informed consent	X														
Demography	X														
Inclusion and exclusion criteria	X	X													
Medical history	X														
COVID-19 history and clinical diagnosis[2]	X														
Chest X-ray/CT scan	X[3]	X[3]													
Study drug administration:															
Randomization		X													
Losmapimod or placebo PO BID		X	X	X	X	X	X	X	X	X	X	X			
Pharmacodynamics:															
Drug levels/PK[4]		P, 4-5h	4-5h	4-5h	4-5h	4-5h	4-5h	4-5h				4-5h			X
[redacted]															
Clinical status and symptoms:															
Respiratory failure and survival assessment[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical status assessment per WHO 9-point scale[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral presence and viral load by central testing [7]		X	X (sentinel only)[7]	X (sentinel only)[7]	X (sentinel only)[7]			X							X
Confirmation of COVID-19 diagnosis by PCR	X[2]	X (PR)[2]													

Assessment[1] \ Time point	SCR	Treatment Period											FU[14]		ET
	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Oxygenation and FiO_2[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments:															
Physical examination	X														X
Weight/height[9]	X												X		X
Hematology, chemistry safety labs[6]	X	X	X		X			X		X		X	X		X
CRP[6]	X														
Urinalysis[10]	X							X							
Urine or serum β-hCG (female subjects only)	X[11]												X		X
ECG[12]	X							X							
HR, BP, RR, temperature[8]	X	X	X	X	X	X	X	X	X	X	X	X			X
(S)AEs[13]	X														X
Concomitant medications (including SOC)	X														X

AE = adverse event; BP = blood pressure; COVID-19 = novel coronavirus; HR = heart rate; P = pre dose; PAO_2 = partial pressure of oxygen; PR – pre-randomization; RR = respiratory rate; sent = sentinel; SOC = standard of care; SCR = screening.

Note: All screening assessments are to be performed before dosing. If procedures required at any time point have already been performed as part of routine clinical care, these assessments do not need to be repeated, and information will be collected and entered on the eCRF from the subject's medical records. Unscheduled visits can take place at any time at the discretion of the site to check for new AEs/SAEs or to repeat key missed assessments or for other reasons.

[1] The order of assessments can be performed at the discretion of the investigator once informed consent is obtained.

[2] COVID-19 diagnosis to be confirmed by local testing (PCR) before randomization and first dosing. Saliva, swab, or sputum testing may be used based on local standard of care.

[3] To be performed while hospitalized based on standard-of-care local assessment. Evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

[4] PK assessments will be performed as a substudy in all sentinel subjects. For those subjects requiring dialysis, a single pre- and post-dialysis PK should be obtained for review by the DMC to decide if dose adjustment is needed. PK should be measured weekly for 2 weeks at C_{max} (4-5 hours post dose) for subjects with renal insufficiency when possible.

[redacted]

[6] Assessments for clinical/respiratory status, progression, and safety serum chemistry and hematology tests to be performed and samples to be collected while hospitalized based on standard-of-care local laboratory assessments and after discharge from the hospital by home visit or outpatient clinic visit or telemedicine call. For subjects who are discharged to home or other outpatient setting after initial hospitalization, the assessments and laboratory samples can be obtained less often but not less than at least once weekly. CRP result required to determine eligibility are based on local laboratory results at screening.

[7] Viral load testing will be collected daily for the first 4 days using central testing in the first 10 enrolled subjects as part of the sentinel safety assessment at select sites. For all subjects, including the sentinel subjects, swabs, saliva, or other sample collection (as specified in the Study Manual) for central viral load testing will be collected on D1 pretreatment and on D7 or earlier if being discharged from the hospital prior to D7.

[8] Vital signs will be performed after subjects have been supine for at least 5 minutes when possible. Vital signs to include oxygen saturation; PaO_2 should be recorded if available from blood gases obtained as part of SOC; oxygen administration should also be recorded (eg, room air or oxygen flow by nasal canula or facial mask or endotracheal tube). For subjects who are discharged to home or other outpatient setting after initial hospitalization, assessments may be obtained less often but at least once per week in the outpatient clinic or at home.
[9] Height assessed at screening only; can be by self-report or from medical records. Weight is an actual recording.
[10] Urinalysis will be performed during the study period only on Day 7 and on any other day only if clinically indicated.
[11] Pregnancy testing to be conducted within 72 hours of the first dose of study treatment.
[12] Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes if possible. ECGs will be performed at Day 7 in all subjects and at any other time during the study if clinically indicated.
[13] Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.
[14] Outpatient assessments to be conducted via telemedicine or outpatient clinic. Outpatient laboratory assessments to be completed at outside local laboratory or home or outpatient visit.

1 BACKGROUND AND RATIONALE

1.1 Scientific rationale for investigation of losmapimod in COVID-19

COVID-19 is a severe pandemic disease with high mortality particularly in older individuals, due to infection with the SARS-CoV-2 coronavirus. The therapeutic hypothesis for the use of losmapimod in COVID-19 disease is that increased mortality and severe disease is caused by p38 mitogen-activated protein kinase (MAPK)-mediated exaggerated acute inflammatory response resulting from SARS-CoV-2 infection. The older population is especially at risk of severe disease and death upon infection with SARS-CoV-2. The hyperactivated immune response in COVID-19 shares features of the cytokine storm syndrome and appears to be responsible for the severe pulmonary edema, ARDS, and cardiac and renal disease responsible for most of the severe morbidity and mortality.

The proposal to develop losmapimod, a potent, specific, and bioavailable p38α/β inhibitor, for treatment of COVID-19 is based on the following rationale:

(1) Nonclinical work has shown that older mice infected with SARS-CoV-1 develop much more severe disease than younger ones, and that treatment with a p38 MAPK small molecule inhibitor greatly reduced their mortality when given after viral inoculation; similar survival benefit of p38 MAPK inhibition has been seen in animal models of severe H5N1 influenza and HSV-1.

(2) Nonclinical work has shown that p38 MAPK inhibition reduces viral load in several experimental models with coronaviruses, including mouse hepatitis virus, human CoV-229E, transmissible gastroenteritis virus, and Middle East respiratory syndrome virus.

(3) p38 MAPK is proposed to play a critical role in the development of ARDS, including regulating the expression and activity of inflammatory mediators such as ICAM-1, HMGB1, and ET-1, neutrophil chemotaxis and apoptosis, the balance of Treg/Th17 cells, and pulmonary endothelial cell apoptosis.

(4) Clinical investigation showing that excessive acute inflammation in response to external stressors in older individuals, including viral antigen challenges, hinders the specific immune response to infection; many of the excessive inflammatory mediators associated with this aberrant immune response in older individuals are associated with activation of the p38 MAPK pathway.

(5) Treatment with losmapimod in older subjects restored the normal immune response to viral antigen challenge and improved the resolution of acute inflammation.

(6) Treatment of various inflammatory diseases with losmapimod, including active rheumatoid arthritis (RA), acute myocardial infarction, and chronic obstructive pulmonary disease (COPD) resulted in significant reduction in markers of acute inflammation, including interleukin-6 (IL-6), C-reactive protein (CRP), chemokines such as CXCL13, and other markers (see Table 5 for further details).

(7) Losmapimod may be beneficial in COVID-19 treatment via reduction of the damaging effects of angiotensin II (Ang II). Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS-CoV viruses and is expressed in the lung and the heart. Upon infection with SARS-CoV-2, there is internalization of and depletion of ACE2. ACE2 converts Ang II into angiotensin 1-7 (Ang 1-7), which counterbalances the vasoconstrictive and pro-inflammatory effects of Ang II. Ang II is significantly elevated in COVID-19, and the levels are positively correlated with viral load and acute lung injury (Liu Y et al, 2020). Blocking the p38 MAPK pathway in nonclinical models has been

shown to reduce many of the adverse effects of elevated Ang II, resulting in lower frequency of cardiac arrhythmias, renal failure, and hypertension.

p38 inhibitors have been explored extensively in clinical trials for numerous chronic inflammatory indications, as summarized in the Investigator Brochure. Losmapimod has been extensively tested in humans and found to be generally well tolerated, including in over 3600 adult healthy volunteers and subjects in 11 different indications. The 15 mg oral (PO) twice per day (BID) dose proposed for the COVID-19 Phase 3 study has been shown to provide robust and sustained inhibition of the p38 MAPK pathway systemically and in tissues, specifically in skeletal muscle needle biopsies of subjects with facioscapulohumeral muscular dystrophy (FSHD). This dose of losmapimod was shown experimentally in older (median 69 years, range: 65, 77 years) human volunteers to restore the normal immune response to viral challenge and improve the resolution of acute inflammation. Furthermore, losmapimod has been shown to significantly reduce markers of hyperactive acute innate immune inflammation in the context of acute myocardial infection, RA, and COPD in clinical trials as listed below:

1- Single-dose study in 50 subjects with RA (RA 3103730). Treatment with losmapimod (N=38) reduced levels of IL-6 compared with placebo (N=12). Losmapimod was dosed as follows: 7.5 mg: 13 subjects; 20 mg: 12 subjects; 60 mg: 13 subjects. Analysis of serum IL-6 at 3 hours post dose showed significantly lower levels with losmapimod than with placebo (Table 2).

Table 2: Change from Baseline in IL-6 Serum Levels with Increasing Single Doses of Losmapimod in Subjects with Rheumatoid Arthritis

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to placebo	95% CI
Placebo	0.92	0.60, 1.41		
Losmapimod 7.5 mg	0.41	0.26, 0.63	0.45	0.24, 0.82
Losmapimod 20 mg	0.43	0.27, 0.68	0.47	0.25, 0.88
Losmapimod 60 mg	0.38	0.25, 0.57	0.41	0.23, 0.75

Abbreviations: CI = confidence interval.

2- Repeated-dose study in subjects with acute coronary syndrome (ACS; PM1111810). A total of 535 subjects with non-ST elevation myocardial infarction were randomized to an initial dose of 7.5 or 15 mg of losmapimod followed by 7.5 mg PO BID (N= 388) or matching placebo (N=138) for 12 weeks. Results showed that relative to placebo, losmapimod significantly suppressed CRP and IL-6 acutely at the 24- to 36-hour assessments (Table 3).

Table 3: Change from Baseline in hsCRP and IL-6 with 7.5mg PO BID Losmapimod Over Placebo in Subjects with Acute Coronary Syndrome

Parameter	Placebo (N=138)	All losmapimod (N=388)	P value
hsCRP at 72 hours or discharge (nmol/L)	110.8 (83.1-147.7)	64.1 (53.0-77.6)	<0.05
IL-6 at 24 hours (ng/L)	10.6 (8.6-13.1)	6.6 (5.8-7.4)	<0.05

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6.

3- Repeated-dose study in subjects with COPD (MKI113006). In this study, subjects with COPD were dosed with losmapimod 2.5 mg BID (N=149), losmapimod 7.5 mg BID (N=151), or placebo BID (N=154) for 24 weeks; or losmapimod 7.5 mg BID for 4 weeks followed by losmapimod 15 mg BID (N=150) for 20 weeks. Over the first 12 weeks of treatment, statistically significant reductions in serum high-sensitivity CRP (hsCRP) levels were observed in the losmapimod 7.5 mg and 15 mg groups compared with placebo. For hsCRP, Week 12, 7.5 mg dose versus placebo: ratio 0.73; 95% confidence interval [CI] 0.57, 0.93;

p=0.011; 15 mg dose versus placebo: ratio 0.64; 95% CI 0.50, 0.82; p<0.001. Table 4 shows the results for the subgroup with higher CRP at baseline.

Table 4: Change from Baseline in CRP Over 12 Weeks of Treatment with Different Doses of Losmapimod Compared with Placebo in Subjects with COPD and High Baseline CRP Levels (>6.4 mg/L)

Week 12 Baseline hsCRP >6.40 mg/L	Placebo BID (N=42)	Losmapimod 2.5 mg BID (N=33)	Losmapimod 7.5 mg BID (N=31)	Losmapimod 15 mg BID (N=31)
Geometric LS mean (SE of logs)	6.75 (0.153)	8.08 (0.180)	5.16 (0.180)	3.54 (0.186)
Geometric LS mean ratio to baseline (SE of logs)	0.49 (0.153)	0.59 (0.180)	0.38 (0.180)	0.26 (0.186)
Column vs placebo				
Ratio		1.20	0.77	0.53
95% CI		0.75, 1.92	0.48, 1.22	0.33, 0.85

Abbreviations: CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; LS = least square; SE = standard error.

Fulcrum Therapeutics is planning to conduct the initial clinical trial for the investigation of losmapimod for the treatment of COVID-19 in these high-risk subjects. Losmapimod is currently in Phase 2 clinical development for the treatment of the root cause of FSHD under an open IND in the United States (US) and open clinical trial applications in Canada, Spain, France, and The Netherlands.

A summary of published literature supporting the therapeutic hypothesis for the clinical development of losmapimod for the treatment of COVID-19 is provided in Table 5.

Table 5: Listing of Evidence Supporting the Development of the p38 Inhibitor Losmapimod for Treatment of COVID-19

Evidence	References
Pneumonitis, acute respiratory distress syndrome, pulmonary edema, and cardiomyopathy drive COVID-19 mortality	• Siddiqi HK et al. J Heart Lung Transplant. 2020 • Ruan Q et al. Intensive Care Med. 2020 Mar 3
Older patients are at greatest risk of COVID-19 mortality	• Ruan Q et al. Intensive Care Med. 2020 Mar 3
Human SARS-CoV-2 pathology is recapitulated in SARS-CoV-1 mice	• Zhou F et al. Lancet. 2020 • Nagata N et al. Am J Pathol. 2008
Exaggerated acute inflammatory response and lymphopenia correlate with mortality in human with COVID-19 and older mice infected with SARS-CoV-1	• Nagata N et al. Am J Pathol. 2008 • Zhou F et al. Lancet. 2020
SARS-CoV-1 activates the p38 MAPK pathway in peripheral blood early in the infection	• Lee CH et al. J Immunol. 2004.
SARS-CoV envelope protein (E) activates the host's inflammatory response via p38 signaling	• Jimenez-Guardeño JM et al. PLOS Pathog. 2014

Evidence	References
Several nonclinical studies have shown evidence of p38 inhibition reducing viral replication including with coronavirus	• Kono M et al. Antiviral Res. 2008 • Dong Y et al. Antiviral Res. 2020 • Kindrachuk D et al. Anti Microb Agents & Chem. 2015
p38 inhibition reduces mortality in older mice infected with SARS-CoV-1	• Jimenez-Guardeño J et al. PLOS Pathog. 2014
Nonclinical efficacy of p38 inhibition also observed in other models of severe acute viral pneumonitis and other severe acute viral infections	• Shapiro L et al. PNAS. 1998 • Iordanov MS et al. Mol Cell Bio. 2000 • Salomon R et al. PNAS. 2007 • Griego SD et al. J Immunol. 2000 • Banerjee S et al. J Virology. 2002 • Börgeling Y et al. J Biol Chem. 2014 • Chen Y et al. J Exp Med. 2017 • He F et al. J Transl Med. 2019
p38 inhibition reduces lung mucous production in mice models of toxic airway injury	• Liu et al. Int Immunopharmacol. 2009
Losmapimod and other p38 inhibitors acutely reduce inflammatory markers in humans	• GSK data in Fulcrum Original IND 138739, Module 4 • Genovese M et al. J Rheumatol. 2011 • Christie J et al. Crit Care Med. 2015
Losmapimod reduces inflammatory markers associated with COVID-19 severity at currently utilized doses	• Fulcrum clinical data on file • GSK clinical data • Newby L et al. Lancet. 2014
Inhibition of p38 with 15 mg losmapimod BID dose in older subjects restored the adaptive immune response to viral challenge	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
Exaggerated acute inflammatory response in older subjects is driven to a large extent by p38 activation	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
In vivo data in Ferrets indicate SARS-Cov-2 induces profoundly lower immune response vs other virus	• Blanco-Melo D et al. bioRxiv. 2020
Evidence that p38 inhibition may treat the deleterious effects of elevated Ang II in COVID-19	• Grimes JM et al. J Mol Cell Cardiol. 2020
Losmapimod is a highly selective p38 inhibitor at advanced stage of clinical development with excellent safety data profile	• Losmapimod Investigator Brochure Fulcrum 2020 • Cadavid D et al. FSHD IRC Poster. 2019

Abbreviations: BID = twice daily; COVID-19 = disease caused by novel coronavirus; IND = investigational new drug application; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1.2 Benefit-risk considerations

This is the first-in-human clinical trial with losmapimod for the treatment of a novel virus (COVID-19) and, therefore, the risk-benefit considerations are based on nonclinical data in conditions related to COVID-19 (e.g., SARS-CoV-1) as well as extensive clinical data in other inflammatory conditions and conditions involving the p38 MAPK pathway (e.g., FSHD, RA, COPD) including in older healthy volunteers; refer to Section 1.1 for further details.

Losmapimod has been found to be generally well tolerated in clinical trials, including in over 3600 adult healthy volunteers and subjects in 11 different indications. The 15 mg PO BID dose proposed for this study has been shown to provide robust and sustained inhibition of the p38 MAPK pathway systemically and in tissues, specifically in skeletal muscle needle biopsies of subjects with FSHD.

Complete clinical safety data and nonclinical data for losmapimod can be found in the Investigator's Brochure. Additional adverse events not previously observed in animals or in humans may also occur in this trial. Subjects in this clinical trial will be monitored closely for the development of adverse effects that may result from study drug administration. In addition, a Data Monitoring Committee (DMC) will monitor the safety of subjects throughout the study on an ongoing basis.

COVID-19 is a severe and rapidly progressive infection, especially in the high-risk population (ie, older, with comorbidities) selected for this trial. Given the extensive clinical experience with losmapimod, the potential benefit of losmapimod treatment in this indication outweighs the risks.

2 STUDY OBJECTIVES AND ENDPOINTS

All study objectives will be evaluated in subjects diagnosed with COVID-19.

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale (WHO 2020): • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation by Day 28 Total number of study days in ICU by Day 28 Total number of study days hospitalized by Day 28 Total number of respiratory failure-free study days by Day 28

Objectives	Endpoints
	Percentage of subjects discharged from the hospital by Day 28
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive by Day 28
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

3 STUDY IMPLEMENTATION

3.1 Overall study design and plan

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥40 years old, who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or ARDS or immediate need for intubation or mechanical ventilation per the judgment of the investigator.

Subjects who sign informed consent (refer to Section 9.1.3) and meet all entry criteria (see Section 4) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg PO BID; OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (approximately 5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent DMC. The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter (see Section 8.10).

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site (refer to Section 6.7).

3.2 Start of study and end of study definitions

The start of the study is defined as the date the first enrolled subject signs an informed consent form (ICF). The end of the study is defined as the date of the last subject’s last assessment (scheduled or unscheduled).

3.3 Selection of doses in the study

In the Phase 1 study in healthy volunteers and FSHD subjects (Study FIS-001-2018), the dose levels of 7.5 mg and 15 mg given by mouth BID with food were based on predictive nonclinical efficacy and published clinical target engagement and safety data for losmapimod previously

generated by GSK. This Phase 1 study was recently completed and demonstrated that the 15 mg PO BID dose gives higher plasma levels and greater and more sustained target engagement in blood and tissues than the 7.5 mg PO BID dose, while resulting in similar safety and tolerability. The 15 mg BID dose is used in the ongoing Phase 2 studies in FSHD (Study FIS-001-2019 and Study FIS-002-2019). Prior results indicated the favorable safety and tolerability of losmapimod for chronic administration in the clinic, including in the context of severe acute diseases, such as acute myocardial infarction, in older people.

Prior studies of biodistribution of radiolabeled losmapimod by GSK showed ample distribution to all tissues including the lungs and the heart. Our recent target engagement data in the FSHD Phase 1 Study FIS-001-2018 indicates that pHSP27 inhibition in blood, an assessment of p38 target engagement, is nearing a plateau at a losmapimod dose of 15 mg BID (see Investigator Brochure [Fulcrum Therapeutics 2020]), so doses of losmapimod higher than 15 mg PO BID are not warranted.

Additionally, at the proposed dose level of 15 mg PO BID, exposures are not expected to exceed those previously demonstrated to be safe in humans in multiple previous studies by GSK in healthy volunteers and various patient populations including older subjects (Cheriyan et al 2011; Barbour et al 2013; Watz et al 2014; Pascoe et al 2017).

In previous clinical studies performed by GSK, it was shown that losmapimod significantly reduced markers of acute inflammation, including IL-6, CRP, and the CXCL13 chemokine after a single dose. Additionally, losmapimod reduced IL-6 after 15 days of treatment (GSK study RA3103718) and CRP acutely in subjects with acute myocardial infarction treated with 7.5 mg PO BID (O'Donoghue et al 2016). In subjects with COPD, losmapimod at 15 mg PO BID significantly reduced CRP over 12 weeks compared with placebo (GSK Study MKI 113006). In one study in healthy older adult volunteers, it was shown that a 15 mg PO BID dose of losmapimod for 4 days restored the normal immune response to varicella-zoster virus antigen challenge (Vukmanovic-Stejic et al 2018). The same formulation used in these previous clinical studies is the one proposed for use in the present clinical study.

The rationale for the proposed study duration of up to 28 days is that in most cases of COVID-19 the disease has resolved or resulted in severe outcomes over the first month from onset of symptoms. COVID-19 is a severe and rapidly progressive infection, especially in the high-risk population selected for the proposed Phase 3 trial. Therefore, treatment for longer than 14 days and study duration for longer than 28 days is not justified.

3.4 Study drug modifications and withdrawal

3.4.1 Dose modifications

Before trial medication is administered, changes in the subject's health status, including laboratory results if applicable, since the previous visit or previous dose should be checked.

Study drug interruptions and reductions are not permitted; subjects who are on dialysis may require a dose adjustment.

Study treatment dose adjustment for subjects on dialysis

The elimination of losmapimod is almost exclusively by metabolism, with only 2% of the administered dose recovered as unchanged drug in urine and feces. The metabolite is clinically inactive and does not exert any toxic effects.

Losmapimod has not been studied in renal insufficiency or renal failure. There has been 1 study of losmapimod in 17 subjects with focal segmental glomerulosclerosis (FSGS; FSG117283). In this study, subjects were given losmapimod 7.5 mg BID for 2 weeks followed by losmapimod 15 mg BID

for 22 weeks. The mean duration of exposure to investigational product in subjects with FSGS was approximately 21 weeks (range: 3.7, 25 weeks).

Creatine and GFR for the population enrolled is in the table below.

Parameter	Mean (SD)	Range
eGFR (mL/min/1.73m^2)	79.4 (34.9)	36, 155
Creatine (µmol/L)	1.1 (0.5)	0.48, 2.07

eGFR = estimated glomerular filtration rate.

Losmapimod plasma concentration data in subjects with FSGS were compared with historical data obtained in the Phase 3 clinical trial in subjects with ACS. In general, exposure in subjects with FSGS was similar to subjects with ACS over the 24-week treatment period.

Consistent with the safety database of over 3500 subjects, the 2 most frequently reported AEs in the FSGS trial were headache (5/17; 29%) and fatigue (4/17; 24%). Seven AEs (by preferred term: vomiting, dizziness, oropharyngeal pain, nausea, blood creatinine increased, muscle spasms, and rash) were reported in 3 subjects (18%) each. All other AEs (by preferred term) were reported in ≤2 subjects each. Four subjects had at least 1 AE that led to withdrawal from the study or from treatment. The AEs that led to discontinuation were increase in blood urea nitrogen (related), increase in creatinine (not related), increase in cystatin C (related), and joint stiffness (related). None of the AEs was serious or severe; 3 of the AEs in 2 subjects were reported as related to study treatment.

Based on the current safety and exposure information, dosing adjustment is likely not needed for subjects with renal insufficiency. However, close monitoring of pharmacokinetics (PK) for such cases will be implemented to ensure that therapeutic concentrations are maintained (refer to Section 6.2). For those subjects requiring dialysis, dose adjustment may be needed and will be determined by pre- and post-dialysis PK by the DMC. Adjustments may be recommended by the DMC also for subjects on placebo who develop acute renal failure to prevent unblinding at the sites.

Study treatment discontinuation

Discontinuation of study treatment should be considered if:

- ALT or AST >8 x the upper limit of normal (ULN)
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (total bilirubin >2 x ULN or international normalized ratio >1.5) in the absence of reasonable alternative etiology
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- QTcF prolongation with QTcF >500 msec or an increase in QTcF of >60 msec over baseline (confirmed by 2 successive repeat measurements)

In addition, the investigator must permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the subject. The premature discontinuation of study drug might be triggered by an adverse event (AE), a diagnostic or therapeutic procedure, an abnormal assessment (eg, ECG or laboratory abnormalities), pregnancy, or for administrative reasons, in particular noncompliance with the protocol or withdrawal of the subject's consent. The reason for study drug interruption or premature discontinuation must be clearly documented in the eCRF.

3.4.2 Subject withdrawal

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. In all cases of impending consent withdrawal, investigators will be given instructions to meet and discuss with the participant their options of continuing in the study. The investigator should ensure understanding and documentation of the reasons for the participant's desire to withdraw consent. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment. Unless the participant provides their written withdrawal of consent or there is other written documentation by the investigator confirming the participant's verbal intent to completely withdraw from the trial, participants should be followed for all protocol-specified evaluations and assessments. The reasons for subjects not completing the study will be recorded.

A subject may be withdrawn from the study if he or she is lost to follow-up. For subjects to be considered as lost to follow-up, 2 attempts should be made to contact the subject to return for the scheduled study visit. After 2 attempts, a certified letter should be sent to the subject's address requesting the subject to contact the investigator to schedule a follow-up assessment. If no reply is provided by the subject within 30 days of receipt of the certified letter, the subject can then be considered lost to follow-up.

3.4.3 Replacement policy

Subjects who withdraw from the study will not be replaced.

3.4.4 Stopping criteria

Dosing will be stopped in case of an unacceptable tolerability profile based on the nature, frequency, and intensity of observed AEs judged jointly by the investigator and the sponsor or as recommended by the DMC.

In the event of a study hold due to unacceptable tolerability, the sponsor will conduct an extensive safety and PK analysis and will communicate to stakeholders, including the Investigators, institutional review boards (IRBs)/independent ethics committees (IEC), and health authorities any potentially emergent safety information as well as the timing of planned resumption of dosing. Dosing and enrollment will not resume unless it is considered safe to do so after consultation with Investigators and health authorities and approval by IRBs/IECs.

4 STUDY POPULATION

4.1 Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening.

1. Able and willing to provide written informed consent.
    a. Note: Subject's legally authorized representative may provide informed consent as applicable based on local guidelines and regulations (see Section 9.1.3). If consent is obtained from a legally authorized representative, then assent should be obtained from the subject.
2. Willing and able to comply with all study procedures.
3. Age ≥40 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for the SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. Oxygen saturation ≥92% at the baseline visit, which can be either on room air or on oxygen supplementation if using ≤ 10LPM by nasal prong or close-fitting mask.
8. Evidence of pulmonary involvement consistent with COVID-19 by either clinical examination or radiographic examination (whichever is per local standard of care), per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator (CDC 2020).
10. CRP at screening >15 mg/L (which is equivalent to >1.5 mg/dL) on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows (as applicable to local [country] guidelines and regulations for sites outside the US):
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

4.2 Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock or ARDS) or immediate need for intubation or mechanical ventilation per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or poorly controlled HIV infection. (Subjects with HIV infection who have normal CD4 counts may participate if they have been on a stable antiviral regimen for the 30 days prior to screening and are anticipated to remain on the regimen throughout the duration of the study.)
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Has been treated with immunomodulators or immunosuppressants including, but not limited to, interleukin (IL)-6 inhibitors, tumor necrosis factor (TNF) inhibitors, anti-IL-1 agents, and Janus kinase inhibitors, within 5 half-lives or 30 days, whichever is longer, prior to randomization, or plan to receive these agents any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.
11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

4.3 Concomitant medications

All medications (prescription and over-the-counter) taken at the time of study screening will be recorded, with indication, route of administration, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Subjects are allowed to use paracetamol (up to 3 g/day) and/or contraceptives (oral or parenteral), and any medications needed for SOC at the local institution. Use of hydroxychloroquine/ chloroquine is not permitted. Use of other experimental treatments for COVID-19 is not permitted unless it is part of SOC at the local institution. SOC for COVID-19 will be documented at each site during the site activation visit; additionally, it will be documented if any restrictions on standard of care treatment administration were encountered due to resource limitations. The use of antiviral medications is permitted.

Concomitant medications used to treat chronic comorbid conditions per SOC are permitted, including but not limited to metered dose inhalers, corticosteroids if on stable doses for at least 30 days prior to screening, or sedative or anesthetic agents.

Concomitant medications initiated or stopped for an AE will be recorded.

Both losmapimod and its major metabolite, GSK198602, are in vitro inhibitors of human BCRP. There is a low risk of interaction of losmapimod with orally administered BCRP substrates with a narrow therapeutic index (eg, methotrexate, topotecan, rosuvastatin). Therefore, such co-administration is indicated only if the medical benefit is considered to outweigh the risk for toxicity, and careful monitoring for adverse effects of these agents is advised.

Losmapimod is a relatively potent in vitro inhibitor of the renal transporters MATE1 and MATE2-K, and it is possible that a mild inhibition of tubular secretion may contribute to the small rise in (model-adjusted geometric mean) serum creatinine observed clinically. GSK198602 is a relatively potent in vitro inhibitor of OAT3 and co-administration of sensitive OAT3 substrates is indicated only if the medical benefit is considered to outweigh the risk for toxicity. Careful monitoring for adverse effects of these agents is advised, especially for those with narrow therapeutic margin (eg, methotrexate, metformin).

4.4 Lifestyle restrictions

Subjects should not donate blood, sperm, or ova from the screening visit through 90 days after the last dose of study treatment.

4.4.1 Contraception requirements

Teratogenicity and effects on embryofetal survival were noted in rat and rabbit reproductive toxicology studies with losmapimod. Therefore, losmapimod should not be taken by women of childbearing potential who are not utilizing adequate contraceptive methods.

All women of childbearing potential and all males must practice effective contraception during the study from the time of the first dose of study medication until 90 days after last dose.

Women of child-bearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy/bilateral salpingectomy with or without hysterectomy;
- Post hysterectomy.

For the purposes of the study, effective contraception is defined as follows (as applicable to local [country] guidelines and regulations for sites outside the US):

- Females of childbearing potential: Using 1 or more of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap).
- Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms.

Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Investigational drug and matching placebo

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Matching placebo tablets will be provided for oral administration.

The tablets are plain white, round, biconvex, film-coated tablets. The proposed dosing regimen is as a twice daily dose of 15 mg (2 × 7.5 mg tablets/dose BID). The proposed duration of treatment is for up to 14 days.

Subjects should take their dose of losmapimod or placebo with food whenever possible and with 240 mL of room temperature water.

5.2 Study drug packaging and labelling

Losmapimod tablets for oral administration are available as white, round, biconvex, plain, film-coated tablets containing 7.5 mg of losmapimod as the micronized base, GW856553X.

Losmapimod tablets also contain the inactive excipients microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, povidone K30, hypromellose, titanium dioxide (E171), and polyethylene glycol.

Placebo tablets are identical in appearance to losmapimod and have the same excipient ingredients as losmapimod but do not have the active compound.

All tablets are packed in opaque, white, square, high-density polyethylene bottles with induction sealed child-resistant closures.

Losmapimod must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature not to exceed 30°C.

5.3 Drug accountability

The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

The Investigator (or designee) will maintain an accurate record of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures by the sponsor. Any unused assembled unit doses will be retained until completion of the study.

After completion of the study, all unused supplies will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

5.4 Treatment assignment and blinding

5.4.1 Randomization and treatment assignment

A total of up to 410 subjects will be recruited into this study and will be randomized in a 1:1 ratio to 15 mg losmapimod (BID) or placebo using an interactive/web voice response system (IxRS) for randomization. The randomization list will be produced by a qualified randomization vendor and will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no) at enrollment.

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug. Randomized subjects will be sequentially assigned a unique subject number from the randomization list per the IxRS. From the time of randomization and throughout the duration of the study, subjects will be identified by their unique randomization number.

The authorized site personnel will prepare the appropriate study drug for each subject based on the randomization schedule. Treatment codes should not be broken except in emergency situations, ie, when knowledge of the treatment is essential for the immediate further management of the subject.

5.4.2 Blinding

This study will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to subject-level treatment assignment until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way.

5.4.3 Treatment compliance

All doses will be administered either in the hospital (anticipated during the first week of study treatment) or taken by the study participants on an outpatient basis.

The subject will bring the study treatment bottle to each visit (clinic or home assessment) for review by the site staff.

The study treatment bottles will be collected at the Day 14 visit whether in the hospital or outpatient or at the ET visit if prior to Day 14.

6 STUDY ASSESSMENTS

See Table 1 for the time points of the assessments.

If additional visits or blood draws are required beyond the planned visits in any part of the study, these visits or samples should be recorded in the eCRF as unscheduled visits prior to the subject's completion of the study.

6.1 Medical history and confirmation of COVID diagnosis

A complete medical history will be taken at Screening and is to include demographic information, prior medical illnesses and conditions, and surgical procedures for at least 3 months prior to screening. The medical history may be collected from medical records, if available, or during the physical examination.

The history of SARS-CoV-2 infection and symptoms at screening should be recorded; the details of how infection history will be assessed and recorded can be found in the Study Manual. Diagnosis of COVID-19 should be confirmed by local PCR testing prior to randomization. Refer to the Study Manual for details on procedures and type(s) of diagnostic testing allowed.

A chest X-ray or CT may be performed while the patient is hospitalized based on standard-of-care local assessment. Evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

A pre-existing condition is one that is present prior to administration of study drug. Such conditions should be recorded as medical history. A pre-existing condition should be recorded as an AE or serious adverse event (SAE) only if the frequency, intensity, or nature of the condition worsens following administration of study drug.

6.2 Pharmacokinetic and pharmacodynamic assessments

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess PK. PK assessments will be performed as a substudy in all sentinel subjects to evaluate the PK of losmapimod in the population of subjects with COVID-19.

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess serum and plasma biomarkers of response to COVID-19, which may include [redacted]

Procedures for collection, processing, and return of blood samples will be detailed in the Study Manual. Specifics of the analytical methods will be provided in separate documents.

Cytokines and chemokines will be evaluated using a multiplex assay. Details of the assay and specimen sampling will be provided in the Study Manual.

Viral load will be assessed by nasopharyngeal (preferred) or oropharyngeal swab, saliva, or other appropriate assay as outlined in the Schedule of Assessments (Table 1). Study samples will be analyzed by central testing. Refer to the Study Manual for details on procedures and type(s) of diagnostic testing allowed.

PK should be measured weekly for 2 weeks at C_{max} (4-5 hours) for subjects with renal insufficiency (eGFR ≤45 mL/min/ 1.73 m^2). For those subjects requiring dialysis, dose adjustment may be needed (see Section 3.4.1) and will be determined by pre- and post-dialysis PK by the DMC to prevent site unblinding.

6.3 Clinical status and symptoms

The investigator may consult with a relevant clinical or other specialist as appropriate per SOC.

6.3.1 Respiratory failure and survival assessment

Total number of study days free of oxygen supplementation and total number of study days free of respiratory failure will be evaluated. Refer to Section 6.5.1 for further details of vital sign collection.

- Note: Respiratory failure is defined as either need for mechanical ventilation (invasive or non-invasive) or high flow oxygen (defined by greater than 15 LPM flow of oxygen to maintain oxygen saturation between 90% and 95%), sustained for at least 48 hours, at any time during the study.

The reason for hospitalization and number of total study days of hospitalization and intensive care unit (ICU) utilization will be recorded.

Details of subject discharge (date of discharge and condition at discharge) from the hospital will be recorded.

Any significant deviation from standard of care due to limited resources will be documented.

Survival status at the end of the study period will be documented, including cause of death for any reason.

6.3.2 Clinical status assessment

Clinical status as outlined in the Schedule of Assessments (Table 1) will be measured on the following clinician-reported 9-point ranking scale (WHO):

- (8) death
- (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO)
- (6) intubation and mechanical ventilation
- (5) noninvasive ventilation or high-flow oxygen therapy
- (4) oxygen therapy but not requiring high-flow or non-invasive ventilation
- (3) hospitalized but not requiring oxygen therapy
- (2) discharged from the hospital but with limitation of activities
- (1) discharged from the hospital and without any limitation
- (0) no clinical evidence of the disease

Instructions for administration will be provided in the Study Manual.

6.4 Extended vital signs

Extended vital signs, including oxygen saturation and fraction of inspired oxygen (FiO_2) will be collected as specified in the schedule of assessments. Refer to Section 6.5.1 for further details of measurements.

6.5 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 7.

6.5.1 Vital signs

Evaluations of systolic and diastolic blood pressure, respiratory rate, and temperature will be performed throughout the study. In addition, oxygen saturation and FiO_2 will be assessed throughout the study. Oxygen administration (eg, room air or oxygen flow by nasal canula or facial mask) will be recorded. Vital signs will be performed after subjects have been supine for at least 5 minutes when possible.

Arterial blood gases may be performed if clinically indicated in some subjects but are not required for this study. If arterial blood gasses are measured, the results for arterial pressure of oxygen (PaO_2) should be reported at each measurement in the eCRF.

Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.2 Weight and height

Weight (kg) will be recorded at screening and the follow-up assessment (by alternative methods including outpatient visit). Height (cm) will be recorded and body mass index (BMI) calculated at screening.

BMI (kg/m^2) = weight (kg)/(height [cm]/100)^2

6.5.3 Physical examination

Physical examination (ie, inspection, percussion, palpation, and auscultation) is performed to determine eligibility and as clinically indicated during the study. Clinically relevant findings that are present prior to study drug initiation must be recorded with the subject's medical history. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.4 Electrocardiography

ECGs will be taken singly after 5 minutes in the supine position as specified in the schedule of assessments. The investigator will assess the ECG recording as 'normal', 'abnormal - not clinically significant', or 'abnormal - clinically significant' and include a description of the abnormality as required. The ECG parameters assessed will include heart rate, PR, QRS, QT, and QTcB and QTcF (calculated using Bazett's and Fridericia's method, respectively). ECGs will be performed to determine eligibility and during the study period only if clinically indicated. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.5 Laboratory assessments

Laboratory parameters

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded. Clinical relevance is defined as:

- Is accompanied by clinical symptoms
- Leads to dose modification of study treatment

- Requires significant changes, addition of, interruption of, discontinuation of a concomitant medication, therapy, or treatment
- Reflects a disease and/or organ toxicity

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria or those that is a result of an AE that has already been reported.

Blood and other biological samples will be collected for the following clinical laboratory tests; refer to the Study Manual for details of collection and analysis and information on central and local laboratories:

Lab	Tests
Hematology	Hemoglobin [including mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration], hematocrit, red cell count, total white cell count, and platelet count. Differential blood count, including: basophils, eosinophils, neutrophils, lymphocytes, and monocytes.
Chemistry and electrolytes	Sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, uric acid, total bilirubin[1], alkaline phosphatase, AST, ALT, gamma-glutamyl transferase, and LDH.
Glucose	Glucose
Urinalysis	Leucocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose. If there is a clinically significant positive result, urine will be sent for microscopy and/or culture.
Pregnancy[2]	hCG (urine or serum). If there is a clinically significant, positive result in urine, urine will be sent for confirmation.
[1]Conjugated bilirubin may be reported when total bilirubin is outside the reference range. [2]Pregnancy test for women of childbearing potential will be performed within 72 hours of first dose and if pregnancy is suspected during the study.	

6.6 Unscheduled visit

Unscheduled visits may be performed at any time at the subject's or the investigator's request and may include (but are not limited to) vital signs/focused physical examination, ECG, AE review, concomitant medications and procedures review, disease-related constitutional symptoms, and/or laboratory and biomarker assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

6.6.1 Early termination visit

When the investigator determines that study treatment will no longer be used, the investigator will perform the ET procedures and document the reason for discontinuation from study treatment in the eCRF. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the time of study treatment discontinuation, these tests need not be repeated. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment.

6.7 Alternative follow-up methods to site visits

Trial participants may not be able to come to the investigational site for protocol-specified or unscheduled visits. The sponsor may use alternative methods for safety assessments, including

telemedicine visits, telephone visits, and/or an alternative location for visits depending on the local or institutional standards.

7 SAFETY REPORTING

7.1 Definitions of adverse events

An adverse event (AE) is any untoward medical occurrence in a subject who is participating in a clinical study performed. The AE does not necessarily have to follow the administration of a study drug, or to have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or vital sign finding), symptom, or disease temporally associated with the study participation whether or not it is related to the study drug.

7.1.1 Recording of adverse events

Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

7.1.2 Intensity of adverse events

The intensity of clinical AEs is graded 3-point scale as defined below:

- Mild: discomfort noticed but no disruption of normal daily activity;
- Moderate: discomfort sufficient to reduce or affect normal daily activity;
- Severe: inability to work or perform daily activity.

7.1.3 Relationship to study drug

For each AE, the relationship to drug as judged by the investigator:

- Probable;
- Possible;
- Unlikely;
- Unrelated.

7.1.4 Serious adverse events

A serious adverse event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatient hospitalization;
    - Note: COVID-19-related hospitalization or ICU admission is excluded from this definition, as SARS-CoV-2, COVID-19 infection, or pulmonary conditions attributable to COVID-19 infection are efficacy-related endpoints
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE.

7.1.5 Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is unexpected (nature or severity of which is not consistent with the applicable product information (eg, the Investigator Brochure for losmapimod) and suspected (a reasonable possibility of causal relationship with investigational drug, regardless of the administered dose).

7.1.6 Reporting of serious adverse events

The investigator must report any AE that meets the SAE criteria (Section 7.1.4) to [redacted] immediately (ie, within 24 hours after the site personnel first learn about the event) via electronic data capture (EDC). In the event that EDC entry is not possible (eg, system failure or access problems), the study site staff should complete the paper SAE report form and fax the form to [redacted] Pharmacovigilance within 24 hours of awareness or call the [redacted] safety hotline to report. The study site staff should update the EDC system as soon as it is available.

A full description of every SAE will need to be provided to [redacted] Pharmacovigilance.

[redacted]

7.1.7 Follow-up of adverse events

All AEs will be followed until they have abated, returned to baseline status or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.1.8 Adverse events of special interest

An AESI (serious or non-serious) is one of scientific and medical concern for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Adverse events of special interest for this study include QTc prolongation as well as liver tests that meet the criteria for potential drug-induced liver injury (DILI), in accordance with the US Food and Drug Administration “Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation”.

Adverse event of special interest: QTc prolongation

A thorough QT study (PM1116628) was conducted in healthy volunteers who received losmapimod at 7.5 mg BID or 20 mg daily or with placebo administered for 5 days. At the 20 mg dose of losmapimod, the upper bound of the 90% CI of the ΔΔQT interval (change from baseline in QTcF compared with that for placebo) exceeded the 10 msec threshold at the 24-hour post-dose time point. For the 7.5 mg BID dose, the upper bound of the 90% CI of ΔΔQTcF exceeded the 10 msec threshold at multiple time points. No subjects experienced QTcF values >480 msec or QTcF changes from baseline ≥60 msec at any time in the study. Although the upper bound of the 90% CI exceeded the 10 msec regulatory threshold of concern in the primary pharmacodynamic analysis, it was determined by GSK that there was no clinically relevant effect on the QT interval, as there was no clinically relevant concentration QTc effect using standard placebo/baseline subtracted measured QTc data. Additional information on the QTc interval and its behavior, as demonstrated in the large cohort of patients with ACS treated with losmapimod (PM1116197), supported the lack of a QT effect. PK/PD modeling using the raw QTcF and plasma concentration data showed that at plasma losmapimod concentrations 4 times the exposure at the therapeutic dose (7.5 mg BID) (ie, at exposures approximately 2-fold higher than 15 mg BID, the predicted upper bound of the 90% CI of ΔΔQTcF) did not exceed 10 msec, and the predicted median ΔΔQTcF was less than 5 msec. Further details are presented in the Investigator Brochure. No drug effect on QT prolongation of

losmapimod over placebo has been documented in any of the phase 2 or the one phase 3 trial completed so far.

Study drug should be discontinued for subjects who meet the QTc prolongation criteria as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.6). Further safety steps should be taken to closely observe and follow-up the event until resolution and treatment initiated per local standard of care.

Adverse event of special interest: Drug-induced liver injury

The following 3 laboratory value criteria must be met for potential DILI, or "Hy's Law":

- An elevated alanine transaminase or aspartate transaminase laboratory value that is ≥3 × ULN
- An elevated total bilirubin laboratory value that is ≥2 × ULN
- An alkaline phosphatase laboratory value that is <2 × ULN

Study drug should be discontinued for subjects who meet the laboratory criteria for potential DILI as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.6). Further safety steps should be taken to closely observe and follow-up the event until resolution. These steps include, but are not limited to:

- Making every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver tests
- Obtaining a more detailed history of symptoms and prior or concurrent disease, concomitant medication use, alcohol use, recreational drug use, and special diets
- Repeating liver enzyme and serum bilirubin tests twice weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic
- Obtaining viral hepatitis serology
- Considering liver imaging and/or hepatology consultation

7.2 Pregnancy

7.2.1 Teratogenicity

If a woman becomes pregnant when on study drug, study drug should be permanently discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known. In the event of pregnancy in the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

7.2.2 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during study drug administration or until follow-up, must be reported within 24 hours of the investigator's knowledge of the event to [redacted] using the Exposure in Utero form. The Investigator must make every effort to follow the pregnant partner of a male subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the SAE form.

8 STATISTICAL METHODOLOGY AND ANALYSES

8.1 Statistical analysis plan

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the interim analysis (IA). The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

All safety and statistical programming will be conducted using SAS 9.4 for Windows or newer (SAS Institute Inc., Cary, NC, USA), and other statistical programming/sample size calculation software as necessary.

8.1.1 Determination of sample size

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of up to 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an IA will be conducted after approximately 206 subjects (103 in the losmapimod arm, and 103 in the placebo arm) have completed the Day 28 visit, to assess early futility, using the rules specified in Section 8.9.

8.1.2 Analysis methods

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% CI.

8.1.3 Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

8.2 Protocol violations/deviations

Protocol deviations will be identified based on conditions related to the categories below:

- Protocol entry criteria
- Forbidden concomitant medications
- Missing evaluations for relevant endpoints

- Other protocol deviations occurring during study conduct.

Major protocol deviations will be identified before study closure and listed where appropriate.

8.3 Missing, unused and spurious data

All missing or incomplete safety and PD data, including dates and times, are treated as such. Missing test results or assessments will not be imputed, and as such, are assumed missing-completely-at-random (MCAR).

For laboratory data, values below the limit of quantitation (recorded as "< LLQ") will be set to half that limit.

Censoring rules for time-to-event endpoints will be discussed in the SAP. Imputation rules for the primary endpoint will be discussed in the SAP. The handling of any missing, unused, and spurious data will be documented in the SAP or the clinical study report.

8.4 Subject disposition

Subject disposition will be listed by subject.

The following subject data will be summarized:

- number and percentage of subjects screened,
- number and percentage of subjects enrolled,
- number and percentage of subjects completed,
- number and percentage of subjects included in safety population

A subject who completed the study is defined as a subject where the last PD assessment was completed.

8.5 Baseline parameters and concomitant medications

8.5.1 Demographics and baseline variables

Demographic and other baseline characteristics will be summarized using descriptive statistics for the treatment group and overall.

8.5.2 Medical history

Medical history will be listed.

8.5.3 Prior and concomitant medications

Prior and concomitant medications will be listed by international nonproprietary names, dose, regimen, route and for which indication it was prescribed.

8.5.4 Treatment compliance/exposure

Exposure to study treatment is described in terms of duration of treatment.

8.5.5 Safety and tolerability endpoints

The safety data set is used to perform all safety analyses.

Baseline is defined as the last value prior to dosing. Change from baseline will be calculated for all continuous safety parameters.

8.5.6 Adverse events

The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used for the coding of AEs. The overall incidence of AEs will be displayed by MedDRA system organ class, preferred term, and treatment group.

All AEs will be displayed in listings. In addition, SAEs and treatment-emergent AEs (TEAEs) leading to discontinuation of study drug will be listed.

Treatment-emergent AEs will be defined as an event that occurs on or after the first dose of study drug or the worsening of a preexisting condition on or after the first dose of study drug. If a subject does experience an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (ie, it is reported with a new start date) after starting administration of the specific treatment, and prior to the start of another treatment, if any. All TEAEs collected during the investigational period will be summarized.

The number of TEAEs and the number of subjects with at least 1 TEAE will be summarized by treatment group for the following:

1. System organ class and preferred term;
2. System organ class, preferred term, and maximum severity
3. System organ class, preferred term, and maximum drug relatedness.

8.5.7 Vital signs

Reported values and change from baseline values of supine blood pressure and pulse rate and temperature will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will be presented by treatment group. Vital sign variables will be listed. Values outside the reference range will be flagged in the listing.

Vital sign results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.5.8 ECG

ECG values will be listed.

8.5.9 Clinical laboratory tests

Reported values and change from baseline values of clinical laboratory variables will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will also be presented by treatment group. Clinical laboratory values will be listed.

Clinical laboratory test results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.6 Primary endpoints

1) Assuming p_t is probability of outcome in the losmapimod arm; p_c is the probability of outcome in the control arm

Study hypothesis: H_0: $= p_t - p_c = 0$

H_1: $= p_t - p_c < 0$

Assuming p_t=0.18, p_c=0.30, we can restate the hypothesis as

H_0: $\theta = \theta_0 = 0$

H_1: $\theta = \theta_1 = -0.12$

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from a regression model, adjusted for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP. An interim analysis to assess futility analysis—and potential sample size re-estimation—is discussed in Section 8.9. All results will be summarized descriptively by treatment arm and

expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p-values.

8.7 Secondary endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and post-baseline will be modelled using regression models appropriate for ordinal data, adjusting for stratification factors, sex, and baseline CRP. Details will be provided in the SAP.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Total number of study days: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, adjusting for stratification factors, sex, baseline CRP and number of days on study (as applicable). Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

8.9 Interim analysis for futility and sample size re-estimation

An interim analysis (IA) will be conducted after 206 subjects have been enrolled (approximately 103 in each of the losmapimod and placebo arms) and have been treated for 14 days with 28 days of follow-up. Only futility—and potential sample size-estimation—will be assessed by the DMC at the IA. The O'Brien-Fleming group sequential method will be used to adjust beta for interim testing. Table 6, Figure 1, Figure 2, and Figure 3 contain sample size requirements, boundary information, and stopping probabilities for testing futility on the primary endpoint at both the IA and final analysis. P-values are single-sided. Sample size estimation was done using SAS® (Proc SeqDesign, Version 4.0). The study will not be stopped for efficacy at the IA.

Table 6: Boundary Values for Interim Analysis Futility Assessment

Analysis Stage	Sample Size		Beta: Futility			Alpha: Efficacy		
	Losmapimod	Control	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under null hypothesis)	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under alternative hypothesis)
Interim Analysis	103	103	-0.67873 (0.24865)	-0.04017	0.75135	Not applicable	--	0.08871
Final Analysis	205	205	-1.91358 (0.02784)	-0.08009	0.97500	--	--	0.20000

Overall alpha=0.025 (1-sided); overall power=80%.
Abbreviations: MLE: maximum likelihood estimate.

Figure 1: Acceptance Region (Standardized-Z Scale)

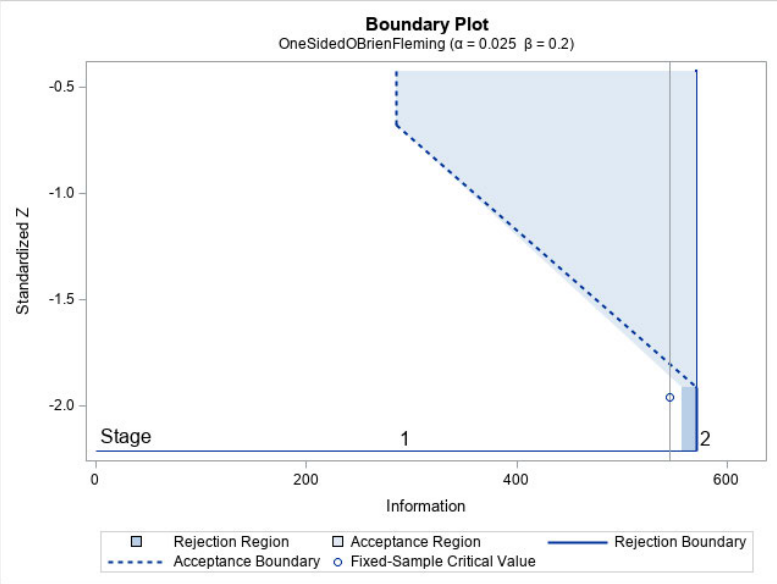


Figure 2: Acceptance Region (P-value)

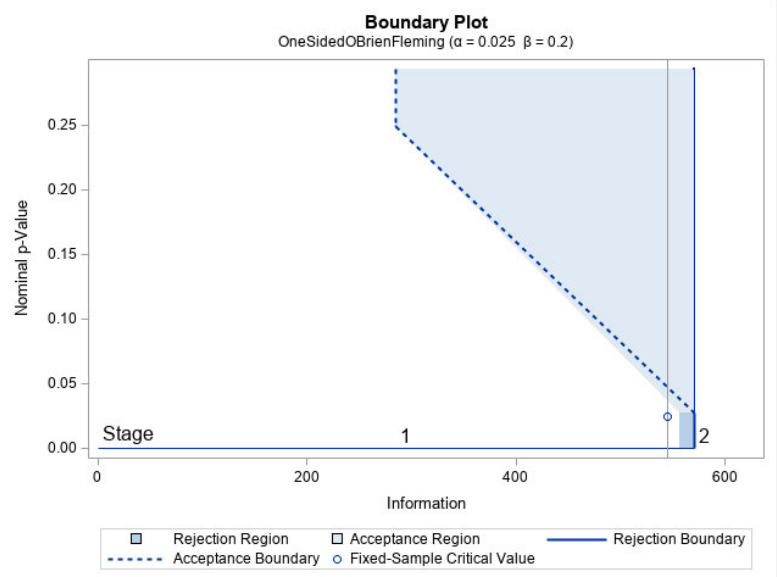
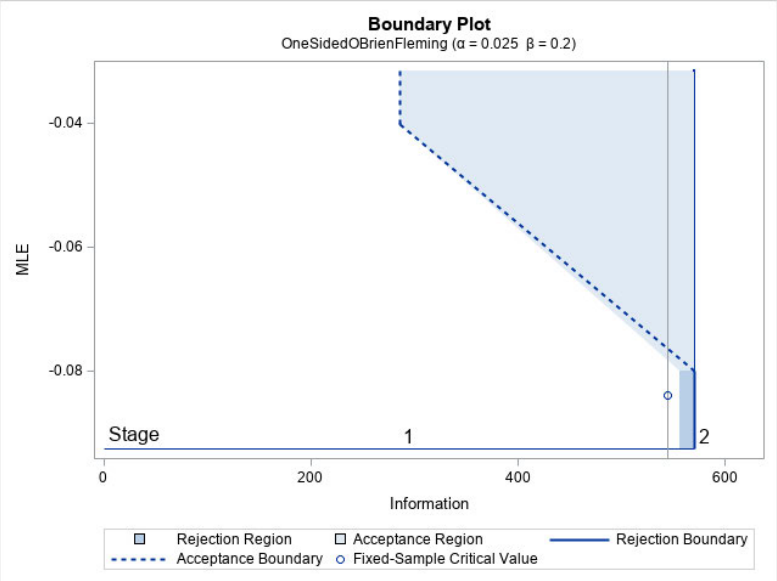


Figure 3: Acceptance Region (Maximum Likelihood Estimate)



8.9.1 Futility Testing

The process is as follows:

1. Futility at IA: If standardized z-value (MLE: maximum likelihood estimate) of $\mathbf{p_t - p_c}$ is ≥ -0.67873 (-0.04017), or p-value ≥0.24865, then stop for futility. Probability of stopping for futility under null hypothesis is ~0.75.
2. At Final Analysis: The final p-value is tested at an adjusted alpha of 0.02784.

8.9.2 Sample Size Re-estimation

The Chen-DeMets-Lan method (Chen et al 2004) will be used for unblinded sample size re-estimation, with IA futility stopping boundaries created using O'Brien-Fleming method, as described above. Wald conditional probabilities will be calculated using the actual observed proportion from both treatment arms.

The maximum sample size allowed is 820 subjects. Sample size will be increased only if the observed data at the IA are promising; that is, if the conditional power is ≥50% and <80%. Sample size will be increased to ensure a target conditional power of at least 80%.

There is only one IA, and conditional power at IA must lie between 50% and 80% for sample size re-estimation to be implemented. These 2 conditions ensure that the target Type I error of 2.5% is not exceeded by increasing sample size to meet the original target power (Chen et al 2004).

Sample size re-estimation will not be done in the following 2 instances:

- If conditional power is <50%, then sample size re-estimation will not be done, and decision on futility will be made based on boundary values from the O'Brien-Fleming method.

- If conditional power is ≥80%, then a sample size re-estimation will not be done, as the study will be considered sufficiently powered to detect the effect of interest at the final analysis.

A Wald Test statistic will be calculated and compared with the boundary value for futility (see Table 6). If the Wald Test statistic lies in the acceptance region then the study will stop for futility.

All calculations for the IA and the unblinded sample size re-estimation will be conducted by an external, unblinded statistician. The DMC will review the results in a closed session and make appropriate recommendations to the Sponsor afterwards.

8.9.3 Possible Recommendations by the DMC

After reviewing the results of the IA, the DMC may select 3 or more possible recommendations, based on the test statistics obtained at the IA:

- Stop for Futility - Stop trial early due to strong evidence for futility due to test statistic being in the futility region.
- Continue without change - Continue until next look with no changes due to test statistic not being in the futility region or the conditional power being <50% or ≥80%.
- Add required additional sample size, n, without exceeding the maximum sample size of 820 and continue the trial.

At the final analysis, 2 recommendations can be made:

- Efficacy is demonstrated.
- Efficacy is NOT demonstrated.

8.10 Data monitoring committee

An independent DMC composed of experts external to the sponsor and investigators will monitor the safety of the trial participants and the conduct of the trial on an ongoing basis and will be responsible for the interim analysis and recommendations regarding sample size re-estimation. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will include at least 2 external clinicians with expertise relevant to the evaluation of COVID-19, such as Critical Care, Pulmonology, or Infectious Disease, as well as at least 1 independent biostatistician with expertise in clinical trial design and statistical methods for clinical research and analysis of research data including interim analysis.

Details on the composition of the DMC and the schedule and format of DMC meetings and data outputs will be presented in the DMC charter. The DMC will review, at a minimum, data for the sentinel subjects prior to continued study drug dosing and cumulative safety data at regular intervals based on subject enrollment.

The safety evaluations will be detailed in the DMC charter and will include review of conventional safety variables, such as serious adverse events. Any safety event that requires unblinding will be immediately reported to the DMC and to the FDA. The DMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of subjects. The DMC will also review the efficacy data at the IA and make recommendations based on the futility criteria and for sample size re-estimation if needed (see Section 8.9). After reviewing study data, the DMC will make recommendations regarding continuation, termination, or modification of the study. The DMC may also perform ad hoc review PK of subjects who require dialysis.

8.11 Type I error for testing key study endpoints

The overall Type I error of the study will be controlled at 0.025 for 1-sided tests of hypotheses for the following key study endpoints, using an appropriate alpha control method:

1. Proportion of progressors to death or respiratory failure by Day 28
2. Change in clinical status using the 9-point WHO scale at Day 14
3. Change in clinical status using the 9-point WHO scale at Day 7
4. Oxygen-free days by Day 28

Further details on the methodology will be provided in the SAP.

9 GOOD CLINICAL PRACTICE, ETHICS AND ADMINISTRATIVE PROCEDURES

9.1 Good clinical practice

9.1.1 Ethics and good clinical practice

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice (GCP), the protocol, and all applicable regulations.

9.1.2 Ethics committee / institutional review board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date on which approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.1.3 Informed consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation. Following discussion of the study with site staff, subjects or their legally authorized representative will be required to provide one of the following:

1. Sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records; OR
2. If a subject is in isolation due to COVID-19 and institutional infection control policy would prevent removal of a document signed by the subject from their hospital room, then one of the following methods will be used to obtain informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable:
    - Obtain the informed consent electronically; OR
    - Obtain the informed consent by teleconference/video conference in alignment with local regulatory guidance.

    How the consent was obtained and reason why it was obtained using that particular method should be documented in the eCRF. The trial record at the investigational site should document how it was confirmed that the subject signed the consent form (ie, either using attestation by the witness and investigator or a photograph of the signed consent).

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

If consent is obtained from a legally authorized representative, then assent should be obtained from the subject using similar methods as described above.

9.2 Data handling and record keeping

This study will be conducted according to ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

Study site personnel will enter subject data into the EDC program. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with standard data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After final database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9.3 Access to source data and documents

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.4 Investigator's obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.6 Financial disclosure and obligations

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

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the subject's disease.

9.7 Investigator documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- FDA Form 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- A curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site.

9.8 Study conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.9 Adherence to protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.10 Adverse events and study report requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.11 Investigator's final report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.12 Records retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.13 Publications

After completion of the study, the data will be submitted for reporting at a scientific meeting and for publication in a peer-reviewed scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld. Further terms concerning publication will be set forth in the clinical trial agreement entered into by the sponsor, the principal investigator, any vendors, and the institution.

10 STUDY MANAGEMENT

The administrative structure will include a DMC (see Section 8.10).

10.1 Monitoring

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor regularly monitors the trial remotely and will periodically visit the investigator based on local restrictions, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation remotely, and discussion of the conduct of the study with the investigator and personnel. All relevant source documents will be uploaded into the [redacted] Site Source Portal system or access to the electronic medical records will be provided for remote monitoring purposes.

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

10.2 Inspection of records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.3 Management of protocol amendments and deviations

10.3.1 Modification of the protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

10.3.2 Protocol deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change of the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the subject being withdrawn from the study. A list of major protocol deviations will be compiled prior to the start of the study.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.4 Study termination

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

the study be required, the sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed written explanation. Fulcrum and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The sponsor has no plans to provide study drug to subjects after study closure or termination. The obligations to provide study results for subjects and reports to IRB/IEC shall continue as required by applicable laws and regulations.

At any time, the sponsor, the investigators, or the IRBs/IECs may terminate this study for reasonable cause. Conditions that may lead to reasonable cause and warrant termination include, but are not limited to the following:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the regulatory authority

Written notification that includes the reason for the clinical study termination is required.

The end of the study is defined as the date on which the last subject completes the last visit (includes the safety follow-up visit).

10.5 Final report

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study reports. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study reports, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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Protocol FIS 001-2020

LOSVID

Protocol Clarification Memo

Date: 18-September-2020

This Protocol Clarification memo is to further clarify some items of the protocol FIS 001-2020 LOSVID.

1. **Primary Endpoint:**

   Please note that the primary endpoint for FIS 001-2020 was defined in agreement with the United States FDA, with a focus on reducing a bad outcome. Fulcrum will ensure that the benefit to participants will be made clear in case of positive results.

2. **Vaccinations:**

   Vaccinations are not to be administered to participants during the study.

3. **Exclusion Criterion 8**

   Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

   <u>Clarification</u>: Special attention should be paid to patients with diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy according to local guidelines. Those patients should be excluded from the study.

4. **Visit and Assessment Schedule: Electrocardiogram**

   ECGs should be conducted for eligibility, after 7 days of treatment and at other times of the study, if clinically indicated.

[redacted] 2020-Sep-18

[redacted]
Clinical Operations Lead, Fulcrum Therapeutics

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

Short Title:	Losmapimod safety and efficacy in COVID-19 (LOSVID Study)
Version:	2.1
Date:	10-Jul-2020
Study number:	FIS-001-2020
Sponsor:	Fulcrum Therapeutics 26 Landsdowne St., 5th floor Cambridge, MA 02139 USA
Sponsor signatory:	[redacted] MD

Information described herein is confidential and may be disclosed only with the express written permission of the sponsor.

CONTACT DETAILS

SPONSOR	Fulcrum Therapeutics 26 Landsdowne Street, 5th floor Cambridge, Massachusetts 02139 USA
Clinical Trial Leader	[redacted] MD Telephone: [redacted] e-mail: [redacted]
Drug Safety Physician	[redacted] MD Telephone: [redacted] e-mail: [redacted]

SIGNATURE PAGE - INVESTIGATOR

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I have read the protocol and agree to conduct the study as described herein.

Investigator Name [redacted] Title MD	DocuSigned by: [redacted] 85FB9C773FFC428...	2020-Jul-11
	Signature	Date (dd Mmm yyyy)

SIGNATURE PAGE - SPONSOR

Fulcrum Therapeutics

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I approve this protocol on behalf of the sponsor.

[redacted]
Chief Scientific Officer

DocuSigned by:
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2020-Jul-10

Signature | Date (dd Mmm yyyy)

[redacted] MD
Senior Vice President
Head, Clinical Development

DocuSigned by:
[redacted]
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2020-Jul-10

Signature | Date (dd Mmm yyyy)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
BID	*bis in diem* / twice per day
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	Maximum concentration
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	disease caused by novel coronavirus
CRP	C-reactive protein
CXCL13	chemokine ligand 13
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
ET-1	endothelin
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSGS	focal segmental glomerulosclerosis
FSHD	facioscapulohumeral muscular dystrophy
GCP	Good Clinical Practice
[redacted]	[redacted]
GSK	GlaxoSmithKline
H5N1	highly pathogenic Asian avian influenza A, subtype H5N1
HIV	human immunodeficiency virus
HMGB-1	high mobility group box protein-1
hsCRP	high-sensitivity C-reactive protein
HSV-1	herpes simplex virus-1
IA	interim analysis

ICAM-1	intercellular adhesion molecule-1
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	independent ethics committee
IL-6	interleukin-6
IND	investigational new drug application
IRB	institutional review board
IxRS	interactive/web voice response system
JAK	Janus kinase
[redacted]	[redacted]
LLQ	lower limit of quantitation
LS	least square
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusions
MCAR	missing-completely-at-random
MedDRA	Medical Dictionary for Regulatory Activities
OAT	organic anion transporter
PAO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PH	proportional hazards
PK	pharmacokinetics
PO	*per os* / orally
PPS	per protocol set
QTcB	QT corrected interval using Bazett's formula
QTcF	QT corrected interval using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SE	standard error
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID Study)

Short Title

Losmapimod safety and efficacy in COVID-19 (LOSVID Study)

Background & Rationale

Poor prognosis for many COVID-19 patients has been attributed to an exaggerated inflammatory response following SARS-CoV-2 infection. This hyperactivated immune response is associated with pulmonary edema, acute respiratory distress syndrome (ARDS), and cardiomyopathy that may lead to increased mortality in the sickest patients.

p38 mitogen-activated protein kinase (MAPK) is an important mediator of inflammation, and extensive nonclinical data have linked p38 to the hyper-inflammatory response to viral infections.

Losmapimod is a potent and selective p38α/β MAPK inhibitor that is currently in Phase 2 clinical trials for the treatment of facioscapulohumeral dystrophy and has previously been administered to more than 3600 adult healthy volunteers and subjects including participants in a Phase 3 trial. Many of these trials were for chronic inflammatory indications for which the compound exhibited a favorable safety profile not significantly different from placebo. These trials have also indicated that losmapimod has good exposure after oral dosing, robust target engagement, and acutely reduces inflammatory biomarkers that have been associated with poor prognosis in COVID-19, including C-reactive protein (CRP) and interleukin-6 (IL-6). Additionally, a clinical study recently concluded that losmapimod restored the normal immune response of older subjects (median 69 years, range: 65, 77 years) following a viral challenge. Further information is available in the losmapimod Investigator Brochure.

Losmapimod is attractive as a potential therapeutic option for COVID-19:

- p38 inhibition improves survival in mouse SARS-CoV-1 models and other nonclinical viral models, suppressing the exaggerated immune response to acute infection.
- Losmapimod acutely has reduced exaggerated inflammatory responses in human trials for multiple inflammatory diseases, including IL-6 and CRP, and has normalized immune response to viral or other acute inflammatory challenges in older subjects.
- Losmapimod is a clinical-stage, potent, and selective p38 inhibitor with extensive human experience and extensive evidence of safety and tolerability, including in a Phase 3 clinical trial in acute myocardial infarction.
- p38 inhibition has the potential to reduce hypothesized deleterious effects of increased angiotensin II in COVID-19, such as vasoconstriction, increased inflammation, cardiac arrhythmias, and organ failure.

Objectives and Endpoints:

All study objectives will be evaluated in subjects diagnosed with COVID-19:

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale: • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation by Day 28 Total number of study days in ICU by Day 28 Total number of study days hospitalized by Day 28 Total number of respiratory failure-free study days by Day 28 Percentage of subjects discharged from the hospital by Day 28
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive by Day 28

Objectives	Endpoints
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted] ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

Design

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥50 years old who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.

Subjects who sign informed consent and meet all entry criteria (listed below) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg orally (PO) twice daily (BID); OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter.

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site.

Investigational drug

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Comparative drug

Matching placebo tablets will be provided for oral administration.

Inclusion criteria

1. Able and willing to provide written informed consent.
    a. Note: Subject’s legally authorized representative may provide informed consent as applicable based on local guidelines and regulations. If consent is obtained from a legally authorized representative, then assent should be obtained from the subject.
2. Willing and able to comply with all study procedures.
3. Age ≥50 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. ≥90% oxygen saturation on room air and/or ≥94% oxygen saturation on oxygen administration at 2 L/min by nasal canula at the baseline visit.
8. Radiographic (X-ray or computed tomography scan, per local standard of care) evidence of pulmonary involvement consistent with COVID-19 at screening or baseline, per the judgment of the investigator.
    a. Note: If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of

pulmonary involvement obtained by clinical examination should be documented in the eCRF.

9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator
10. CRP at screening >15 mg/L (ie, >1.5 mg/dL) on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows (as applicable to local [country] guidelines and regulations for sites outside the United States):
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock) or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or HIV infection.
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

9. Has been treated with immunomodulators or immunosuppressants including, but not limited to, interleukin (IL)-6 inhibitors, tumor necrosis factor (TNF) inhibitors, anti-IL-1 agents, and Janus kinase inhibitors, within 5 half-lives or 30 days, whichever is longer, prior to randomization, or plan to receive these agents any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.
11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

Sample size justification

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an interim analysis (IA) will be conducted after approximately 206 subjects (103 in each of the losmapimod and placebo arms) have completed the Day 28 visit, to assess futility.

Statistical methodology

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the IA. The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% confidence intervals.

Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

Primary endpoint

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from a regression model, adjusted for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP. An interim analysis to assess futility analysis—and potential sample size re estimation—will be conducted. All results will be summarized descriptively by treatment arm and expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p values.

Secondary endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and post-baseline will be modelled using regression models appropriate for ordinal data, adjusting for stratification factors, sex, and baseline CRP. Details will be provided in the SAP.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Total number of study days by Day 28: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, adjusting for stratification factors, sex, baseline CRP and number of days on study (as applicable). Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital by Day 28: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Table 1: Visit and Assessment Schedule

Assessment[1] / Time point	SCR	Treatment Period											FU[14]		ET
	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Informed consent	X														
Demography	X														
Inclusion and exclusion criteria	X	X													
Medical history	X														
COVID-19 history and clinical diagnosis[2]	X														
Chest X-ray/CT scan	X[3]	X[3]													
Study drug administration:															
Randomization		X													
Losmapimod or placebo PO BID		X	X	X	X	X	X	X	X	X	X	X			
Pharmacodynamics:															
Drug levels/PK[4]		P, 4-5h	4-5h	4-5h	4-5h	4-5h	4-5h	4-5h				4-5h			X
[redacted]															
Clinical status and symptoms:															
Respiratory failure and survival assessment[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical status assessment per WHO 9-point scale[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral presence and viral load by central testing[7]		X	X (sentinel only)[7]	X (sentinel only)[7]	X (sentinel only)[7]			X							X
Confirmation of COVID-19 diagnosis by PCR	X[2]	X (PR)[2]													

Time point / Assessment[1]	SCR	Treatment Period											FU[14]		ET
	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Oxygenation and FiO_2[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments:															
Physical examination	X														X
Weight/height[9]	X												X		X
Hematology, chemistry safety labs[6]	X	X	X		X			X		X		X	X		X
CRP[6]	X														
Urinalysis[10]	X							X							
Urine or serum β-hCG (female subjects only)	X[11]												X		X
ECG[12]	X							X							
HR, BP, RR, temperature[8]	X	X	X	X	X	X	X	X	X	X	X	X			X
(S)AEs[13]	X														X
Concomitant medications (including SOC)	X														X

AE = adverse event; BP = blood pressure; COVID-19 = novel coronavirus; HR = heart rate; P = pre dose; PAO_2 = partial pressure of oxygen; PR – pre-randomization; RR = respiratory rate; sent = sentinel; SOC = standard of care; SCR = screening.

Note: All screening assessments are to be performed before dosing. If procedures required at any time point have already been performed as part of routine clinical care, these assessments do not need to be repeated, and information will be collected and entered on the eCRF from the subject's medical records. Unscheduled visits can take place at any time at the discretion of the site to check for new AEs/SAEs or to repeat key missed assessments or for other reasons.

[1] The order of assessments can be performed at the discretion of the investigator once informed consent is obtained.

[2] COVID-19 diagnosis to be confirmed by local testing (PCR) before randomization and first dosing. Saliva, swab, or sputum testing may be used based on local standard of care.

[3] To be performed while hospitalized based on standard-of-care local assessment. Result required for eligibility assessment to confirm radiographic evidence of COVID-19. If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

[4] PK assessments will be performed as a substudy in all sentinel subjects. For those subjects requiring dialysis, a single pre- and post-dialysis PK should be obtained for review by the DMC to decide if dose adjustment is needed. PK should be measured weekly for 2 weeks at C_{max} (4-5 hours post dose) for subjects with renal insufficiency when possible.
[redacted].

[6] Assessments for clinical/respiratory status, progression, and safety serum chemistry and hematology tests to be performed and samples to be collected while hospitalized based on standard-of-care local laboratory assessments and after discharge from the hospital by home visit or outpatient clinic visit or telemedicine call. For subjects who are discharged to home or other outpatient setting after initial hospitalization, the assessments and laboratory samples can be obtained less often but not less than at least once weekly. CRP result required to determine eligibility are based on local laboratory results at screening.

[7] Viral load testing will be collected daily for the first 4 days using central testing in the first 10 enrolled subjects as part of the sentinel safety assessment at select sites. For all subjects, including the sentinel subjects, swabs, saliva, or other sample collection (as specified in the Study Manual) for central viral load testing will be collected on D1 pretreatment and on D7 or earlier if being discharged from the hospital prior to D7.

[8] Vital signs will be performed after subjects have been supine for at least 5 minutes when possible. Vital signs to include oxygen saturation; PaO_2 should be recorded if available from blood gases obtained as part of SOC; oxygen administration should also be recorded (eg, room air or oxygen flow by nasal canula or facial mask or endotracheal tube). For subjects

who are discharged to home or other outpatient setting after initial hospitalization, assessments may be obtained less often but at least once per week in the outpatient clinic or at home.

[9] Height assessed at screening only; can be by self-report or from medical records. Weight is an actual recording.

[10] Urinalysis will be performed during the study period only on Day 7 and on any other day only if clinically indicated.

[11] Pregnancy testing to be conducted within 72 hours of the first dose of study treatment.

[12] Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes if possible. ECGs will be performed at Day 7 in all subjects and at any other time during the study if clinically indicated.

[13] Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.

[14] Outpatient assessments to be conducted via telemedicine or outpatient clinic. Outpatient laboratory assessments to be completed at outside local laboratory or home or outpatient visit.

1 BACKGROUND AND RATIONALE

1.1 Scientific rationale for investigation of losmapimod in COVID-19

COVID-19 is a severe pandemic disease with high mortality particularly in older individuals, due to infection with the SARS-CoV-2 coronavirus. The therapeutic hypothesis for the use of losmapimod in COVID-19 disease is that increased mortality and severe disease is caused by p38 mitogen-activated protein kinase (MAPK)-mediated exaggerated acute inflammatory response resulting from SARS-CoV-2 infection. The older population is especially at risk of severe disease and death upon infection with SARS-CoV-2. The hyperactivated immune response in COVID-19 shares features of the cytokine storm syndrome and appears to be responsible for the severe pulmonary edema, ARDS, and cardiac and renal disease responsible for most of the severe morbidity and mortality.

The proposal to develop losmapimod, a potent, specific, and bioavailable p38α/β inhibitor, for treatment of COVID-19 is based on the following rationale:

(1) Nonclinical work has shown that older mice infected with SARS-CoV-1 develop much more severe disease than younger ones, and that treatment with a p38 MAPK small molecule inhibitor greatly reduced their mortality when given after viral inoculation; similar survival benefit of p38 MAPK inhibition has been seen in animal models of severe H5N1 influenza and HSV-1.

(2) Nonclinical work has shown that p38 MAPK inhibition reduces viral load in several experimental models with coronaviruses, including mouse hepatitis virus, human CoV-229E, transmissible gastroenteritis virus, and Middle East respiratory syndrome virus.

(3) p38 MAPK is proposed to play a critical role in the development of ARDS, including regulating the expression and activity of inflammatory mediators such as ICAM-1, HMGB1, and ET-1, neutrophil chemotaxis and apoptosis, the balance of Treg/Th17 cells, and pulmonary endothelial cell apoptosis.

(4) Clinical investigation showing that excessive acute inflammation in response to external stressors in older individuals, including viral antigen challenges, hinders the specific immune response to infection; many of the excessive inflammatory mediators associated with this aberrant immune response in older individuals are associated with activation of the p38 MAPK pathway.

(5) Treatment with losmapimod in older subjects restored the normal immune response to viral antigen challenge and improved the resolution of acute inflammation.

(6) Treatment of various inflammatory diseases with losmapimod, including active rheumatoid arthritis (RA), acute myocardial infarction, and chronic obstructive pulmonary disease (COPD) resulted in significant reduction in markers of acute inflammation, including interleukin-6 (IL-6), C-reactive protein (CRP), chemokines such as CXCL13, and other markers (see Table 5 for further details).

(7) Losmapimod may be beneficial in COVID-19 treatment via reduction of the damaging effects of angiotensin II (Ang II). Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS-CoV viruses and is expressed in the lung and the heart. Upon infection with SARS-CoV-2, there is internalization of and depletion of ACE2. ACE2 converts Ang II into angiotensin 1-7 (Ang 1-7), which counterbalances the vasoconstrictive and pro-inflammatory effects of Ang II. Ang II is significantly elevated in COVID-19, and the levels are positively correlated with viral load and acute lung injury (Liu Y et al, 2020). Blocking the p38 MAPK pathway in nonclinical models has been

shown to reduce many of the adverse effects of elevated Ang II, resulting in lower frequency of cardiac arrhythmias, renal failure, and hypertension.

p38 inhibitors have been explored extensively in clinical trials for numerous chronic inflammatory indications, as summarized in the Investigator Brochure. Losmapimod has been extensively tested in humans and found to be generally well tolerated, including in over 3600 adult healthy volunteers and subjects in 11 different indications. The 15 mg oral (PO) twice per day (BID) dose proposed for the COVID-19 Phase 3 study has been shown to provide robust and sustained inhibition of the p38 MAPK pathway systemically and in tissues, specifically in skeletal muscle needle biopsies of subjects with facioscapulohumeral muscular dystrophy (FSHD). This dose of losmapimod was shown experimentally in older (median 69 years, range: 65, 77 years) human volunteers to restore the normal immune response to viral challenge and improve the resolution of acute inflammation. Furthermore, losmapimod has been shown to significantly reduce markers of hyperactive acute innate immune inflammation in the context of acute myocardial infection, RA, and COPD in clinical trials as listed below:

1- Single-dose study in 50 subjects with RA (RA 3103730). Treatment with losmapimod (N=38) reduced levels of IL-6 compared with placebo (N=12). Losmapimod was dosed as follows: 7.5 mg: 13 subjects; 20 mg: 12 subjects; 60 mg: 13 subjects. Analysis of serum IL-6 at 3 hours post dose showed significantly lower levels with losmapimod than with placebo (Table 2).

Table 2: Change from Baseline in IL-6 Serum Levels with Increasing Single Doses of Losmapimod in Subjects with Rheumatoid Arthritis

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to placebo	95% CI
Placebo	0.92	0.60, 1.41		
Losmapimod 7.5 mg	0.41	0.26, 0.63	0.45	0.24, 0.82
Losmapimod 20 mg	0.43	0.27, 0.68	0.47	0.25, 0.88
Losmapimod 60 mg	0.38	0.25, 0.57	0.41	0.23, 0.75

Abbreviations: CI = confidence interval.

2- Repeated-dose study in subjects with acute coronary syndrome (ACS; PM1111810). A total of 535 subjects with non-ST elevation myocardial infarction were randomized to an initial dose of 7.5 or 15 mg of losmapimod followed by 7.5 mg PO BID (N= 388) or matching placebo (N=138) for 12 weeks. Results showed that relative to placebo, losmapimod significantly suppressed CRP and IL-6 acutely at the 24- to 36-hour assessments (Table 3).

Table 3: Change from Baseline in hsCRP and IL-6 with 7.5mg PO BID Losmapimod Over Placebo in Subjects with Acute Coronary Syndrome

Parameter	Placebo (N=138)	All losmapimod (N=388)	P value
hsCRP at 72 hours or discharge (nmol/L)	110.8 (83.1-147.7)	64.1 (53.0-77.6)	<0.05
IL-6 at 24 hours (ng/L)	10.6 (8.6-13.1)	6.6 (5.8-7.4)	<0.05

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6.

3- Repeated-dose study in subjects with COPD (MKI113006). In this study, subjects with COPD were dosed with losmapimod 2.5 mg BID (N=149), losmapimod 7.5 mg BID (N=151), or placebo BID (N=154) for 24 weeks; or losmapimod 7.5 mg BID for 4 weeks followed by losmapimod 15 mg BID (N=150) for 20 weeks. Over the first 12 weeks of treatment, statistically significant reductions in serum high-sensitivity CRP (hsCRP) levels were observed in the losmapimod 7.5 mg and 15 mg groups compared with placebo. For hsCRP, Week 12, 7.5 mg dose versus placebo: ratio 0.73; 95% confidence interval [CI] 0.57, 0.93;

p=0.011; 15 mg dose versus placebo: ratio 0.64; 95% CI 0.50, 0.82; p<0.001. Table 4 shows the results for the subgroup with higher CRP at baseline.

Table 4: Change from Baseline in CRP Over 12 Weeks of Treatment with Different Doses of Losmapimod Compared with Placebo in Subjects with COPD and High Baseline CRP Levels (>6.4 mg/L)

Week 12 Baseline hsCRP >6.40 mg/L	Placebo BID (N=42)	Losmapimod 2.5 mg BID (N=33)	Losmapimod 7.5 mg BID (N=31)	Losmapimod 15 mg BID (N=31)
Geometric LS mean (SE of logs)	6.75 (0.153)	8.08 (0.180)	5.16 (0.180)	3.54 (0.186)
Geometric LS mean ratio to baseline (SE of logs)	0.49 (0.153)	0.59 (0.180)	0.38 (0.180)	0.26 (0.186)
Column vs placebo				
Ratio		1.20	0.77	0.53
95% CI		0.75, 1.92	0.48, 1.22	0.33, 0.85

Abbreviations: CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; LS = least square; SE = standard error.

Fulcrum Therapeutics is planning to conduct the initial clinical trial for the investigation of losmapimod for the treatment of COVID-19 in these high-risk subjects. Losmapimod is currently in Phase 2 clinical development for the treatment of the root cause of FSHD under an open IND in the United States (US) and open clinical trial applications in Canada, Spain, France, and The Netherlands.

A summary of published literature supporting the therapeutic hypothesis for the clinical development of losmapimod for the treatment of COVID-19 is provided in Table 5.

Table 5: Listing of Evidence Supporting the Development of the p38 Inhibitor Losmapimod for Treatment of COVID-19

Evidence	References
Pneumonitis, acute respiratory distress syndrome, pulmonary edema, and cardiomyopathy drive COVID-19 mortality	• Siddiqi HK et al. J Heart Lung Transplant. 2020 • Ruan Q et al. Intensive Care Med. 2020 Mar 3
Older patients are at greatest risk of COVID-19 mortality	• Ruan Q et al. Intensive Care Med. 2020 Mar 3
Human SARS-CoV-2 pathology is recapitulated in SARS-CoV-1 mice	• Zhou F et al. Lancet. 2020 • Nagata N et al. Am J Pathol. 2008
Exaggerated acute inflammatory response and lymphopenia correlate with mortality in human with COVID-19 and older mice infected with SARS-CoV-1	• Nagata N et al. Am J Pathol. 2008 • Zhou F et al. Lancet. 2020
SARS-CoV-1 activates the p38 MAPK pathway in peripheral blood early in the infection	• Lee CH et al. J Immunol. 2004.
SARS-CoV envelope protein (E) activates the host's inflammatory response via p38 signaling	• Jimenez-Guardeño JM et al. PLOS Pathog. 2014

Evidence	References
Several nonclinical studies have shown evidence of p38 inhibition reducing viral replication including with coronavirus	• Kono M et al. Antiviral Res. 2008 • Dong Y et al. Antiviral Res. 2020 • Kindrachuk D et al. Anti Microb Agents & Chem. 2015
p38 inhibition reduces mortality in older mice infected with SARS-CoV-1	• Jimenez-Guardeño J et al. PLOS Pathog. 2014
Nonclinical efficacy of p38 inhibition also observed in other models of severe acute viral pneumonitis and other severe acute viral infections	• Shapiro L et al. PNAS. 1998 • Iordanov MS et al. Mol Cell Bio. 2000 • Salomon R et al. PNAS. 2007 • Griego SD et al. J Immunol. 2000 • Banerjee S et al. J Virology. 2002 • Börgeling Y et al. J Biol Chem. 2014 • Chen Y et al. J Exp Med. 2017 • He F et al. J Transl Med. 2019
p38 inhibition reduces lung mucous production in mice models of toxic airway injury	• Liu et al. Int Immunopharmacol. 2009
Losmapimod and other p38 inhibitors acutely reduce inflammatory markers in humans	• GSK data in Fulcrum Original IND 138739, Module 4 • Genovese M et al. J Rheumatol. 2011 • Christie J et al. Crit Care Med. 2015
Losmapimod reduces inflammatory markers associated with COVID-19 severity at currently utilized doses	• Fulcrum clinical data on file • GSK clinical data • Newby L et al. Lancet. 2014
Inhibition of p38 with 15 mg losmapimod BID dose in older subjects restored the adaptive immune response to viral challenge	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
Exaggerated acute inflammatory response in older subjects is driven to a large extent by p38 activation	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
In vivo data in Ferrets indicate SARS-Cov-2 induces profoundly lower immune response vs other virus	• Blanco-Melo D et al. bioRxiv. 2020
Evidence that p38 inhibition may treat the deleterious effects of elevated Ang II in COVID-19	• Grimes JM et al. J Mol Cell Cardiol. 2020
Losmapimod is a highly selective p38 inhibitor at advanced stage of clinical development with excellent safety data profile	• Losmapimod Investigator Brochure Fulcrum 2020 • Cadavid D et al. FSHD IRC Poster. 2019

Abbreviations: BID = twice daily; COVID-19 = disease caused by novel coronavirus; IND = investigational new drug application; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1.2 Benefit-risk considerations

This is the first-in-human clinical trial with losmapimod for the treatment of a novel virus (COVID-19) and, therefore, the risk-benefit considerations are based on nonclinical data in conditions related to COVID-19 (e.g., SARS-CoV-1) as well as extensive clinical data in other inflammatory conditions and conditions involving the p38 MAPK pathway (e.g., FSHD, RA, COPD) including in older healthy volunteers; refer to Section 1.1 for further details.

Losmapimod has been found to be generally well tolerated in clinical trials, including in over 3600 adult healthy volunteers and subjects in 11 different indications. The 15 mg PO BID dose proposed for this study has been shown to provide robust and sustained inhibition of the p38 MAPK pathway systemically and in tissues, specifically in skeletal muscle needle biopsies of subjects with FSHD.

Complete clinical safety data and nonclinical data for losmapimod can be found in the Investigator's Brochure. Additional adverse events not previously observed in animals or in humans may also occur in this trial. Subjects in this clinical trial will be monitored closely for the development of adverse effects that may result from study drug administration. In addition, a Data Monitoring Committee (DMC) will monitor the safety of subjects throughout the study on an ongoing basis.

COVID-19 is a severe and rapidly progressive infection, especially in the high-risk population (ie, older, with comorbidities) selected for this trial. Given the extensive clinical experience with losmapimod, the potential benefit of losmapimod treatment in this indication outweighs the risks.

2 STUDY OBJECTIVES AND ENDPOINTS

All study objectives will be evaluated in subjects diagnosed with COVID-19.

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale (WHO 2020): • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation by Day 28 Total number of study days in ICU by Day 28 Total number of study days hospitalized by Day 28 Total number of respiratory failure-free study days by Day 28

Objectives	Endpoints
	Percentage of subjects discharged from the hospital by Day 28
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive by Day 28
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	[redacted]

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

3 STUDY IMPLEMENTATION

3.1 Overall study design and plan

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥50 years old, who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.

Subjects who sign informed consent (refer to Section 9.1.3) and meet all entry criteria (see Section 4) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg PO BID; OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent DMC. The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter (see Section 8.10).

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site (refer to Section 6.7).

3.2 Start of study and end of study definitions

The start of the study is defined as the date the first enrolled subject signs an informed consent form (ICF). The end of the study is defined as the date of the last subject’s last assessment (scheduled or unscheduled).

3.3 Selection of doses in the study

In the Phase 1 study in healthy volunteers and FSHD subjects (Study FIS-001-2018), the dose levels of 7.5 mg and 15 mg given by mouth BID with food were based on predictive nonclinical efficacy and published clinical target engagement and safety data for losmapimod previously generated by GSK. This Phase 1 study was recently completed and demonstrated that the 15 mg PO BID dose gives higher plasma levels and greater and more sustained target engagement in blood and tissues than the 7.5 mg PO BID dose, while resulting in similar safety and tolerability. The 15 mg BID dose is used in the ongoing Phase 2 studies in FSHD (Study FIS-001-2019 and Study FIS-002-2019). Prior results indicated the favorable safety and tolerability of losmapimod for chronic administration in the clinic, including in the context of severe acute diseases, such as acute myocardial infarction, in older people.

Prior studies of biodistribution of radiolabeled losmapimod by GSK showed ample distribution to all tissues including the lungs and the heart. Our recent target engagement data in the FSHD Phase 1 Study FIS-001-2018 indicates that pHSP27 inhibition in blood, an assessment of p38 target engagement, is nearing a plateau at a losmapimod dose of 15 mg BID (see Investigator Brochure [Fulcrum Therapeutics 2020]), so doses of losmapimod higher than 15 mg PO BID are not warranted.

Additionally, at the proposed dose level of 15 mg PO BID, exposures are not expected to exceed those previously demonstrated to be safe in humans in multiple previous studies by GSK in healthy volunteers and various patient populations including older subjects (Cheriyan et al 2011; Barbour et al 2013; Watz et al 2014; Pascoe et al 2017).

In previous clinical studies performed by GSK, it was shown that losmapimod significantly reduced markers of acute inflammation, including IL-6, CRP, and the CXCL13 chemokine after a single dose. Additionally, losmapimod reduced IL-6 after 15 days of treatment (GSK study RA3103718) and CRP acutely in subjects with acute myocardial infarction treated with 7.5 mg PO BID (O'Donoghue et al 2016). In subjects with COPD, losmapimod at 15 mg PO BID significantly reduced CRP over 12 weeks compared with placebo (GSK Study MKI 113006). In one study in healthy older adult volunteers, it was shown that a 15 mg PO BID dose of losmapimod for 4 days restored the normal immune response to varicella-zoster virus antigen challenge (Vukmanovic-Stejic et al 2018). The same formulation used in these previous clinical studies is the one proposed for use in the present clinical study.

The rationale for the proposed study duration of up to 28 days is that in most cases of COVID-19 the disease has resolved or resulted in severe outcomes over the first month from onset of symptoms. COVID-19 is a severe and rapidly progressive infection, especially in the high-risk population selected for the proposed Phase 3 trial. Therefore, treatment for longer than 14 days and study duration for longer than 28 days is not justified.

3.4 Study drug modifications and withdrawal

3.4.1 Dose modifications

Before trial medication is administered, changes in the subject's health status, including laboratory results if applicable, since the previous visit or previous dose should be checked.

Study drug interruptions and reductions are not permitted; subjects who are on dialysis may require a dose adjustment.

Study treatment dose adjustment for subjects on dialysis

The elimination of losmapimod is almost exclusively by metabolism, with only 2% of the administered dose recovered as unchanged drug in urine and feces. The metabolite is clinically inactive and does not exert any toxic effects.

Losmapimod has not been studied in renal insufficiency or renal failure. There has been 1 study of losmapimod in 17 subjects with focal segmental glomerulosclerosis (FSGS; FSG117283). In this study, subjects were given losmapimod 7.5 mg BID for 2 weeks followed by losmapimod 15 mg BID for 22 weeks. The mean duration of exposure to investigational product in subjects with FSGS was approximately 21 weeks (range: 3.7, 25 weeks).

Creatine and GFR for the population enrolled is in the table below.

Parameter	Mean (SD)	Range
eGFR (mL/min/1.73m^2)	79.4 (34.9)	36, 155
Creatine (µmol/L)	1.1 (0.5)	0.48, 2.07

eGFR = estimated glomerular filtration rate.

Losmapimod plasma concentration data in subjects with FSGS were compared with historical data obtained in the Phase 3 clinical trial in subjects with ACS. In general, exposure in subjects with FSGS was similar to subjects with ACS over the 24-week treatment period.

Consistent with the safety database of over 3500 subjects, the 2 most frequently reported AEs in the FSGS trial were headache (5/17; 29%) and fatigue (4/17; 24%). Seven AEs (by preferred term: vomiting, dizziness, oropharyngeal pain, nausea, blood creatinine increased, muscle spasms, and rash) were reported in 3 subjects (18%) each. All other AEs (by preferred term) were reported in ≤2 subjects each. Four subjects had at least 1 AE that led to withdrawal from the study or from treatment. The AEs that led to discontinuation were increase in blood urea nitrogen (related), increase in creatinine (not related), increase in cystatin C (related), and joint stiffness (related). None of the AEs was serious or severe; 3 of the AEs in 2 subjects were reported as related to study treatment.

Based on the current safety and exposure information, dosing adjustment is likely not needed for subjects with renal insufficiency. However, close monitoring of pharmacokinetics (PK) for such cases will be implemented to ensure that therapeutic concentrations are maintained (refer to Section 6.2). For those subjects requiring dialysis, dose adjustment may be needed and will be determined by pre- and post-dialysis PK by the DMC. Adjustments may be recommended by the DMC also for subjects on placebo who develop acute renal failure to prevent unblinding at the sites.

Study treatment discontinuation

Discontinuation of study treatment should be considered if:

- ALT or AST >8 x the upper limit of normal (ULN)
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (total bilirubin >2 x ULN or international normalized ratio >1.5) in the absence of reasonable alternative etiology
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- QTcF prolongation with QTcF >500 msec or an increase in QTcF of >60 msec over baseline (confirmed by 2 successive repeat measurements)

In addition, the investigator must permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the subject. The premature discontinuation of study drug might be triggered by an adverse event (AE), a diagnostic or therapeutic procedure, an abnormal assessment (eg, ECG or laboratory abnormalities), pregnancy,

or for administrative reasons, in particular noncompliance with the protocol or withdrawal of the subject's consent. The reason for study drug interruption or premature discontinuation must be clearly documented in the eCRF.

3.4.2 Subject withdrawal

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. In all cases of impending consent withdrawal, investigators will be given instructions to meet and discuss with the participant their options of continuing in the study. The investigator should ensure understanding and documentation of the reasons for the participant's desire to withdraw consent. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment. Unless the participant provides their written withdrawal of consent or there is other written documentation by the investigator confirming the participant's verbal intent to completely withdraw from the trial, participants should be followed for all protocol-specified evaluations and assessments. The reasons for subjects not completing the study will be recorded.

A subject may be withdrawn from the study if he or she is lost to follow-up. For subjects to be considered as lost to follow-up, 2 attempts should be made to contact the subject to return for the scheduled study visit. After 2 attempts, a certified letter should be sent to the subject's address requesting the subject to contact the investigator to schedule a follow-up assessment. If no reply is provided by the subject within 30 days of receipt of the certified letter, the subject can then be considered lost to follow-up.

3.4.3 Replacement policy

Subjects who withdraw from the study will not be replaced.

3.4.4 Stopping criteria

Dosing will be stopped in case of an unacceptable tolerability profile based on the nature, frequency, and intensity of observed AEs judged jointly by the investigator and the sponsor or as recommended by the DMC.

In the event of a study hold due to unacceptable tolerability, the sponsor will conduct an extensive safety and PK analysis and will communicate to stakeholders, including the Investigators, institutional review boards (IRBs)/independent ethics committees (IEC), and health authorities any potentially emergent safety information as well as the timing of planned resumption of dosing. Dosing and enrollment will not resume unless it is considered safe to do so after consultation with Investigators and health authorities and approval by IRBs/IECs.

4 STUDY POPULATION

4.1 Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening.

1. Able and willing to provide written informed consent.
    a. Note: Subject's legally authorized representative may provide informed consent as applicable based on local guidelines and regulations (see Section 9.1.3). If consent is obtained from a legally authorized representative, then assent should be obtained from the subject.
2. Willing and able to comply with all study procedures.
3. Age ≥50 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for the SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. ≥90% oxygen saturation on room air and/or ≥94% oxygen saturation on oxygen administration at 2 L/min by nasal canula at the baseline visit.
8. Radiographic (X-ray or computed tomography scan, per local standard of care) evidence of pulmonary involvement consistent with COVID-19 at screening or baseline, per the judgment of the investigator.
    a. Note: If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator (CDC 2020).
10. CRP at screening >15 mg/L (ie, >1.5 mg/dL) on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows (as applicable to local [country] guidelines and regulations for sites outside the US):
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

4.2 Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock) or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or HIV infection.
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Has been treated with immunomodulators or immunosuppressants including, but not limited to, interleukin (IL)-6 inhibitors, tumor necrosis factor (TNF) inhibitors, anti-IL-1 agents, and Janus kinase inhibitors, within 5 half-lives or 30 days, whichever is longer, prior to randomization, or plan to receive these agents any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.
11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

4.3 Concomitant medications

All medications (prescription and over-the-counter) taken at the time of study screening will be recorded, with indication, route of administration, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Subjects are allowed to use paracetamol (up to 3 g/day) and/or contraceptives (oral or parenteral), and any medications needed for SOC at the local institution. Use of hydroxychloroquine/ chloroquine is not permitted. Use of other experimental treatments for COVID-19 is not permitted

unless it is part of SOC at the local institution. SOC for COVID-19 will be documented at each site during the site activation visit; additionally, it will be documented if any restrictions on standard of care treatment administration were encountered due to resource limitations. The use of antiviral medications is permitted.

Concomitant medications used to treat chronic comorbid conditions per SOC are permitted, including but not limited to metered dose inhalers, corticosteroids if on stable doses for at least 30 days prior to screening, or sedative or anesthetic agents.

Concomitant medications initiated or stopped for an AE will be recorded.

Both losmapimod and its major metabolite, GSK198602, are in vitro inhibitors of human BCRP. There is a low risk of interaction of losmapimod with orally administered BCRP substrates with a narrow therapeutic index (eg, methotrexate, topotecan, rosuvastatin). Therefore, such co-administration is indicated only if the medical benefit is considered to outweigh the risk for toxicity, and careful monitoring for adverse effects of these agents is advised.

Losmapimod is a relatively potent in vitro inhibitor of the renal transporters MATE1 and MATE2-K, and it is possible that a mild inhibition of tubular secretion may contribute to the small rise in (model-adjusted geometric mean) serum creatinine observed clinically. GSK198602 is a relatively potent in vitro inhibitor of OAT3 and co-administration of sensitive OAT3 substrates is indicated only if the medical benefit is considered to outweigh the risk for toxicity. Careful monitoring for adverse effects of these agents is advised, especially for those with narrow therapeutic margin (eg, methotrexate, metformin).

4.4 Lifestyle restrictions

Subjects should not donate blood, sperm, or ova from the screening visit through 90 days after the last dose of study treatment.

4.4.1 Contraception requirements

Teratogenicity and effects on embryofetal survival were noted in rat and rabbit reproductive toxicology studies with losmapimod. Therefore, losmapimod should not be taken by women of childbearing potential who are not utilizing adequate contraceptive methods.

All women of childbearing potential and all males must practice effective contraception during the study from the time of the first dose of study medication until 90 days after last dose.

Women of child-bearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy/bilateral salpingectomy with or without hysterectomy;
- Post hysterectomy.

For the purposes of the study, effective contraception is defined as follows (as applicable to local [country] guidelines and regulations for sites outside the US):

- Females of childbearing potential: Using 1 or more of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap).

- Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms.

Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Investigational drug and matching placebo

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Matching placebo tablets will be provided for oral administration.

The tablets are plain white, round, biconvex, film-coated tablets. The proposed dosing regimen is as a twice daily dose of 15 mg (2 × 7.5 mg tablets/dose BID). The proposed duration of treatment is for up to 14 days.

Subjects should take their dose of losmapimod or placebo with food whenever possible and with 240 mL of room temperature water.

5.2 Study drug packaging and labelling

Losmapimod tablets for oral administration are available as white, round, biconvex, plain, film-coated tablets containing 7.5 mg of losmapimod as the micronized base, GW856553X.

Losmapimod tablets also contain the inactive excipients microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, povidone K30, hypromellose, titanium dioxide (E171), and polyethylene glycol.

Placebo tablets are identical in appearance to losmapimod and have the same excipient ingredients as losmapimod but do not have the active compound.

All tablets are packed in opaque, white, square, high-density polyethylene bottles with induction sealed child-resistant closures.

Losmapimod must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature not to exceed 30°C.

5.3 Drug accountability

The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

The Investigator (or designee) will maintain an accurate record of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures by the sponsor. Any unused assembled unit doses will be retained until completion of the study.

After completion of the study, all unused supplies will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

5.4 Treatment assignment and blinding

5.4.1 Randomization and treatment assignment

A total of up to 410 subjects will be recruited into this study and will be randomized in a 1:1 ratio to 15 mg losmapimod (BID) or placebo using an interactive/web voice response system (IxRS) for randomization. The randomization list will be produced by a qualified randomization vendor and will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no) at enrollment.

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug. Randomized subjects will be sequentially assigned a unique subject number from the randomization list per the IxRS. From the time of randomization and throughout the duration of the study, subjects will be identified by their unique randomization number.

The authorized site personnel will prepare the appropriate study drug for each subject based on the randomization schedule. Treatment codes should not be broken except in emergency situations, ie, when knowledge of the treatment is essential for the immediate further management of the subject.

5.4.2 Blinding

This study will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to subject-level treatment assignment until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way.

5.4.3 Treatment compliance

All doses will be administered either in the hospital (anticipated during the first week of study treatment) or taken by the study participants on an outpatient basis.

The subject will bring the study treatment bottle to each visit (clinic or home assessment) for review by the site staff.

The study treatment bottles will be collected at the Day 14 visit whether in the hospital or outpatient or at the ET visit if prior to Day 14.

6 STUDY ASSESSMENTS

See Table 1 for the time points of the assessments.

If additional visits or blood draws are required beyond the planned visits in any part of the study, these visits or samples should be recorded in the eCRF as unscheduled visits prior to the subject's completion of the study.

6.1 Medical history and confirmation of COVID diagnosis

A complete medical history will be taken at Screening and is to include demographic information, prior medical illnesses and conditions, and surgical procedures for at least 3 months prior to screening. The medical history may be collected from medical records, if available, or during the physical examination.

The history of SARS-CoV-2 infection and symptoms at screening should be recorded; the details of how infection history will be assessed and recorded can be found in the Study Manual. Diagnosis of COVID-19 should be confirmed by local PCR testing prior to randomization. Refer to the Study Manual for details on procedures and type(s) of diagnostic testing allowed.

A chest X-ray or CT will be performed while the patient is hospitalized based on standard-of-care local assessment. The results are required for eligibility assessment to confirm radiographic evidence of COVID 19. If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

A pre-existing condition is one that is present prior to administration of study drug. Such conditions should be recorded as medical history. A pre-existing condition should be recorded as an AE or serious adverse event (SAE) only if the frequency, intensity, or nature of the condition worsens following administration of study drug.

6.2 Pharmacokinetic and pharmacodynamic assessments

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess PK. PK assessments will be performed as a substudy in all sentinel subjects to evaluate the PK of losmapimod in the population of subjects with COVID-19.

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess serum and plasma biomarkers of response to COVID-19, which may include [redacted]

Procedures for collection, processing, and return of blood samples will be detailed in the Study Manual. Specifics of the analytical methods will be provided in separate documents.

Cytokines and chemokines will be evaluated using a multiplex assay. Details of the assay and specimen sampling will be provided in the Study Manual.

Viral load will be assessed by nasopharyngeal (preferred) or oropharyngeal swab, saliva, or other appropriate assay as outlined in the Schedule of Assessments (Table 1). Study samples will be analyzed by central testing. Refer to the Study Manual for details on procedures and type(s) of diagnostic testing allowed.

PK should be measured weekly for 2 weeks at C_{max} (4-5 hours) for subjects with renal insufficiency (eGFR ≤45 mL/min/ 1.73 m^2). For those subjects requiring dialysis, dose adjustment may be

needed (see Section 3.4.1) and will be determined by pre- and post-dialysis PK by the DMC to prevent site unblinding.

6.3 Clinical status and symptoms

The investigator may consult with a relevant clinical or other specialist as appropriate per SOC.

6.3.1 Respiratory failure and survival assessment

Total number of study days free of oxygen supplementation and total number of study days free of respiratory failure will be evaluated. Refer to Section 6.5.1 for further details of vital sign collection.

- Note: Respiratory failure is defined as either need for mechanical ventilation (invasive or non-invasive) or high flow oxygen (defined by greater than 15 LPM flow of oxygen to maintain oxygen saturation between 90% and 95%), sustained for at least 48 hours, at any time during the study.

The reason for hospitalization and number of total study days of hospitalization and intensive care unit (ICU) utilization will be recorded.

Details of subject discharge (date of discharge and condition at discharge) from the hospital will be recorded.

Any significant deviation from standard of care due to limited resources will be documented.

Survival status at the end of the study period will be documented, including cause of death for any reason.

6.3.2 Clinical status assessment

Clinical status as outlined in the Schedule of Assessments (Table 1) will be measured on the following clinician-reported 9-point ranking scale (WHO):

- (8) death
- (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO)
- (6) intubation and mechanical ventilation
- (5) noninvasive ventilation or high-flow oxygen therapy
- (4) oxygen therapy but not requiring high-flow or non-invasive ventilation
- (3) hospitalized but not requiring oxygen therapy
- (2) discharged from the hospital but with limitation of activities
- (1) discharged from the hospital and without any limitation
- (0) no clinical evidence of the disease

Instructions for administration will be provided in the Study Manual.

6.4 Extended vital signs

Extended vital signs, including oxygen saturation and fraction of inspired oxygen (FiO_2) will be collected as specified in the schedule of assessments. Refer to Section 6.5.1 for further details of measurements.

6.5 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 7.

6.5.1 Vital signs

Evaluations of systolic and diastolic blood pressure, respiratory rate, and temperature will be performed throughout the study. In addition, oxygen saturation and FiO_2 will be assessed throughout the study. Oxygen administration (eg, room air or oxygen flow by nasal canula or facial mask) will be recorded. Vital signs will be performed after subjects have been supine for at least 5 minutes when possible.

Arterial blood gases may be performed if clinically indicated in some subjects but are not required for this study. If arterial blood gasses are measured, the results for arterial pressure of oxygen (PaO_2) should be reported at each measurement in the eCRF.

Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.2 Weight and height

Weight (kg) will be recorded at screening and the follow-up assessment (by alternative methods including outpatient visit). Height (cm) will be recorded and body mass index (BMI) calculated at screening.

BMI (kg/m^2) = weight (kg)/(height [cm]/100)^2

6.5.3 Physical examination

Physical examination (ie, inspection, percussion, palpation, and auscultation) is performed to determine eligibility and as clinically indicated during the study. Clinically relevant findings that are present prior to study drug initiation must be recorded with the subject's medical history. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.4 Electrocardiography

ECGs will be taken singly after 5 minutes in the supine position as specified in the schedule of assessments. The investigator will assess the ECG recording as 'normal', 'abnormal - not clinically significant', or 'abnormal - clinically significant' and include a description of the abnormality as required. The ECG parameters assessed will include heart rate, PR, QRS, QT, and QTcB and QTcF (calculated using Bazett's and Fridericia's method, respectively). ECGs will be performed to determine eligibility and during the study period only if clinically indicated. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.5 Laboratory assessments

Laboratory parameters

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded. Clinical relevance is defined as:

- Is accompanied by clinical symptoms
- Leads to dose modification of study treatment
- Requires significant changes, addition of, interruption of, discontinuation of a concomitant medication, therapy, or treatment
- Reflects a disease and/or organ toxicity

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria or those that is a result of an AE that has already been reported.

Blood and other biological samples will be collected for the following clinical laboratory tests; refer to the Study Manual for details of collection and analysis and information on central and local laboratories:

Lab	Tests
Hematology	Hemoglobin [including mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration], hematocrit, red cell count, total white cell count, and platelet count. Differential blood count, including: basophils, eosinophils, neutrophils, lymphocytes, and monocytes.
Chemistry and electrolytes	Sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, uric acid, total bilirubin[1], alkaline phosphatase, [redacted], gamma-glutamyl transferase, and [redacted]. D
Glucose	Glucose
Urinalysis	Leucocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose. If there is a clinically significant positive result, urine will be sent for microscopy and/or culture.
Pregnancy[2]	hCG (urine or serum). If there is a clinically significant, positive result in urine, urine will be sent for confirmation.
[1]Conjugated bilirubin may be reported when total bilirubin is outside the reference range. [2]Pregnancy test for women of childbearing potential will be performed within 72 hours of first dose and if pregnancy is suspected during the study.	

6.6 Unscheduled visit

Unscheduled visits may be performed at any time at the subject's or the investigator's request and may include (but are not limited to) vital signs/focused physical examination, ECG, AE review, concomitant medications and procedures review, disease-related constitutional symptoms, and/or laboratory and biomarker assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

6.6.1 Early termination visit

When the investigator determines that study treatment will no longer be used, the investigator will perform the ET procedures and document the reason for discontinuation from study treatment in the eCRF. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the time of study treatment discontinuation, these tests need not be repeated. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment.

6.7 Alternative follow-up methods to site visits

Trial participants may not be able to come to the investigational site for protocol-specified or unscheduled visits. The sponsor may use alternative methods for safety assessments, including telemedicine visits, telephone visits, and/or an alternative location for visits depending on the local or institutional standards.

7 SAFETY REPORTING

7.1 Definitions of adverse events

An adverse event (AE) is any untoward medical occurrence in a subject who is participating in a clinical study performed. The AE does not necessarily have to follow the administration of a study drug, or to have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or vital sign finding), symptom, or disease temporally associated with the study participation whether or not it is related to the study drug.

7.1.1 Recording of adverse events

Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

7.1.2 Intensity of adverse events

The intensity of clinical AEs is graded 3-point scale as defined below:

- Mild: discomfort noticed but no disruption of normal daily activity;
- Moderate: discomfort sufficient to reduce or affect normal daily activity;
- Severe: inability to work or perform daily activity.

7.1.3 Relationship to study drug

For each AE, the relationship to drug as judged by the investigator:

- Probable;
- Possible;
- Unlikely;
- Unrelated.

7.1.4 Serious adverse events

A serious adverse event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatient hospitalization;
    - Note: COVID-19-related hospitalization or ICU admission is excluded from this definition, as SARS-CoV-2, COVID-19 infection, or pulmonary conditions attributable to COVID-19 infection are efficacy-related endpoints
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE.

7.1.5 Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is unexpected (nature or severity of which is not consistent with the applicable product information (eg, the Investigator Brochure for losmapimod) and suspected (a reasonable possibility of causal relationship with investigational drug, regardless of the administered dose).

7.1.6 Reporting of serious adverse events

The investigator must report any AE that meets the SAE criteria (Section 7.1.4) to [redacted] immediately (ie, within 24 hours after the site personnel first learn about the event) via electronic data capture (EDC). In the event that EDC entry is not possible (eg, system failure or access problems), the study site staff should complete the paper SAE report form and fax the form to [redacted] Pharmacovigilance within 24 hours of awareness or call the [redacted] safety hotline to report. The study site staff should update the EDC system as soon as it is available.

A full description of every SAE will need to be provided to [redacted] Pharmacovigilance.

[redacted]

7.1.7 Follow-up of adverse events

All AEs will be followed until they have abated, returned to baseline status or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.1.8 Adverse events of special interest

An AESI (serious or non-serious) is one of scientific and medical concern for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Adverse events of special interest for this study include QTc prolongation as well as liver tests that meet the criteria for potential drug-induced liver injury (DILI), in accordance with the US Food and Drug Administration “Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation”.

Adverse event of special interest: QTc prolongation

A thorough QT study (PM1116628) was conducted in healthy volunteers who received losmapimod at 7.5 mg BID or 20 mg daily or with placebo administered for 5 days. At the 20 mg dose of losmapimod, the upper bound of the 90% CI of the ΔΔQT interval (change from baseline in QTcF compared with that for placebo) exceeded the 10 msec threshold at the 24-hour post-dose time point. For the 7.5 mg BID dose, the upper bound of the 90% CI of ΔΔQTcF exceeded the 10 msec threshold at multiple time points. No subjects experienced QTcF values >480 msec or QTcF changes from baseline ≥60 msec at any time in the study. Although the upper bound of the 90% CI exceeded the 10 msec regulatory threshold of concern in the primary pharmacodynamic analysis, it was determined by GSK that there was no clinically relevant effect on the QT interval, as there was no clinically relevant concentration QTc effect using standard placebo/baseline subtracted measured QTc data. Additional information on the QTc interval and its behavior, as demonstrated in the large cohort of patients with ACS treated with losmapimod (PM1116197), supported the lack of a QT effect. PK/PD modeling using the raw QTcF and plasma concentration data showed that at plasma losmapimod concentrations 4 times the exposure at the therapeutic dose (7.5 mg BID) (ie, at exposures approximately 2-fold higher than 15 mg BID, the predicted upper bound of the 90% CI of ΔΔQTcF) did not exceed 10 msec, and the predicted median ΔΔQTcF was less than 5 msec. Further details are presented in the Investigator Brochure. No drug effect on QT prolongation of

losmapimod over placebo has been documented in any of the phase 2 or the one phase 3 trial completed so far.

Study drug should be discontinued for subjects who meet the QTc prolongation criteria as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.6). Further safety steps should be taken to closely observe and follow-up the event until resolution and treatment initiated per local standard of care.

Adverse event of special interest: Drug-induced liver injury

The following 3 laboratory value criteria must be met for potential DILI, or "Hy's Law":

- An elevated alanine transaminase or aspartate transaminase laboratory value that is ≥3 × ULN
- An elevated total bilirubin laboratory value that is ≥2 × ULN
- An alkaline phosphatase laboratory value that is <2 × ULN

Study drug should be discontinued for subjects who meet the laboratory criteria for potential DILI as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.6). Further safety steps should be taken to closely observe and follow-up the event until resolution. These steps include, but are not limited to:

- Making every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver tests
- Obtaining a more detailed history of symptoms and prior or concurrent disease, concomitant medication use, alcohol use, recreational drug use, and special diets
- Repeating liver enzyme and serum bilirubin tests twice weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic
- Obtaining viral hepatitis serology
- Considering liver imaging and/or hepatology consultation

7.2 Pregnancy

7.2.1 Teratogenicity

If a woman becomes pregnant when on study drug, study drug should be permanently discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known. In the event of pregnancy in the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

7.2.2 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during study drug administration or until follow-up, must be reported within 24 hours of the investigator's knowledge of the event to [redacted] using the Exposure in Utero form. The Investigator must make every effort to follow the pregnant partner of a male subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the SAE form.

8 STATISTICAL METHODOLOGY AND ANALYSES

8.1 Statistical analysis plan

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the interim analysis (IA). The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

All safety and statistical programming will be conducted using SAS 9.4 for Windows or newer (SAS Institute Inc., Cary, NC, USA), and other statistical programming/sample size calculation software as necessary.

8.1.1 Determination of sample size

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of up to 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an IA will be conducted after approximately 206 subjects (103 in the losmapimod arm, and 103 in the placebo arm) have completed the Day 28 visit, to assess early futility, using the rules specified in Section 8.9.

8.1.2 Analysis methods

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% CI.

8.1.3 Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

8.2 Protocol violations/deviations

Protocol deviations will be identified based on conditions related to the categories below:

- Protocol entry criteria
- Forbidden concomitant medications
- Missing evaluations for relevant endpoints

- Other protocol deviations occurring during study conduct.

Major protocol deviations will be identified before study closure and listed where appropriate.

8.3 Missing, unused and spurious data

All missing or incomplete safety and PD data, including dates and times, are treated as such. Missing test results or assessments will not be imputed, and as such, are assumed missing-completely-at-random (MCAR).

For laboratory data, values below the limit of quantitation (recorded as "< LLQ") will be set to half that limit.

Censoring rules for time-to-event endpoints will be discussed in the SAP. Imputation rules for the primary endpoint will be discussed in the SAP. The handling of any missing, unused, and spurious data will be documented in the SAP or the clinical study report.

8.4 Subject disposition

Subject disposition will be listed by subject.

The following subject data will be summarized:

- number and percentage of subjects screened,
- number and percentage of subjects enrolled,
- number and percentage of subjects completed,
- number and percentage of subjects included in safety population

A subject who completed the study is defined as a subject where the last PD assessment was completed.

8.5 Baseline parameters and concomitant medications

8.5.1 Demographics and baseline variables

Demographic and other baseline characteristics will be summarized using descriptive statistics for the treatment group and overall.

8.5.2 Medical history

Medical history will be listed.

8.5.3 Prior and concomitant medications

Prior and concomitant medications will be listed by international nonproprietary names, dose, regimen, route and for which indication it was prescribed.

8.5.4 Treatment compliance/exposure

Exposure to study treatment is described in terms of duration of treatment.

8.5.5 Safety and tolerability endpoints

The safety data set is used to perform all safety analyses.

Baseline is defined as the last value prior to dosing. Change from baseline will be calculated for all continuous safety parameters.

8.5.6 Adverse events

The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used for the coding of AEs. The overall incidence of AEs will be displayed by MedDRA system organ class, preferred term, and treatment group.

All AEs will be displayed in listings. In addition, SAEs and treatment-emergent AEs (TEAEs) leading to discontinuation of study drug will be listed.

Treatment-emergent AEs will be defined as an event that occurs on or after the first dose of study drug or the worsening of a preexisting condition on or after the first dose of study drug. If a subject does experience an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (ie, it is reported with a new start date) after starting administration of the specific treatment, and prior to the start of another treatment, if any. All TEAEs collected during the investigational period will be summarized.

The number of TEAEs and the number of subjects with at least 1 TEAE will be summarized by treatment group for the following:

1. System organ class and preferred term;
2. System organ class, preferred term, and maximum severity
3. System organ class, preferred term, and maximum drug relatedness.

8.5.7 Vital signs

Reported values and change from baseline values of supine blood pressure and pulse rate and temperature will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will be presented by treatment group. Vital sign variables will be listed. Values outside the reference range will be flagged in the listing.

Vital sign results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.5.8 ECG

ECG values will be listed.

8.5.9 Clinical laboratory tests

Reported values and change from baseline values of clinical laboratory variables will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will also be presented by treatment group. Clinical laboratory values will be listed.

Clinical laboratory test results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.6 Primary endpoints

1) Assuming p_t is probability of outcome in the losmapimod arm; p_c is the probability of outcome in the control arm

Study hypothesis: H_0: $= p_t - p_c = 0$

H_1: $= p_t - p_c < 0$

Assuming p_t=0.18, p_c=0.30, we can restate the hypothesis as

H_0: $\theta = \theta_0 = 0$

H_1: $\theta = \theta_1 = -0.12$

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from a regression model, adjusted for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP. An interim analysis to assess futility analysis—and potential sample size re-estimation—is discussed in Section 8.9. All results will be summarized descriptively by treatment arm and

expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p-values.

8.7 Secondary endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and post-baseline will be modelled using regression models appropriate for ordinal data, adjusting for stratification factors, sex, and baseline CRP. Details will be provided in the SAP.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Total number of study days: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, adjusting for stratification factors, sex, baseline CRP and number of days on study (as applicable). Details of the model, including censoring rules, if any, will be provided in the SAP.

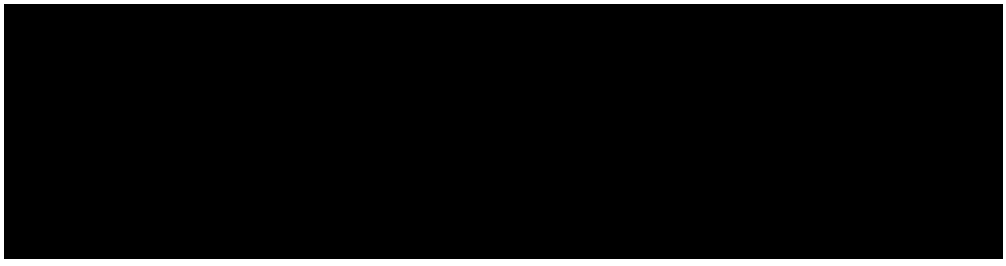
Percentage of subjects discharged from the hospital: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and baseline CRP. Full details of the regression model will be provided in the SAP.



8.9 Interim analysis for futility and sample size re-estimation

An interim analysis (IA) will be conducted after 206 subjects have been enrolled (approximately 103 in each of the losmapimod and placebo arms) and have been treated for 14 days with 28 days of follow-up. Only futility—and potential sample size-estimation—will be assessed by the DMC at the IA. The O'Brien-Fleming group sequential method will be used to adjust beta for interim testing. Table 6, Figure 1, Figure 2, and Figure 3 contain sample size requirements, boundary information, and stopping probabilities for testing futility on the primary endpoint at both the IA and final analysis. P-values are single-sided. Sample size estimation was done using SAS® (Proc SeqDesign, Version 4.0). The study will not be stopped for efficacy at the IA.

Table 6: Boundary Values for Interim Analysis Futility Assessment

Analysis Stage	Sample Size		Beta: Futility			Alpha: Efficacy		
	Losmapimod	Control	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under null hypothesis)	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under alternative hypothesis)
Interim Analysis	103	103	-0.67873 (0.24865)	-0.04017	0.75135	Not applicable	--	0.08871
Final Analysis	205	205	-1.91358 (0.02784)	-0.08009	0.97500	--	--	0.20000

Overall alpha=0.025 (1-sided); overall power=80%.
Abbreviations: MLE: maximum likelihood estimate.

Figure 1: Acceptance Region (Standardized-Z Scale)

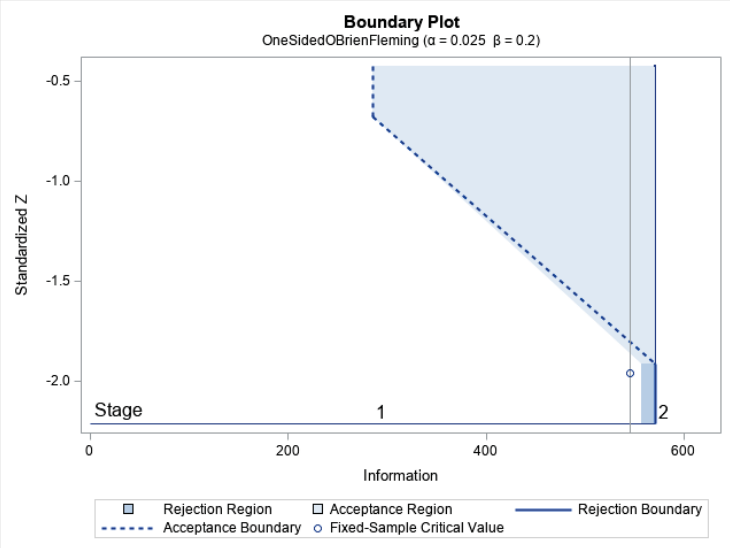


Figure 2: Acceptance Region (P-value)

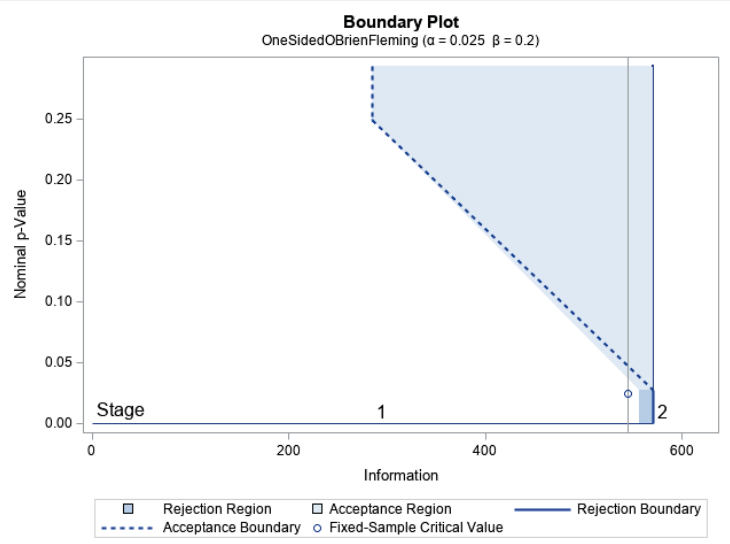
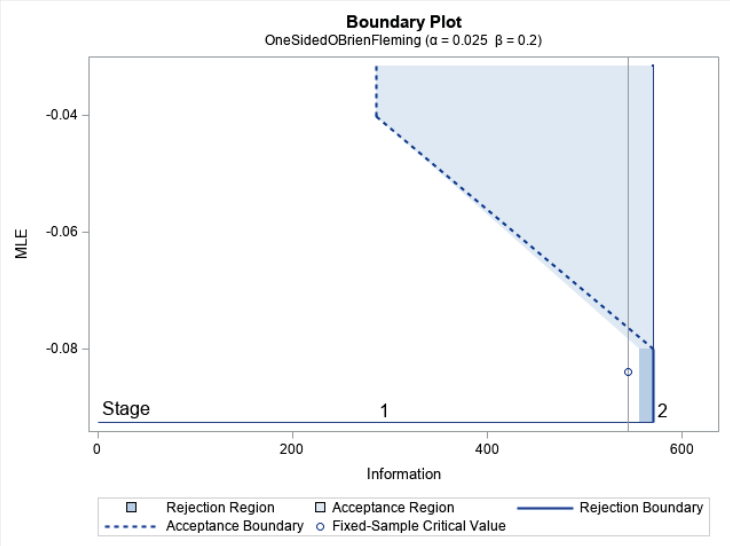


Figure 3: Acceptance Region (Maximum Likelihood Estimate)



8.9.1 Futility Testing

The process is as follows:

1. Futility at IA: If standardized z-value (MLE: maximum likelihood estimate) of $\mathbf{p_t - p_c}$ is ≥ -0.67873 (-0.04017), or p-value ≥0.24865, then stop for futility. Probability of stopping for futility under null hypothesis is ~0.75.
2. At Final Analysis: The final p-value is tested at an adjusted alpha of 0.02784.

8.9.2 Sample Size Re-estimation

The Chen-DeMets-Lan method (Chen et al 2004) will be used for unblinded sample size re-estimation, with IA futility stopping boundaries created using O'Brien-Fleming method, as described above. Wald conditional probabilities will be calculated using the actual observed proportion from both treatment arms.

The maximum sample size allowed is 820 subjects. Sample size will be increased only if the observed data at the IA are promising; that is, if the conditional power is ≥50% and <80%. Sample size will be increased to ensure a target conditional power of at least 80%.

There is only one IA, and conditional power at IA must lie between 50% and 80% for sample size re-estimation to be implemented. These 2 conditions ensure that the target Type I error of 2.5% is not exceeded by increasing sample size to meet the original target power (Chen et al 2004).

Sample size re-estimation will not be done in the following 2 instances:

- If conditional power is <50%, then sample size re-estimation will not be done, and decision on futility will be made based on boundary values from the O'Brien-Fleming method.

- If conditional power is ≥80%, then a sample size re-estimation will not be done, as the study will be considered sufficiently powered to detect the effect of interest at the final analysis.

A Wald Test statistic will be calculated and compared with the boundary value for futility (see Table 6). If the Wald Test statistic lies in the acceptance region then the study will stop for futility.

All calculations for the IA and the unblinded sample size re-estimation will be conducted by an external, unblinded statistician. The DMC will review the results in a closed session and make appropriate recommendations to the Sponsor afterwards.

8.9.3 Possible Recommendations by the DMC

After reviewing the results of the IA, the DMC may select 3 or more possible recommendations, based on the test statistics obtained at the IA:

- Stop for Futility - Stop trial early due to strong evidence for futility due to test statistic being in the futility region.
- Continue without change - Continue until next look with no changes due to test statistic not being in the futility region or the conditional power being <50% or ≥80%.
- Add required additional sample size, n, without exceeding the maximum sample size of 820 and continue the trial.

At the final analysis, 2 recommendations can be made:

- Efficacy is demonstrated.
- Efficacy is NOT demonstrated.

8.10 Data monitoring committee

An independent DMC composed of experts external to the sponsor and investigators will monitor the safety of the trial participants and the conduct of the trial on an ongoing basis and will be responsible for the interim analysis and recommendations regarding sample size re-estimation. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will include at least 2 external clinicians with expertise relevant to the evaluation of COVID-19, such as Critical Care, Pulmonology, or Infectious Disease, as well as at least 1 independent biostatistician with expertise in clinical trial design and statistical methods for clinical research and analysis of research data including interim analysis.

Details on the composition of the DMC and the schedule and format of DMC meetings and data outputs will be presented in the DMC charter. The DMC will review, at a minimum, data for the sentinel subjects prior to continued study drug dosing and cumulative safety data at regular intervals based on subject enrollment.

The safety evaluations will be detailed in the DMC charter and will include review of conventional safety variables, such as serious adverse events. Any safety event that requires unblinding will be immediately reported to the DMC and to the FDA. The DMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of subjects. The DMC will also review the efficacy data at the IA and make recommendations based on the futility criteria and for sample size re-estimation if needed (see Section 8.9). After reviewing study data, the DMC will make recommendations regarding continuation, termination, or modification of the study. The DMC may also perform ad hoc review PK of subjects who require dialysis.

8.11 Type I error for testing key study endpoints

The overall Type I error of the study will be controlled at 0.025 for 1-sided tests of hypotheses for the following key study endpoints, using an appropriate alpha control method:

1. Proportion of progressors to death or respiratory failure by Day 28
2. Change in clinical status using the 9-point WHO scale at Day 14
3. Change in clinical status using the 9-point WHO scale at Day 7
4. Oxygen-free days by Day 28

Further details on the methodology will be provided in the SAP.

9 GOOD CLINICAL PRACTICE, ETHICS AND ADMINISTRATIVE PROCEDURES

9.1 Good clinical practice

9.1.1 Ethics and good clinical practice

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice (GCP), the protocol, and all applicable regulations.

9.1.2 Ethics committee / institutional review board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date on which approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.1.3 Informed consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation. Following discussion of the study with site staff, subjects or their legally authorized representative will be required to provide one of the following:

1. Sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records; OR
2. If a subject is in isolation due to COVID-19 and institutional infection control policy would prevent removal of a document signed by the subject from their hospital room, then one of the following methods will be used to obtain informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable:
    - Obtain the informed consent electronically; OR
    - Obtain the informed consent by teleconference/video conference in alignment with local regulatory guidance.

    How the consent was obtained and reason why it was obtained using that particular method should be documented in the eCRF. The trial record at the investigational site should document how it was confirmed that the subject signed the consent form (ie, either using attestation by the witness and investigator or a photograph of the signed consent).

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

If consent is obtained from a legally authorized representative, then assent should be obtained from the subject using similar methods as described above.

9.2 Data handling and record keeping

This study will be conducted according to ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

Study site personnel will enter subject data into the EDC program. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with standard data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After final database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9.3 Access to source data and documents

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.4 Investigator's obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.6 Financial disclosure and obligations

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

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the subject's disease.

9.7 Investigator documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- FDA Form 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- A curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site.

9.8 Study conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.9 Adherence to protocol
The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.10 Adverse events and study report requirements
By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.11 Investigator's final report
Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.12 Records retention
Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.13 Publications
After completion of the study, the data will be submitted for reporting at a scientific meeting and for publication in a peer-reviewed scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.
Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld. Further terms concerning publication will be set forth in the clinical trial agreement entered into by the sponsor, the principal investigator, any vendors, and the institution.

10 STUDY MANAGEMENT

The administrative structure will include a DMC (see Section 8.10).

10.1 Monitoring

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor regularly monitors the trial remotely and will periodically visit the investigator based on local restrictions, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation remotely, and discussion of the conduct of the study with the investigator and personnel. All relevant source documents will be uploaded into the IBM electronic system or access to the electronic medical records will be provided for remote monitoring purposes.
All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.2 Inspection of records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.
The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.3 Management of protocol amendments and deviations

10.3.1 Modification of the protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

10.3.2 Protocol deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change of the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.
A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the subject being withdrawn from the study. A list of major protocol deviations will be compiled prior to the start of the study.
Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.4 Study termination

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

the study be required, the sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed written explanation. Fulcrum and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The sponsor has no plans to provide study drug to subjects after study closure or termination. The obligations to provide study results for subjects and reports to IRB/IEC shall continue as required by applicable laws and regulations.

At any time, the sponsor, the investigators, or the IRBs/IECs may terminate this study for reasonable cause. Conditions that may lead to reasonable cause and warrant termination include, but are not limited to the following:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the regulatory authority

Written notification that includes the reason for the clinical study termination is required.

The end of the study is defined as the date on which the last subject completes the last visit (includes the safety follow-up visit).

10.5 Final report

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study reports. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study reports, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

Short Title:	Losmapimod safety and efficacy in COVID-19 (LOSVID Study)
Version:	2
Date:	29-Jun-2020
Study number:	FIS-001-2020
IND number	149208
Sponsor:	Fulcrum Therapeutics 26 Landsdowne St., 5th floor Cambridge, MA 02139 USA
Sponsor signatory:	[redacted] MD

CONTACT DETAILS

SPONSOR	Fulcrum Therapeutics 26 Landsdowne Street, 5th floor Cambridge, Massachusetts 02139 USA
Clinical Trial Leader	[redacted] MD Telephone: [redacted] e-mail: [redacted]
Drug Safety Physician	[redacted] MD Telephone: [redacted] e-mail: [redacted]

SIGNATURE PAGE - INVESTIGATOR

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I have read the protocol and agree to conduct the study as described herein.

SIGNATURE PAGE - SPONSOR

Fulcrum Therapeutics

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I approve this protocol on behalf of the sponsor.

[redacted]
Chief Scientific Officer

DocuSigned by:
[redacted]
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Signature

2020-Jun-30

Date (dd Mmm yyyy)

[redacted], MD
Senior Vice President
Head, Clinical Development

DocuSigned by:
[redacted]
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Signature

2020-Jun-30

Date (dd Mmm yyyy)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
BID	*bis in diem* / twice per day
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	Maximum concentration
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	disease caused by novel coronavirus
CRP	C-reactive protein
CXCL13	chemokine ligand 13
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
ET-1	endothelin
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSGS	focal segmental glomerulosclerosis
FSHD	facioscapulohumeral muscular dystrophy
GCP	Good Clinical Practice
[redacted]	[redacted]
GSK	GlaxoSmithKline
H5N1	highly pathogenic Asian avian influenza A, subtype H5N1
HIV	human immunodeficiency virus
HMGB-1	high mobility group box protein-1
hsCRP	high-sensitivity C-reactive protein
HSV-1	herpes simplex virus-1
IA	interim analysis

ICAM-1	intercellular adhesion molecule-1
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	independent ethics committee
IL-6	interleukin-6
IND	investigational new drug application
IRB	institutional review board
IxRS	interactive/web voice response system
JAK	Janus kinase
[redacted]	[redacted]
LLQ	lower limit of quantitation
LS	least square
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusions
MCAR	missing-completely-at-random
MedDRA	Medical Dictionary for Regulatory Activities
OAT	organic anion transporter
PAO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PH	proportional hazards
PK	pharmacokinetics
PO	*per os* / orally
PPS	per protocol set
QTcB	QT corrected interval using Bazett's formula
QTcF	QT corrected interval using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SE	standard error
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID Study)

Short Title

Losmapimod safety and efficacy in COVID-19 (LOSVID Study)

Background & Rationale

Poor prognosis for many COVID-19 patients has been attributed to an exaggerated inflammatory response following SARS-CoV-2 infection. This hyperactivated immune response is associated with pulmonary edema, acute respiratory distress syndrome (ARDS), and cardiomyopathy that may lead to increased mortality in the sickest patients.

p38 mitogen-activated protein kinase (MAPK) is an important mediator of inflammation, and extensive nonclinical data have linked p38 to the hyper-inflammatory response to viral infections.

Losmapimod is a potent and selective p38α/β MAPK inhibitor that is currently in Phase 2 clinical trials for the treatment of facioscapulohumeral dystrophy and has previously been administered to more than 3600 adult healthy volunteers and subjects including participants in a Phase 3 trial. Many of these trials were for chronic inflammatory indications for which the compound exhibited a favorable safety profile not significantly different from placebo. These trials have also indicated that losmapimod has good exposure after oral dosing, robust target engagement, and acutely reduces inflammatory biomarkers that have been associated with poor prognosis in COVID-19, including C-reactive protein (CRP) and interleukin-6 (IL-6). Additionally, a clinical study recently concluded that losmapimod restored the normal immune response of older subjects (median 69 years, range: 65, 77 years) following a viral challenge. Further information is available in the losmapimod Investigator Brochure.

Losmapimod is attractive as a potential therapeutic option for COVID-19:

- p38 inhibition improves survival in mouse SARS-CoV-1 models and other nonclinical viral models, suppressing the exaggerated immune response to acute infection.
- Losmapimod acutely has reduced exaggerated inflammatory responses in human trials for multiple inflammatory diseases, including IL-6 and CRP, and has normalized immune response to viral or other acute inflammatory challenges in older subjects.
- Losmapimod is a clinical-stage, potent, and selective p38 inhibitor with extensive human experience and extensive evidence of safety and tolerability, including in a Phase 3 clinical trial in acute myocardial infarction.
- p38 inhibition has the potential to reduce hypothesized deleterious effects of increased angiotensin II in COVID-19, such as vasoconstriction, increased inflammation, cardiac arrhythmias, and organ failure.

Objectives and Endpoints:

All study objectives will be evaluated in subjects diagnosed with COVID-19:

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale: • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation Total number of study days in ICU Total number of study days hospitalized Total number of respiratory failure-free study days Percentage of subjects discharged from the hospital
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive

Objectives	Endpoints
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted] PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

Design

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥50 years old who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.

Subjects who sign informed consent and meet all entry criteria (listed below) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg orally (PO) twice daily (BID); OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter.

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site.

Investigational drug

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Comparative drug

Matching placebo tablets will be provided for oral administration.

Inclusion criteria

1. Able and willing to provide written informed consent.
2. Willing and able to comply with all study procedures.
3. Age ≥50 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. ≥90% oxygen saturation on room air and/or ≥94% oxygen saturation on oxygen administration at 2 L/min by nasal canula at the baseline visit.
8. Radiographic (X-ray or computed tomography scan, per local standard of care) evidence of pulmonary involvement consistent with COVID-19 at screening or baseline, per the judgment of the investigator.
    a. Note: If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator

10. CRP at screening >15 mg/L on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows:
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock) or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or HIV infection.
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Treatment with anti-IL 6, anti-IL-6R antibodies, Janus kinase (JAK) inhibitors, or other immune modulators (unless considered part of local standard of care) in the past 30 days or 5 half-lives (whichever is longer) or plan to receive these agents as part of investigational clinical trials any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.

11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

Sample size justification

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an interim analysis (IA) will be conducted after approximately 206 subjects (103 in each of the losmapimod and placebo arms) have completed the Day 28 visit, to assess futility.

Statistical methodology

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the IA. The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

Summaries of change from baseline variables and GMR will include only subjects who have both a baseline value and corresponding value at the post-baseline time point of interest. Baseline will be defined as the last value prior to initiation of blinded treatment.

Where appropriate, descriptive statistics may be presented with 95% confidence intervals.

Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

Primary endpoint

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from a regression model, adjusted for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP. An interim analysis to assess futility analysis—and potential sample size re estimation—will be conducted. All results will be summarized descriptively by treatment arm and expressed as

proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p values.

Secondary endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and post-baseline will be modelled using regression models appropriate for ordinal data. Details will be provided in the SAP.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

Total number of study days: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, with age group as a covariate with stratification factors as covariates. Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

Table 1: Visit and Assessment Schedule

Assessment[1] / Time point	SCR	Treatment Period											FU[14]		ET
	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Informed consent	X														
Demography	X														
Inclusion and exclusion criteria	X	X													
Medical history	X														
COVID-19 history and clinical diagnosis[2]	X														
Chest X-ray/CT scan	X[3]	X[3]													
Study drug administration:															
Randomization		X													
Losmapimod or placebo PO BID		X	X	X	X	X	X	X	X	X	X	X			
Pharmacodynamics:															
Drug levels/PK[4]		P, 4-5h	4-5h	4-5h	4-5h	4-5h	4-5h	4-5h				4-5h			X
[redacted]															
Clinical status and symptoms:															
Respiratory failure and survival assessment[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical status assessment per WHO 9-point scale[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral presence and viral load by central testing (nasopharyngeal [preferred] or oropharyngeal swab) [7]		X	X (sentinel only)[7]	X (sentinel only)[7]	X (sentinel only)[7]			X							X
Confirmation of COVID-19 diagnosis (nasopharyngeal [preferred] or oropharyngeal swab)	X[2]	X (PR)[2]													
Oxygenation and FiO_2[8]	X	X	X	X	X	X	X	X	X	X	X	X			X

Fulcrum Therapeutics Losmapimod
Protocol FIS-001-2020

Assessment[1] / Time point	SCR	Treatment Period											FU[14]		ET
	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Safety assessments:															
Physical examination	X														X
Weight/height[9]	X												X		X
Hematology, chemistry safety labs[6]	X	X	X		X			X		X		X	X		X
CRP[6]	X														
Urinalysis[10]	X							X							
Urine or serum β-hCG (female subjects only)	X[11]												X		X
ECG[12]	X							X							
HR, BP, RR, temperature[8]	X	X	X	X	X	X	X	X	X	X	X	X			X
(S)AEs[13]	X														X
Concomitant medications (including SOC)	X														X

AE = adverse event; BP = blood pressure; COVID-19 = novel coronavirus; HR = heart rate; P = pre dose; PAO_2 = partial pressure of oxygen; PR – pre-randomization; RR = respiratory rate; sent = sentinel; SOC = standard of care; SCR = screening.

Note: All screening assessments are to be performed before dosing. If procedures required at any time point have already been performed as part of routine clinical care, these assessments do not need to be repeated, and information will be collected and entered on the eCRF from the subject's medical records. Unscheduled visits can take place at any time at the discretion of the site to check for new AEs/SAEs or to repeat key missed assessments or for other reasons.

[1] The order of assessments can be performed at the discretion of the investigator once informed consent is obtained.

[2] COVID-19 diagnosis to be confirmed by local testing (PCR) before randomization and first dosing.

[3] To be performed while hospitalized based on standard-of-care local assessment. Result required for eligibility assessment to confirm radiographic evidence of COVID-19. If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

[4] PK assessments will be performed as a substudy in all sentinel subjects. For those subjects requiring dialysis, a single pre- and post-dialysis PK should be obtained for review by the DMC to decide if dose adjustment is needed. PK should be measured weekly at C_{max} (4-5 hours post dose) for subjects with renal insufficiency when possible.

[redacted]

Assessments for clinical/respiratory status, progression, and safety serum chemistry and hematology tests to be performed and samples to be collected while hospitalized based on standard-of-care local laboratory assessments and after discharge from the hospital by home visit or outpatient clinic visit or telemedicine call. For subjects who are discharged to home or other outpatient setting after initial hospitalization, the assessments and laboratory samples can be obtained less often but not less than at least once weekly. CRP result required to determine eligibility are based on local laboratory results at screening.

[7] Viral load testing will be collected daily for the first 4 days using local testing in the first 10 enrolled subjects as part of the sentinel safety assessment. For all subjects, including the sentinel subjects, swabs or other sample collection for central viral load testing will be collected on D1 pretreatment and on D7 or earlier if being discharged from the hospital prior to D7.

[8] Vital signs will be performed after subjects have been supine for at least 5 minutes when possible. Vital signs to include oxygen saturation; PaO_2 should be recorded if available from blood gases obtained as part of SOC; oxygen administration should also be recorded (eg, room air or oxygen flow by nasal canula or facial mask or endotracheal tube). For subjects who are discharged to home or other outpatient setting after initial hospitalization, assessments may be obtained less often but at least once per week in the outpatient clinic or at home.

[9] Height assessed at screening only; can be by self-report or from medical records. Weight is an actual recording.
[10] Urinalysis will be performed during the study period only on Day 7 and on any other day only if clinically indicated.
[11] Pregnancy testing to be conducted within 72 hours of the first dose of study treatment.
[12] Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes if possible. ECGs will be performed at Day 7 in all subjects and at any other time during the study if clinically indicated.
[13] Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.
[14] Outpatient assessments to be conducted via telemedicine or outpatient clinic. Outpatient laboratory assessments to be completed at outside local laboratory or home or outpatient visit.

1 BACKGROUND AND RATIONALE

1.1 Scientific rationale for investigation of losmapimod in COVID-19

COVID-19 is a severe pandemic disease with high mortality particularly in older individuals, due to infection with the SARS-CoV-2 coronavirus. The therapeutic hypothesis for the use of losmapimod in COVID-19 disease is that increased mortality and severe disease is caused by p38 mitogen-activated protein kinase (MAPK)-mediated exaggerated acute inflammatory response resulting from SARS-CoV-2 infection. The older population is especially at risk of severe disease and death upon infection with SARS-CoV-2. The hyperactivated immune response in COVID-19 shares features of the cytokine storm syndrome and appears to be responsible for the severe pulmonary edema, ARDS, and cardiac and renal disease responsible for most of the severe morbidity and mortality.

The proposal to develop losmapimod, a potent, specific, and bioavailable p38α/β inhibitor, for treatment of COVID-19 is based on the following rationale:

(1) Nonclinical work has shown that older mice infected with SARS-CoV-1 develop much more severe disease than younger ones, and that treatment with a p38 MAPK small molecule inhibitor greatly reduced their mortality when given after viral inoculation; similar survival benefit of p38 MAPK inhibition has been seen in animal models of severe H5N1 influenza and HSV-1.

(2) Nonclinical work has shown that p38 MAPK inhibition reduces viral load in several experimental models with coronaviruses, including mouse hepatitis virus, human CoV-229E, transmissible gastroenteritis virus, and Middle East respiratory syndrome virus.

(3) p38 MAPK is proposed to play a critical role in the development of ARDS, including regulating the expression and activity of inflammatory mediators such as ICAM-1, HMGB1, and ET-1, neutrophil chemotaxis and apoptosis, the balance of Treg/Th17 cells, and pulmonary endothelial cell apoptosis.

(4) Clinical investigation showing that excessive acute inflammation in response to external stressors in older individuals, including viral antigen challenges, hinders the specific immune response to infection; many of the excessive inflammatory mediators associated with this aberrant immune response in older individuals are associated with activation of the p38 MAPK pathway.

(5) Treatment with losmapimod in older subjects restored the normal immune response to viral antigen challenge and improved the resolution of acute inflammation.

(6) Treatment of various inflammatory diseases with losmapimod, including active rheumatoid arthritis (RA), acute myocardial infarction, and chronic obstructive pulmonary disease (COPD) resulted in significant reduction in markers of acute inflammation, including interleukin-6 (IL-6), C-reactive protein (CRP), chemokines such as CXCL13, and other markers (see Table 5 for further details).

(7) Losmapimod may be beneficial in COVID-19 treatment via reduction of the damaging effects of angiotensin II (Ang II). Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS-CoV viruses and is expressed in the lung and the heart. Upon infection with SARS-CoV-2, there is internalization of and depletion of ACE2. ACE2 converts Ang II into angiotensin 1-7 (Ang 1-7), which counterbalances the vasoconstrictive and pro-inflammatory effects of Ang II. Ang II is significantly elevated in COVID-19, and the levels are positively correlated with viral load and acute lung injury (Liu Y et al, 2020). Blocking the p38 MAPK pathway in nonclinical models has been

shown to reduce many of the adverse effects of elevated Ang II, resulting in lower frequency of cardiac arrhythmias, renal failure, and hypertension.

p38 inhibitors have been explored extensively in clinical trials for numerous chronic inflammatory indications, as summarized in the Investigator Brochure. Losmapimod has been extensively tested in humans and found to be generally well tolerated, including in over 3600 adult healthy volunteers and subjects in 11 different indications. The 15 mg oral (PO) twice per day (BID) dose proposed for the COVID-19 Phase 3 study has been shown to provide robust and sustained inhibition of the p38 MAPK pathway systemically and in tissues, specifically in skeletal muscle needle biopsies of subjects with facioscapulohumeral muscular dystrophy (FSHD). This dose of losmapimod was shown experimentally in older (median 69 years, range: 65, 77 years) human volunteers to restore the normal immune response to viral challenge and improve the resolution of acute inflammation. Furthermore, losmapimod has been shown to significantly reduce markers of hyperactive acute innate immune inflammation in the context of acute myocardial infection, RA, and COPD in clinical trials as listed below:

1- Single-dose study in 50 subjects with RA (RA 3103730). Treatment with losmapimod (N=38) reduced levels of IL-6 compared with placebo (N=12). Losmapimod was dosed as follows: 7.5 mg: 13 subjects; 20 mg: 12 subjects; 60 mg: 13 subjects. Analysis of serum IL-6 at 3 hours post dose showed significantly lower levels with losmapimod than with placebo (Table 2).

Table 2: Change from Baseline in IL-6 Serum Levels with Increasing Single Doses of Losmapimod in Subjects with Rheumatoid Arthritis

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to placebo	95% CI
Placebo	0.92	0.60, 1.41		
Losmapimod 7.5 mg	0.41	0.26, 0.63	0.45	0.24, 0.82
Losmapimod 20 mg	0.43	0.27, 0.68	0.47	0.25, 0.88
Losmapimod 60 mg	0.38	0.25, 0.57	0.41	0.23, 0.75

Abbreviations: CI = confidence interval.

2- Repeated-dose study in subjects with acute coronary syndrome (ACS; PM1111810). A total of 535 subjects with non-ST elevation myocardial infarction were randomized to an initial dose of 7.5 or 15 mg of losmapimod followed by 7.5 mg PO BID (N= 388) or matching placebo (N=138) for 12 weeks. Results showed that relative to placebo, losmapimod significantly suppressed CRP and IL-6 acutely at the 24- to 36-hour assessments (Table 3).

Table 3: Change from Baseline in hsCRP and IL-6 with 7.5mg PO BID Losmapimod Over Placebo in Subjects with Acute Coronary Syndrome

Parameter	Placebo (N=138)	All losmapimod (N=388)	P value
hsCRP at 72 hours or discharge (nmol/L)	110.8 (83.1-147.7)	64.1 (53.0-77.6)	<0.05
IL-6 at 24 hours (ng/L)	10.6 (8.6-13.1)	6.6 (5.8-7.4)	<0.05

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6.

3- Repeated-dose study in subjects with COPD (MKI113006). In this study, subjects with COPD were dosed with losmapimod 2.5 mg BID (N=149), losmapimod 7.5 mg BID (N=151), or placebo BID (N=154) for 24 weeks; or losmapimod 7.5 mg BID for 4 weeks followed by losmapimod 15 mg BID (N=150) for 20 weeks. Over the first 12 weeks of treatment, statistically significant reductions in serum high-sensitivity CRP (hsCRP) levels were observed in the losmapimod 7.5 mg and 15 mg groups compared with placebo. For hsCRP, Week 12, 7.5 mg dose versus placebo: ratio 0.73; 95% confidence interval [CI] 0.57, 0.93;

p=0.011; 15 mg dose versus placebo: ratio 0.64; 95% CI 0.50, 0.82; p<0.001. Table 4 shows the results for the subgroup with higher CRP at baseline.

Table 4: Change from Baseline in CRP Over 12 Weeks of Treatment with Different Doses of Losmapimod Compared with Placebo in Subjects with COPD and High Baseline CRP Levels (>6.4 mg/L)

Week 12 Baseline hsCRP >6.40 mg/L	Placebo BID (N=42)	Losmapimod 2.5 mg BID (N=33)	Losmapimod 7.5 mg BID (N=31)	Losmapimod 15 mg BID (N=31)
Geometric LS mean (SE of logs)	6.75 (0.153)	8.08 (0.180)	5.16 (0.180)	3.54 (0.186)
Geometric LS mean ratio to baseline (SE of logs)	0.49 (0.153)	0.59 (0.180)	0.38 (0.180)	0.26 (0.186)
Column vs placebo				
Ratio		1.20	0.77	0.53
95% CI		0.75, 1.92	0.48, 1.22	0.33, 0.85

Abbreviations: CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; LS = least square; SE = standard error.

Fulcrum Therapeutics is planning to conduct the initial clinical trial for the investigation of losmapimod for the treatment of COVID-19 in these high-risk subjects. Losmapimod is currently in Phase 2 clinical development for the treatment of the root cause of FSHD under an open IND in the United States and open clinical trial applications in Canada, Spain, France, and The Netherlands.

A summary of published literature supporting the therapeutic hypothesis for the clinical development of losmapimod for the treatment of COVID-19 is provided in Table 5.

Table 5: Listing of Evidence Supporting the Development of the p38 Inhibitor Losmapimod for Treatment of COVID-19

Evidence	References
Pneumonitis, acute respiratory distress syndrome, pulmonary edema, and cardiomyopathy drive COVID-19 mortality	• Siddiqi HK et al. J Heart Lung Transplant. 2020 • Ruan Q et al. Intensive Care Med. 2020 Mar 3
Older patients are at greatest risk of COVID-19 mortality	• Ruan Q et al. Intensive Care Med. 2020 Mar 3
Human SARS-CoV-2 pathology is recapitulated in SARS-CoV-1 mice	• Zhou F et al. Lancet. 2020 • Nagata N et al. Am J Pathol. 2008
Exaggerated acute inflammatory response and lymphopenia correlate with mortality in human with COVID-19 and older mice infected with SARS-CoV-1	• Nagata N et al. Am J Pathol. 2008 • Zhou F et al. Lancet. 2020
SARS-CoV-1 activates the p38 MAPK pathway in peripheral blood early in the infection	• Lee CH et al. J Immunol. 2004.
SARS-CoV envelope protein (E) activates the host's inflammatory response via p38 signaling	• Jimenez-Guardeño JM et al. PLOS Pathog. 2014

Evidence	References
Several nonclinical studies have shown evidence of p38 inhibition reducing viral replication including with coronavirus	• Kono M et al. Antiviral Res. 2008 • Dong Y et al. Antiviral Res. 2020 • Kindrachuk D et al. Anti Microb Agents & Chem. 2015
p38 inhibition reduces mortality in older mice infected with SARS-CoV-1	• Jimenez-Guardeño J et al. PLOS Pathog. 2014
Nonclinical efficacy of p38 inhibition also observed in other models of severe acute viral pneumonitis and other severe acute viral infections	• Shapiro L et al. PNAS. 1998 • Iordanov MS et al. Mol Cell Bio. 2000 • Salomon R et al. PNAS. 2007 • Griego SD et al. J Immunol. 2000 • Banerjee S et al. J Virology. 2002 • Börgeling Y et al. J Biol Chem. 2014 • Chen Y et al. J Exp Med. 2017 • He F et al. J Transl Med. 2019
p38 inhibition reduces lung mucous production in mice models of toxic airway injury	• Liu et al. Int Immunopharmacol. 2009
Losmapimod and other p38 inhibitors acutely reduce inflammatory markers in humans	• GSK data in Fulcrum Original IND 138739, Module 4 • Genovese M et al. J Rheumatol. 2011 • Christie J et al. Crit Care Med. 2015
Losmapimod reduces inflammatory markers associated with COVID-19 severity at currently utilized doses	• Fulcrum clinical data on file • GSK clinical data • Newby L et al. Lancet. 2014
Inhibition of p38 with 15 mg losmapimod BID dose in older subjects restored the adaptive immune response to viral challenge	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
Exaggerated acute inflammatory response in older subjects is driven to a large extent by p38 activation	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
In vivo data in Ferrets indicate SARS-Cov-2 induces profoundly lower immune response vs other virus	• Blanco-Melo D et al. bioRxiv. 2020
Evidence that p38 inhibition may treat the deleterious effects of elevated Ang II in COVID-19	• Grimes JM et al. J Mol Cell Cardiol. 2020
Losmapimod is a highly selective p38 inhibitor at advanced stage of clinical development with excellent safety data profile	• Losmapimod Investigator Brochure Fulcrum 2020 • Cadavid D et al. FSHD IRC Poster. 2019

Abbreviations: BID = twice daily; COVID-19 = disease caused by novel coronavirus; IND = investigational new drug application; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2 STUDY OBJECTIVES AND ENDPOINTS

All study objectives will be evaluated in subjects diagnosed with COVID-19.

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale (WHO 2020): • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation Total number of study days in ICU Total number of study days hospitalized Total number of respiratory failure-free study days Percentage of subjects discharged from the hospital

Objectives	Endpoints
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted] ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

3 STUDY IMPLEMENTATION

3.1 Overall study design and plan

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥50 years old, who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.

Subjects who sign informed consent (refer to Section 9.1.3) and meet all entry criteria (see Section 4) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg PO BID; OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter (see Section 8.10).

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site (refer to Section 6.7).

3.2 Start of study and end of study definitions

The start of the study is defined as the date the first enrolled subject signs an informed consent form (ICF). The end of the study is defined as the date of the last subject’s last assessment (scheduled or unscheduled).

3.3 Selection of doses in the study

In the Phase 1 study in healthy volunteers and FSHD subjects (Study FIS-001-2018), the dose levels of 7.5 mg and 15 mg given by mouth BID with food were based on predictive nonclinical efficacy and published clinical target engagement and safety data for losmapimod previously generated by GSK. This Phase 1 study was recently completed and demonstrated that the 15 mg PO BID dose gives higher plasma levels and greater and more sustained target engagement in blood and tissues than the 7.5 mg PO BID dose, while resulting in similar safety and tolerability. The 15 mg BID dose is used in the ongoing Phase 2 studies in FSHD (Study FIS-001-2019 and Study FIS-002-2019). Prior results indicated the favorable safety and tolerability of losmapimod for chronic administration in the clinic, including in the context of severe acute diseases, such as acute myocardial infarction, in older people.

Prior studies of biodistribution of radiolabeled losmapimod by GSK showed ample distribution to all tissues including the lungs and the heart. Our recent target engagement data in the FSHD Phase 1 Study FIS-001-2018 indicates that pHSP27 inhibition in blood, an assessment of p38 target engagement, is nearing a plateau at a losmapimod dose of 15 mg BID (see Investigator Brochure [Fulcrum Therapeutics 2020]), so doses of losmapimod higher than 15 mg PO BID are not warranted.

Additionally, at the proposed dose level of 15 mg PO BID, exposures are not expected to exceed those previously demonstrated to be safe in humans in multiple previous studies by GSK in healthy volunteers and various patient populations including older subjects (Cheriyan et al 2011; Barbour et al 2013; Watz et al 2014; Pascoe et al 2017).

In previous clinical studies performed by GSK, it was shown that losmapimod significantly reduced markers of acute inflammation, including IL-6, CRP, and the CXCL13 chemokine after a single dose. Additionally, losmapimod reduced IL-6 after 15 days of treatment (GSK study RA3103718) and CRP acutely in subjects with acute myocardial infarction treated with 7.5 mg PO BID (O'Donoghue et al 2016). In subjects with COPD, losmapimod at 15 mg PO BID significantly reduced CRP over 12 weeks compared with placebo (GSK Study MKI 113006). In one study in healthy older adult volunteers, it was shown that a 15 mg PO BID dose of losmapimod for 4 days restored the normal immune response to varicella-zoster virus antigen challenge (Vukmanovic-Stejic et al 2018). The same formulation used in these previous clinical studies is the one proposed for use in the present clinical study.

The rationale for the proposed study duration of up to 28 days is that in most cases of COVID-19 the disease has resolved or resulted in severe outcomes over the first month from onset of symptoms. COVID-19 is a severe and rapidly progressive infection, especially in the high-risk population selected for the proposed Phase 3 trial. Therefore, treatment for longer than 14 days and study duration for longer than 28 days is not justified.

3.4 Study drug modifications and withdrawal

3.4.1 Dose modifications

Before trial medication is administered, changes in the subject's health status, including laboratory results if applicable, since the previous visit or previous dose should be checked.

Study drug interruptions and reductions are not permitted; subjects who are on dialysis may require a dose adjustment.

Study treatment dose adjustment for subjects on dialysis

The elimination of losmapimod is almost exclusively by metabolism, with only 2% of the administered dose recovered as unchanged drug in urine and feces. The metabolite is clinically inactive and does not exert any toxic effects.

Losmapimod has not been studied in renal insufficiency or renal failure. There has been 1 study of losmapimod in 17 subjects with focal segmental glomerulosclerosis (FSGS; FSG117283). In this study, subjects were given losmapimod 7.5 mg BID for 2 weeks followed by losmapimod 15 mg BID for 22 weeks. The mean duration of exposure to investigational product in subjects with FSGS was approximately 21 weeks (range: 3.7, 25 weeks).

Creatine and GFR for the population enrolled is in the table below.

Parameter	Mean (SD)	Range
eGFR (mL/min/1.73m^2)	79.4 (34.9)	36, 155
Creatine (µmol/L)	1.1 (0.5)	0.48, 2.07

eGFR = estimated glomerular filtration rate.

Losmapimod plasma concentration data in subjects with FSGS were compared with historical data obtained in the Phase 3 clinical trial in subjects with ACS. In general, exposure in subjects with FSGS was similar to that in subjects with ACS over the 24-week treatment period.

Consistent with the safety database of over 3500 subjects, the 2 most frequently reported AEs in the FSGS trial were headache (5/17; 29%) and fatigue (4/17; 24%). Seven AEs (by preferred term: vomiting, dizziness, oropharyngeal pain, nausea, blood creatinine increased, muscle spasms, and rash) were reported in 3 subjects (18%) each. All other AEs (by preferred term) were reported in ≤2 subjects each. Four subjects had at least 1 AE that led to withdrawal from the study or from treatment. The AEs that led to discontinuation were increase in blood urea nitrogen (related), increase in creatinine (not related), increase in cystatin C (related), and joint stiffness (related). None of the AEs was serious or severe; 3 of the AEs in 2 subjects were reported as related to study treatment.

Based on the current safety and exposure information, dosing adjustment is likely not needed for subjects with renal insufficiency. However, close monitoring of pharmacokinetics (PK) for such cases will be implemented to ensure that therapeutic concentrations are maintained (refer to Section 6.2). For those subjects requiring dialysis, dose adjustment may be needed and will be determined by pre- and post-dialysis PK by the DMC. Adjustments may be recommended by the DMC also for subjects on placebo who develop acute renal failure to prevent unblinding at the sites.

Study treatment discontinuation

Discontinuation of study treatment should be considered if:

- ALT or AST >8 x the upper limit of normal (ULN)
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (total bilirubin >2 x ULN or international normalized ratio >1.5) in the absence of reasonable alternative etiology
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- QTcF prolongation with QTcF >500 msec or an increase in QTcF of >60 msec over baseline (confirmed by 2 successive repeat measurements)

In addition, the investigator must permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the subject. The premature discontinuation of study drug might be triggered by an adverse event (AE), a diagnostic or therapeutic procedure, an abnormal assessment (eg, ECG or laboratory abnormalities), pregnancy,

or for administrative reasons, in particular noncompliance with the protocol or withdrawal of the subject's consent. The reason for study drug interruption or premature discontinuation must be clearly documented in the eCRF.

3.4.2 Subject withdrawal

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. In all cases of impending consent withdrawal, investigators will be given instructions to meet and discuss with the participant their options of continuing in the study. The investigator should ensure understanding and documentation of the reasons for the participant's desire to withdraw consent. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment. Unless the participant provides their written withdrawal of consent or there is other written documentation by the investigator confirming the participant's verbal intent to completely withdraw from the trial, participants should be followed for all protocol-specified evaluations and assessments. The reasons for subjects not completing the study will be recorded.

A subject may be withdrawn from the study if he or she is lost to follow-up. For subjects to be considered as lost to follow-up, 2 attempts should be made to contact the subject to return for the scheduled study visit. After 2 attempts, a certified letter should be sent to the subject's address requesting the subject to contact the investigator to schedule a follow-up assessment. If no reply is provided by the subject within 30 days of receipt of the certified letter, the subject can then be considered lost to follow-up.

3.4.3 Replacement policy

Subjects who withdraw from the study will not be replaced.

3.4.4 Stopping criteria

Dosing will be stopped in case of an unacceptable tolerability profile based on the nature, frequency, and intensity of observed AEs judged jointly by the investigator and the sponsor or as recommended by the DMC.

In the event of a study hold due to unacceptable tolerability, the sponsor will conduct an extensive safety and PK analysis and will communicate to stakeholders, including the Investigators, institutional review boards (IRBs)/independent ethics committees (IEC), and health authorities any potentially emergent safety information as well as the timing of planned resumption of dosing. Dosing and enrollment will not resume unless it is considered safe to do so after consultation with Investigators and health authorities and approval by IRBs/IECs.

4 STUDY POPULATION

4.1 Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening.

1. Able and willing to provide written informed consent.
2. Willing and able to comply with all study procedures.
3. Age ≥50 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for the SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. ≥90% oxygen saturation on room air and/or ≥94% oxygen saturation on oxygen administration at 2 L/min by nasal canula at the baseline visit.
8. Radiographic (X-ray or computed tomography scan, per local standard of care) evidence of pulmonary involvement consistent with COVID-19 at screening or baseline, per the judgment of the investigator.
    a. Note: If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator (CDC 2020).
10. CRP at screening >15 mg/L on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows:
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

4.2 Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock) or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or HIV infection.
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Treatment with anti-IL 6, anti-IL-6R antibodies, Janus kinase (JAK) inhibitors, or other immune modulators (unless considered part of local standard of care) in the past 30 days or 5 half-lives (whichever is longer) or plan to receive these agents as part of investigational clinical trials any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.
11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

4.3 Concomitant medications

All medications (prescription and over-the-counter) taken at the time of study screening will be recorded, with indication, route of administration, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Subjects are allowed to use paracetamol (up to 3 g/day) and/or contraceptives (oral or parenteral), and any medications needed for SOC at the local institution. Use of hydroxychloroquine/ chloroquine is not permitted. Use of other experimental treatments for COVID-19 is not permitted unless it is part of SOC at the local institution. SOC for COVID-19 will be documented at each site during the site activation visit; additionally, it will be documented if any restrictions on standard of care treatment administration were encountered due to resource limitations. The use of antiviral medications is permitted.

Concomitant medications used to treat chronic comorbid conditions per SOC are permitted, including but not limited to metered dose inhalers, corticosteroids if on stable doses for at least 30 days prior to screening, or sedative or anesthetic agents.

Concomitant medications initiated or stopped for an AE will be recorded.

Both losmapimod and its major metabolite, GSK198602, are in vitro inhibitors of human BCRP. There is a low risk of interaction of losmapimod with orally administered BCRP substrates with a narrow therapeutic index (eg, methotrexate, topotecan, rosuvastatin). Therefore, such co-administration is indicated only if the medical benefit is considered to outweigh the risk for toxicity, and careful monitoring for adverse effects of these agents is advised.

Losmapimod is a relatively potent in vitro inhibitor of the renal transporters MATE1 and MATE2-K, and it is possible that a mild inhibition of tubular secretion may contribute to the small rise in (model-adjusted geometric mean) serum creatinine observed clinically. GSK198602 is a relatively potent in vitro inhibitor of OAT3 and co-administration of sensitive OAT3 substrates is indicated only if the medical benefit is considered to outweigh the risk for toxicity. Careful monitoring for adverse effects of these agents is advised, especially for those with narrow therapeutic margin (eg, methotrexate, metformin).

4.4 Lifestyle restrictions

Subjects should not donate blood, sperm, or ova from the screening visit through 90 days after the last dose of study treatment.

4.4.1 Contraception requirements

Teratogenicity and effects on embryofetal survival were noted in rat and rabbit reproductive toxicology studies with losmapimod. Therefore, losmapimod should not be taken by women of childbearing potential who are not utilizing adequate contraceptive methods.

All women of childbearing potential and all males must practice effective contraception during the study from the time of the first dose of study medication until 90 days after last dose.

Women of child-bearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy/bilateral salpingectomy with or without hysterectomy;
- Post hysterectomy.

For the purposes of the study, effective contraception is defined as follows:

- Females of childbearing potential: Using 1 or more of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap).
- Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms.

Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Investigational drug and matching placebo

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Matching placebo tablets will be provided for oral administration.

The tablets are plain white, round, biconvex, film-coated tablets. The proposed dosing regimen is as a twice daily dose of 15 mg (2 × 7.5 mg tablets/dose BID). The proposed duration of treatment is for up to 14 days.

Subjects should take their dose of losmapimod or placebo with food whenever possible and with 240 mL of room temperature water.

5.2 Study drug packaging and labelling

Losmapimod tablets for oral administration are available as white, round, biconvex, plain, film-coated tablets containing 7.5 mg of losmapimod as the micronized base, GW856553X.

Losmapimod tablets also contain the inactive excipients microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, povidone K30, hypromellose, titanium dioxide (E171), and polyethylene glycol.

Placebo tablets are identical in appearance to losmapimod and have the same excipient ingredients as losmapimod but do not have the active compound.

All tablets are packed in opaque, white, square, high-density polyethylene bottles with induction sealed child-resistant closures.

Losmapimod must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature not to exceed 30°C.

5.3 Drug accountability

The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

The Investigator (or designee) will maintain an accurate record of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures by the sponsor. Any unused assembled unit doses will be retained until completion of the study.

After completion of the study, all unused supplies will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

5.4 Treatment assignment and blinding

5.4.1 Randomization and treatment assignment

A total of up to 410 subjects will be recruited into this study and will be randomized in a 1:1 ratio to 15 mg losmapimod (BID) or placebo using an interactive/web voice response system (IxRS) for randomization. The randomization list will be produced by a qualified randomization vendor and will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no) at enrollment.

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug. Randomized subjects will be sequentially assigned a unique subject number from the randomization list per the IxRS. From the time of randomization and throughout the duration of the study, subjects will be identified by their unique randomization number.

The authorized site personnel will prepare the appropriate study drug for each subject based on the randomization schedule. Treatment codes should not be broken except in emergency situations, ie, when knowledge of the treatment is essential for the immediate further management of the subject.

5.4.2 Blinding

This study will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to subject-level treatment assignment until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way.

5.4.3 Treatment compliance

All doses will be administered either in the hospital (anticipated during the first week of study treatment) or taken by the study participants on an outpatient basis.

The subject will bring the study treatment bottle to each visit (clinic or home assessment) for review by the site staff.

The study treatment bottles will be collected at the Day 14 visit whether in the hospital or outpatient or at the ET visit if prior to Day 14.

6 STUDY ASSESSMENTS

See Table 1 for the time points of the assessments.

If additional visits or blood draws are required beyond the planned visits in any part of the study, these visits or samples should be recorded in the eCRF as unscheduled visits prior to the subject's completion of the study.

6.1 Medical history

A complete medical history will be taken at Screening and is to include demographic information, prior medical illnesses and conditions, and surgical procedures for at least 3 months prior to screening. The medical history may be collected from medical records, if available, or during the physical examination.

The history of SARS-CoV-2 infection and symptoms at screening should be recorded; the details of how infection history will be assessed and recorded can be found in the Study Manual.

A chest X-ray or CT will be performed while the patient is hospitalized based on standard-of-care local assessment. The results are required for eligibility assessment to confirm radiographic evidence of COVID 19. If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

A pre-existing condition is one that is present prior to administration of study drug. Such conditions should be recorded as medical history. A pre-existing condition should be recorded as an AE or serious adverse event (SAE) only if the frequency, intensity, or nature of the condition worsens following administration of study drug.

6.2 Pharmacokinetic and pharmacodynamic assessments

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess PK. PK assessments will be performed as a substudy in all sentinel subjects to evaluate the PK of losmapimod in the population of subjects with COVID-19.

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess plasma biomarkers of response to COVID-19, including [redacted]

Procedures for collection, processing, and return of blood samples will be detailed in the Study Manual. Specifics of the analytical methods will be provided in separate documents.

Cytokines and chemokines will be evaluated using a multiplex assay. Details of the assay and specimen sampling will be provided in the Study Manual.

Viral load will be assessed by nasopharyngeal (preferred) or oropharyngeal swab or saliva assay as outlined in the Schedule of Assessments (Table 1). Diagnosis of COVID-19 should be confirmed by local PCR testing prior to randomization. Refer to the Study Manual for details on procedures and type(s) of diagnostic testing allowed.

PK should be measured weekly at C_{max} (4-5 hours) for subjects with renal insufficiency (eGFR ≤45 mL/min/ 1.73 m^2). For those subjects requiring dialysis, dose adjustment may be needed (see Section 3.4.1) and will be determined by pre- and post-dialysis PK by the DMC to prevent site unblinding.

6.3 Clinical status and symptoms

The investigator may consult with a relevant clinical or other specialist as appropriate per SOC.

6.3.1 Respiratory failure and survival assessment

Total number of study days free of oxygen supplementation and total number of study days free of respiratory failure will be evaluated. Refer to Section 6.5.1 for further details of vital sign collection.

- Note: Respiratory failure is defined as either need for mechanical ventilation (invasive or non-invasive) or high flow oxygen (defined by greater than 15 LPM flow of oxygen to maintain oxygen saturation between 90% and 95%), sustained for at least 48 hours, at any time during the study.

The reason for hospitalization and number of total study days of hospitalization and intensive care unit (ICU) utilization will be recorded.

Details of subject discharge (date of discharge and condition at discharge) from the hospital will be recorded.

Any significant deviation from standard of care due to limited resources will be documented.

Survival status at the end of the study period will be documented, including cause of death for any reason.

6.3.2 Clinical status assessment

Clinical status as outlined in the Schedule of Assessments (Table 1) will be measured on the following clinician-reported 9-point ranking scale (WHO):

- (8) death
- (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO)
- (6) intubation and mechanical ventilation
- (5) noninvasive ventilation or high-flow oxygen therapy
- (4) oxygen therapy but not requiring high-flow or non-invasive ventilation
- (3) hospitalized but not requiring oxygen therapy
- (2) discharged from the hospital but with limitation of activities
- (1) discharged from the hospital and without any limitation
- (0) no clinical evidence of the disease

Instructions for administration will be provided in the Study Manual.

6.4 Extended vital signs

Extended vital signs, including oxygen saturation and fraction of inspired oxygen (FiO_2) will be collected as specified in the schedule of assessments. Refer to Section 6.5.1 for further details of measurements.

6.5 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 7.

6.5.1 Vital signs

Evaluations of systolic and diastolic blood pressure, respiratory rate, and temperature will be performed throughout the study. In addition, oxygen saturation and FiO_2 will be assessed throughout the study. Oxygen administration (eg, room air or oxygen flow by nasal canula or facial mask) will be recorded. Vital signs will be performed after subjects have been supine for at least 5 minutes when possible.

Arterial blood gases may be performed if clinically indicated in some subjects but are not required for this study. If arterial blood gasses are measured, the results for arterial pressure of oxygen (PaO_2) should be reported at each measurement in the eCRF.

Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.2 Weight and height

Weight (kg) will be recorded at screening and the follow-up assessment (by alternative methods including outpatient visit). Height (cm) will be recorded and body mass index (BMI) calculated at screening.

BMI (kg/m^2) = weight (kg)/(height [cm]/100)^2

6.5.3 Physical examination

Physical examination (ie, inspection, percussion, palpation, and auscultation) is performed to determine eligibility and as clinically indicated during the study. Clinically relevant findings that are present prior to study drug initiation must be recorded with the subject's medical history. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.4 Electrocardiography

ECGs will be taken singly after 5 minutes in the supine position as specified in the schedule of assessments. The investigator will assess the ECG recording as 'normal', 'abnormal - not clinically significant', or 'abnormal - clinically significant' and include a description of the abnormality as required. The ECG parameters assessed will include heart rate, PR, QRS, QT, and QTcB and QTcF (calculated using Bazett's and Fridericia's method, respectively). ECGs will be performed to determine eligibility and during the study period only if clinically indicated. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.5 Laboratory assessments

Laboratory parameters

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded. Clinical relevance is defined as:

- Is accompanied by clinical symptoms
- Leads to dose modification of study treatment

- Requires significant changes, addition of, interruption of, discontinuation of a concomitant medication, therapy, or treatment
- Reflects a disease and/or organ toxicity

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria or those that is a result of an AE that has already been reported.

Blood and other biological samples will be collected for the following clinical laboratory tests; refer to the Study Manual for details of collection and analysis and information on central and local laboratories:

Lab	Tests
Hematology	Hemoglobin [including mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration], hematocrit, red cell count, total white cell count, and platelet count. Differential blood count, including: basophils, eosinophils, neutrophils, lymphocytes, and monocytes.
Chemistry and electrolytes	Sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, uric acid, total bilirubin[1], alkaline phosphatase, [redacted], [redacted], gamma-glutamyl transferase, and [redacted].
Glucose	Glucose
Urinalysis	Leucocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose. If there is a clinically significant positive result, urine will be sent for microscopy and/or culture.
Pregnancy[2]	hCG (urine or serum). If there is a clinically significant, positive result in urine, urine will be sent for confirmation.
[1]Conjugated bilirubin may be reported when total bilirubin is outside the reference range. [2]Pregnancy test for women of childbearing potential will be performed within 72 hours of first dose and if pregnancy is suspected during the study.	

6.6 Unscheduled visit

Unscheduled visits may be performed at any time at the subject's or the investigator's request and may include (but are not limited to) vital signs/focused physical examination, ECG, AE review, concomitant medications and procedures review, disease-related constitutional symptoms, and/or laboratory and biomarker assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

6.6.1 Early termination visit

When the investigator determines that study treatment will no longer be used, the investigator will perform the ET procedures and document the reason for discontinuation from study treatment in the eCRF. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the time of study treatment discontinuation, these tests need not be repeated. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment.

6.7 Alternative follow-up methods to site visits

Trial participants may not be able to come to the investigational site for protocol-specified or unscheduled visits. The sponsor may use alternative methods for safety assessments, including

telemedicine visits, telephone visits, and/or an alternative location for visits depending on the local or institutional standards.

7 SAFETY REPORTING

7.1 Definitions of adverse events

An adverse event (AE) is any untoward medical occurrence in a subject who is participating in a clinical study performed. The AE does not necessarily have to follow the administration of a study drug, or to have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or vital sign finding), symptom, or disease temporally associated with the study participation whether or not it is related to the study drug.

7.1.1 Recording of adverse events

Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.

7.1.2 Intensity of adverse events

The intensity of clinical AEs is graded 3-point scale as defined below:

- Mild: discomfort noticed but no disruption of normal daily activity;
- Moderate: discomfort sufficient to reduce or affect normal daily activity;
- Severe: inability to work or perform daily activity.

7.1.3 Relationship to study drug

For each AE, the relationship to drug as judged by the investigator:

- Probable;
- Possible;
- Unlikely;
- Unrelated.

7.1.4 Serious adverse events

A serious adverse event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatient hospitalization;
    - Note: COVID-19-related hospitalization or ICU admission is excluded from this definition, as SARS-CoV-2, COVID-19 infection, or pulmonary conditions attributable to COVID-19 infection are efficacy-related endpoints
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE.

7.1.5 Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is unexpected (nature or severity of which is not consistent with the applicable product information (eg, the Investigator

Brochure for losmapimod) and suspected (a reasonable possibility of causal relationship with investigational drug, regardless of the administered dose).

7.1.6 Reporting of serious adverse events

The investigator must report any AE that meets the SAE criteria (Section 7.1.4) to Medpace immediately (ie, within 24 hours after the site personnel first learn about the event) via electronic data capture (EDC). In the event that EDC entry is not possible (eg, system failure or access problems), the study site staff should complete the paper SAE report form and fax the form to Medpace Pharmacovigilance within 24 hours of awareness or call the Medpace safety hotline to report. The study site staff should update the EDC system as soon as it is available.

A full description of every SAE will need to be provided to Medpace Pharmacovigilance.

The following contact information should be used if reporting SAEs via fax or phone:

[redacted]

7.1.7 Follow-up of adverse events

All AEs will be followed until they have abated, returned to baseline status or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.1.8 Adverse events of special interest

An AESI (serious or non-serious) is one of scientific and medical concern for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Adverse events of special interest for this study include QTc prolongation as well as liver tests that meet the criteria for potential drug-induced liver injury (DILI), in accordance with the US Food and Drug Administration “Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation”.

Adverse event of special interest: QTc prolongation

A thorough QT study (PM1116628) was conducted in healthy volunteers who received losmapimod at 7.5 mg BID or 20 mg daily or with placebo administered for 5 days. At the 20 mg dose of losmapimod, the upper bound of the 90% CI of the ΔΔQT interval (change from baseline in QTcF compared with that for placebo) exceeded the 10 msec threshold at the 24-hour post-dose time point. For the 7.5 mg BID dose, the upper bound of the 90% CI of ΔΔQTcF exceeded the 10 msec threshold at multiple time points. No subjects experienced QTcF values >480 msec or QTcF changes from baseline ≥60 msec at any time in the study. Although the upper bound of the 90% CI exceeded the 10 msec regulatory threshold of concern in the primary pharmacodynamic analysis, it was determined by GSK that there was no clinically relevant effect on the QT interval, as there was no clinically relevant concentration QTc effect using standard placebo/baseline subtracted measured QTc data. Additional information on the QTc interval and its behavior, as demonstrated in the large cohort of patients with ACS treated with losmapimod (PM1116197), supported the lack of a QT effect. PK/PD modeling using the raw QTcF and plasma concentration data showed that at plasma losmapimod concentrations 4 times the exposure at the therapeutic dose (7.5 mg BID) (ie, at exposures approximately 2-fold higher than 15 mg BID, the predicted upper bound of the 90% CI of ΔΔQTcF) did not exceed 10 msec, and the predicted median ΔΔQTcF was less than 5 msec. Further details are presented in the Investigator Brochure. No drug effect on QT prolongation of losmapimod over placebo has been documented in any of the phase 2 or the one phase 3 trial completed so far.

Study drug should be discontinued for subjects who meet the QTc prolongation criteria as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.6). Further safety steps should be taken to closely observe and follow-up the event until resolution and treatment initiated per local standard of care.

Adverse event of special interest: Drug-induced liver injury

The following 3 laboratory value criteria must be met for potential DILI, or "Hy's Law":

- An elevated alanine transaminase or aspartate transaminase laboratory value that is ≥3 × ULN
- An elevated total bilirubin laboratory value that is ≥2 × ULN
- An alkaline phosphatase laboratory value that is <2 × ULN

Study drug should be discontinued for subjects who meet the laboratory criteria for potential DILI as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.6). Further safety steps should be taken to closely observe and follow-up the event until resolution. These steps include, but are not limited to:

- Making every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver tests
- Obtaining a more detailed history of symptoms and prior or concurrent disease, concomitant medication use, alcohol use, recreational drug use, and special diets
- Repeating liver enzyme and serum bilirubin tests twice weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic
- Obtaining viral hepatitis serology
- Considering liver imaging and/or hepatology consultation

7.2 Pregnancy

7.2.1 Teratogenicity

If a woman becomes pregnant when on study drug, study drug should be permanently discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known. In the event of pregnancy in the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

7.2.2 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during study drug administration or until follow-up, must be reported within 24 hours of the investigator's knowledge of the event to the sponsor. The Investigator must make every effort to follow the pregnant partner of a male subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the SAE form.

8 STATISTICAL METHODOLOGY AND ANALYSES

8.1 Statistical analysis plan

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the interim analysis (IA). The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

All safety and statistical programming will be conducted using SAS 9.4 for Windows or newer (SAS Institute Inc., Cary, NC, USA), and other statistical programming/sample size calculation software as necessary.

8.1.1 Determination of sample size

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of up to 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an IA will be conducted after approximately 206 subjects (103 in the losmapimod arm, and 103 in the placebo arm) have completed the Day 28 visit, to assess early futility, using the rules specified in Section 8.9.

8.1.2 Analysis methods

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

Summaries of change from baseline variables and GMR will include only subjects who have both a baseline value and corresponding value at the post-baseline time point of interest. Baseline will be defined as the last value prior to initiation of blinded treatment.

Where appropriate, descriptive statistics may be presented with 95% CI.

8.1.3 Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

8.2 Protocol violations/deviations

Protocol deviations will be identified based on conditions related to the categories below:

- Protocol entry criteria
- Forbidden concomitant medications
- Missing evaluations for relevant endpoints

- Other protocol deviations occurring during study conduct.

Major protocol deviations will be identified before study closure and listed where appropriate.

8.3 Missing, unused and spurious data

All missing or incomplete safety and PD data, including dates and times, are treated as such. Missing test results or assessments will not be imputed, and as such, are assumed missing-completely-at-random (MCAR).

For laboratory data, values below the limit of quantitation (recorded as "< LLQ") will be set to half that limit.

Censoring rules for time-to-event endpoints will be discussed in the SAP. Imputation rules for the primary endpoint will be discussed in the SAP. The handling of any missing, unused, and spurious data will be documented in the SAP or the clinical study report.

8.4 Subject disposition

Subject disposition will be listed by subject.

The following subject data will be summarized:

- number and percentage of subjects screened,
- number and percentage of subjects enrolled,
- number and percentage of subjects completed,
- number and percentage of subjects included in safety population

A subject who completed the study is defined as a subject where the last PD assessment was completed.

8.5 Baseline parameters and concomitant medications

8.5.1 Demographics and baseline variables

Demographic and other baseline characteristics will be summarized using descriptive statistics for the treatment group and overall.

8.5.2 Medical history

Medical history will be listed.

8.5.3 Prior and concomitant medications

Prior and concomitant medications will be listed by international nonproprietary names, dose, regimen, route and for which indication it was prescribed.

8.5.4 Treatment compliance/exposure

Exposure to study treatment is described in terms of duration of treatment.

8.5.5 Safety and tolerability endpoints

The safety data set is used to perform all safety analyses.

Baseline is defined as the last value prior to dosing. Change from baseline will be calculated for all continuous safety parameters.

8.5.6 Adverse events

The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used for the coding of AEs. The overall incidence of AEs will be displayed by MedDRA system organ class, preferred term, and treatment group.

All AEs will be displayed in listings. In addition, SAEs and treatment-emergent AEs (TEAEs) leading to discontinuation of study drug will be listed.

Treatment-emergent AEs will be defined as an event that occurs on or after the first dose of study drug or the worsening of a preexisting condition on or after the first dose of study drug. If a subject does experience an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (ie, it is reported with a new start date) after starting administration of the specific treatment, and prior to the start of another treatment, if any. All TEAEs collected during the investigational period will be summarized.

The number of TEAEs and the number of subjects with at least 1 TEAE will be summarized by treatment group for the following:

1. System organ class and preferred term;
2. System organ class, preferred term, and maximum severity
3. System organ class, preferred term, and maximum drug relatedness.

8.5.7 Vital signs

Reported values and change from baseline values of supine blood pressure and pulse rate and temperature will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will be presented by treatment group. Vital sign variables will be listed. Values outside the reference range will be flagged in the listing.

Vital sign results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.5.8 ECG

ECG values will be listed.

8.5.9 Clinical laboratory tests

Reported values and change from baseline values of clinical laboratory variables will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will also be presented by treatment group. Clinical laboratory values will be listed.

Clinical laboratory test results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.6 Primary endpoints

1) Assuming p_t is probability of outcome in the losmapimod arm; p_c is the probability of outcome in the control arm

Study hypothesis: H_0: $= p_t - p_c = 0$

H_1: $= p_t - p_c > 0$

Assuming p_t=0.18, p_c=0.30, we can restate the hypothesis as

H_0: $\theta = \theta_0 = 0$

H_1: $\theta = \theta_1 = -0.12$

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from a regression model, adjusted for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP. An interim analysis to assess futility analysis—and potential sample size re-estimation—is discussed in Section 8.9. All results will be summarized descriptively by treatment arm and

expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p-values.

8.7 Secondary endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and post-baseline will be modelled using regression models appropriate for ordinal data. Details will be provided in the SAP.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

Total number of study days: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, with age group as a covariate with stratification factors as covariates. Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a regression model, adjusting for stratification factors, sex, and CRP. Full details of the regression model will be provided in the SAP.

[redacted]

8.9 Interim analysis for futility and sample size re-estimation

An interim analysis (IA) will be conducted after 206 subjects have been enrolled (approximately 103 in each of the losmapimod and placebo arms) and have been treated for 14 days with 28 days of follow-up. Only futility—and potential sample size-estimation—will be assessed by the DMC at the IA. The O'Brien-Fleming group sequential method will be used to adjust beta for interim testing. Table 6, Figure 1, Figure 2, and Figure 3 contain sample size requirements, boundary information, and stopping probabilities for testing futility on the primary endpoint at both the IA and final analysis. P-values are single-sided. Sample size estimation was done using SAS® (Proc SeqDesign, Version 4.0). The study will not be stopped for efficacy at the IA.

Table 6: Boundary Values for Interim Analysis Futility Assessment

Analysis Stage	Sample Size		Beta: Futility			Alpha: Efficacy		
	Losmapimod	Control	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under null hypothesis)	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under alternative hypothesis)
Interim Analysis	103	103	-0.67873 (0.24865)	-0.04017	0.75135	Not applicable	--	0.08871
Final Analysis	205	205	-1.91358 (0.02784)	-0.08009	0.97500	--	--	0.20000

Overall alpha=0.025 (1-sided); overall power=80%.
Abbreviations: MLE: maximum likelihood estimate.

Figure 1: Acceptance Region (Standardized-Z Scale)

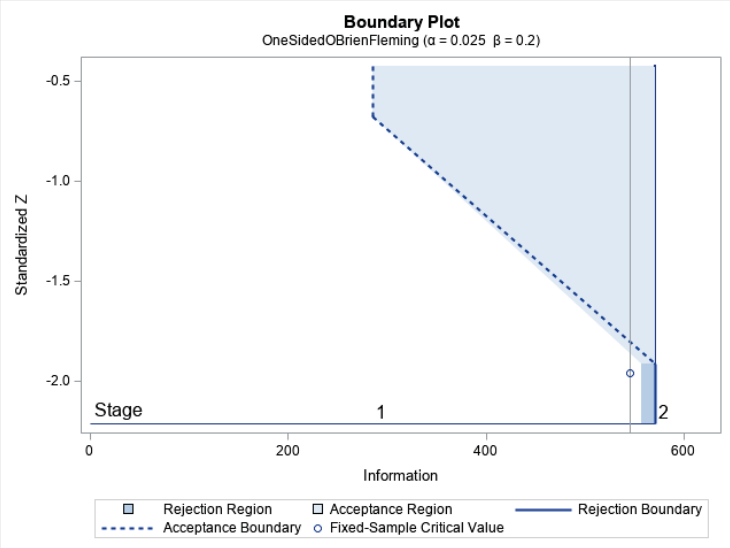


Figure 2: Acceptance Region (P-value)

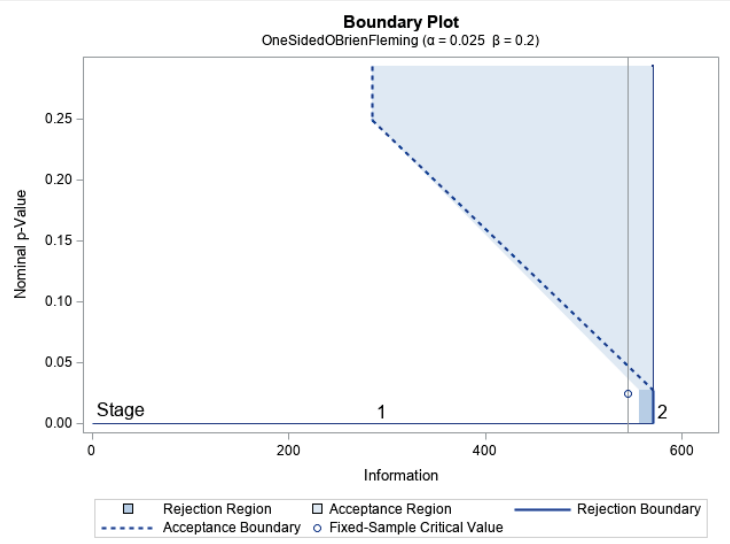
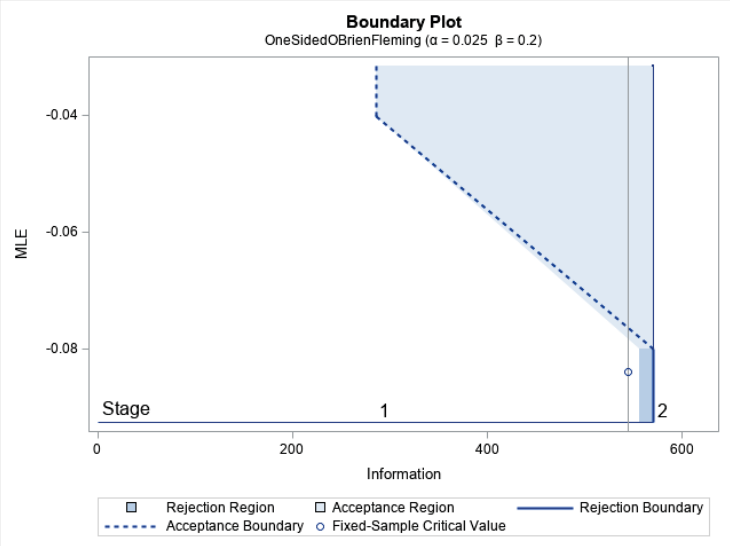


Figure 3: Acceptance Region (Maximum Likelihood Estimate)



8.9.1 Futility Testing

The process is as follows:

1. Futility at IA: If standardized z-value (MLE: maximum likelihood estimate) of $\mathbf{p_t - p_c}$ is ≥ -0.67873 (-0.04017), or p-value ≥0.24865, then stop for futility. Probability of stopping for futility under null hypothesis is ~0.75.
2. At Final Analysis: The final p-value is tested at an adjusted alpha of 0.02784.

8.9.2 Sample Size Re-estimation

The Chen-DeMets-Lan method (Chen et al 2004) will be used for unblinded sample size re-estimation, with IA futility stopping boundaries created using O'Brien-Fleming method, as described above. Wald conditional probabilities will be calculated using the actual observed proportion from both treatment arms.

The maximum sample size allowed is 820 subjects. Sample size will be increased only if the observed data at the IA are promising; that is, if the conditional power is ≥50% and <80%. Sample size will be increased to ensure a target conditional power of at least 80%.

There is only one IA, and conditional power at IA must lie between 50% and 80% for sample size re-estimation to be implemented. These 2 conditions ensure that the target Type I error of 2.5% is not exceeded by increasing sample size to meet the original target power (Chen et al 2004).

Sample size re-estimation will not be done in the following 2 instances:

- If conditional power is <50%, then sample size re-estimation will not be done, and decision on futility will be made based on boundary values from the O'Brien-Fleming method.

- If conditional power is ≥80%, then a sample size re-estimation will not be done, as the study will be considered sufficiently powered to detect the effect of interest at the final analysis.

A Wald Test statistic will be calculated and compared with the boundary value for futility (see Table 6). If the Wald Test statistic lies in the acceptance region then the study will stop for futility.

All calculations for the IA and the unblinded sample size re-estimation will be conducted by an external, unblinded statistician. The DMC will review the results in a closed session and make appropriate recommendations to the Sponsor afterwards.

8.9.3 Possible Recommendations by the DMC

After reviewing the results of the IA, the DMC may select 3 or more possible recommendations, based on the test statistics obtained at the IA:

- Stop for Futility - Stop trial early due to strong evidence for futility due to test statistic being in the futility region.
- Continue without change - Continue until next look with no changes due to test statistic not being in the futility region or the conditional power being <50% or ≥80%.
- Add required additional sample size, n, without exceeding the maximum sample size of 820 and continue the trial.

At the final analysis, 2 recommendations can be made:

- Efficacy is demonstrated.
- Efficacy is NOT demonstrated.

8.10 Data monitoring committee

An independent DMC composed of experts external to the sponsor and investigators will monitor the safety of the trial participants and the conduct of the trial on an ongoing basis and will be responsible for the interim analysis and recommendations regarding sample size re-estimation. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will include at least 2 external clinicians with expertise relevant to the evaluation of COVID-19, such as Critical Care, Pulmonology, or Infectious Disease, as well as at least 1 independent biostatistician with expertise in clinical trial design and statistical methods for clinical research and analysis of research data including interim analysis.

Details on the composition of the DMC and the schedule and format of DMC meetings and data outputs will be presented in the DMC charter. The DMC will review, at a minimum, data for the sentinel subjects prior to continued study drug dosing and cumulative safety data at regular intervals based on subject enrollment.

The safety evaluations will be detailed in the DMC charter and will include review of conventional safety variables, such as serious adverse events. Any safety event that requires unblinding will be immediately reported to the DMC and to the FDA. The DMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of subjects. The DMC will also review the efficacy data at the IA and make recommendations based on the futility criteria and for sample size re-estimation if needed (see Section 8.9). After reviewing study data, the DMC will make recommendations regarding continuation, termination, or modification of the study. The DMC may also perform ad hoc review PK of subjects who require dialysis.

8.11 Type I error for testing key study endpoints

The overall Type I error of the study will be controlled at 0.025 for 1-sided tests of hypotheses for the following key study endpoints, using an appropriate alpha control method:

1. Proportion of progressors to death or respiratory failure by Day 28
2. Change in clinical status using the 9-point WHO scale at Day 14
3. Change in clinical status using the 9-point WHO scale at Day 7
4. Oxygen-free days by Day 28

Further details on the methodology will be provided in the SAP.

9 GOOD CLINICAL PRACTICE, ETHICS AND ADMINISTRATIVE PROCEDURES

9.1 Good clinical practice

9.1.1 Ethics and good clinical practice

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice (GCP), the protocol, and all applicable regulations.

9.1.2 Ethics committee / institutional review board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date on which approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.1.3 Informed consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation. Following discussion of the study with site staff, subjects or their legally authorized representative will be required to provide one of the following:

1. Sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records; OR
2. If a subject is in isolation due to COVID-19 and institutional infection control policy would prevent removal of a document signed by the subject from their hospital room, then one of the following methods will be used to obtain informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable:
    - Obtain the informed consent electronically; OR
    - Obtain the informed consent by teleconference/video conference in alignment with local regulatory guidance.

    How the consent was obtained and reason why it was obtained using that particular method should be documented in the eCRF. The trial record at the investigational site should document how it was confirmed that the subject signed the consent form (ie, either using attestation by the witness and investigator or a photograph of the signed consent).

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

9.2 Data handling and record keeping

This study will be conducted according to ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

Study site personnel will enter subject data into the EDC program. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with standard data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After final database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. Medpace will maintain a duplicate CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9.3 Access to source data and documents

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.4 Investigator's obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject

(or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.
To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.
The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.6 Financial disclosure and obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
Neither the sponsor nor Medpace is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor Medpace is financially responsible for further treatment of the subject's disease.

9.7 Investigator documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- FDA Form 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- A curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site.

9.8 Study conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.9 Adherence to protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.10 Adverse events and study report requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.11 Investigator's final report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.12 Records retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.13 Publications

After completion of the study, the data will be submitted for reporting at a scientific meeting and for publication in a peer-reviewed scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld. Further terms concerning publication will be set forth in the clinical trial agreement entered into by the sponsor, the principal investigator, any vendors, and the institution.

10 STUDY MANAGEMENT

The administrative structure will include a DMC (see Section 8.10).

10.1 Monitoring

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor regularly monitors the trial remotely and will periodically visit the investigator based on local restrictions, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation remotely, and discussion of the conduct of the study with the investigator and personnel. All relevant source documents will be uploaded into the IBM electronic system or access to the electronic medical records will be provided for remote monitoring purposes.
All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.2 Inspection of records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.
The investigator should promptly notify the sponsor and Medpace of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.3 Management of protocol amendments and deviations

10.3.1 Modification of the protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

10.3.2 Protocol deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change of the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.
A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the subject being withdrawn from the study. A list of major protocol deviations will be compiled prior to the start of the study.
Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.4 Study termination

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

the study be required, the sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed written explanation. Fulcrum and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The sponsor has no plans to provide study drug to subjects after study closure or termination. The obligations to provide study results for subjects and reports to IRB/IEC shall continue as required by applicable laws and regulations.

At any time, the sponsor, the investigators, or the IRBs/IECs may terminate this study for reasonable cause. Conditions that may lead to reasonable cause and warrant termination include, but are not limited to the following:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the regulatory authority

Written notification that includes the reason for the clinical study termination is required.

The end of the study is defined as the date on which the last subject completes the last visit (includes the safety follow-up visit).

10.5 Final report

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study reports. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study reports, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

Short Title:	Losmapimod safety and efficacy in COVID-19 (LOSVID Study)
Version:	1
Date:	29-May-2020
Study number:	FIS-001-2020
IND number	149208
Sponsor:	Fulcrum Therapeutics 26 Landsdowne St., 5th floor Cambridge, MA 02139 USA
Sponsor signatory:	[redacted], MD

Information described herein is confidential and may be disclosed only with the express written permission of the sponsor.

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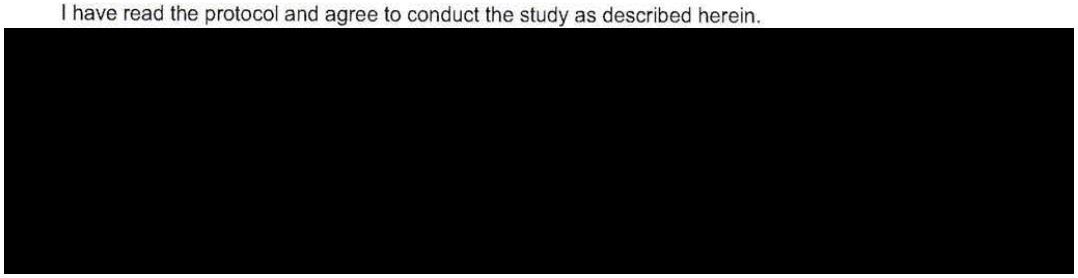
Clinical Trial Leader	[redacted] MD Telephone: [redacted] e-mail: [redacted]
Drug Safety Physician	[redacted] MD Teleph[redacted] e-mail: [redacted]

SIGNATURE PAGE - INVESTIGATOR

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I have read the protocol and agree to conduct the study as described herein.



SIGNATURE PAGE - SPONSOR

Fulcrum Therapeutics

Study Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)

I approve this protocol on behalf of the sponsor.

[redacted]
Chief Scientific Officer

DocuSigned by:
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Signature

5/31/2020

Date (dd Mmm yyyy)

[redacted], MD
Senior Vice President
Head, Clinical Development

DocuSigned by:
[redacted]
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Signature

5/31/2020

Date (dd Mmm yyyy)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
BID	*bis in diem* / twice per day
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	Maximum concentration
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	disease caused by novel coronavirus
CRP	C-reactive protein
CXCL13	chemokine ligand 13
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
ET-1	endothelin
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSGS	focal segmental glomerulosclerosis
FSHD	facioscapulohumeral muscular dystrophy
GCP	Good Clinical Practice
[redacted]	[redacted]
GSK	GlaxoSmithKline
H5N1	highly pathogenic Asian avian influenza A, subtype H5N1
HIV	human immunodeficiency virus
HMGB-1	high mobility group box protein-1
hsCRP	high-sensitivity C-reactive protein
HSV-1	herpes simplex virus-1
IA	interim analysis

ICAM-1	intercellular adhesion molecule-1
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	independent ethics committee
IL-6	interleukin-6
IND	investigational new drug application
IRB	institutional review board
IxRS	interactive/web voice response system
JAK	Janus kinase
[redacted]	[redacted]
LLQ	lower limit of quantitation
LS	least square
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusions
MCAR	missing-completely-at-random
MedDRA	Medical Dictionary for Regulatory Activities
OAT	organic anion transporter
PAO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PH	proportional hazards
PK	pharmacokinetics
PO	*per os* / orally
PPS	per protocol set
QTcB	QT corrected interval using Bazett's formula
QTcF	QT corrected interval using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SE	standard error
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID Study)

Short Title

Losmapimod safety and efficacy in COVID-19 (LOSVID Study)

Background & Rationale

Poor prognosis for many COVID-19 patients has been attributed to an exaggerated inflammatory response following SARS-CoV-2 infection. This hyperactivated immune response is associated with pulmonary edema, acute respiratory distress syndrome (ARDS), and cardiomyopathy that may lead to increased mortality in the sickest patients.

p38 mitogen-activated protein kinase (MAPK) is an important mediator of inflammation, and extensive nonclinical data have linked p38 to the hyper-inflammatory response to viral infections.

Losmapimod is a potent and selective p38α/β MAPK inhibitor that is currently in Phase 2 clinical trials for the treatment of facioscapulohumeral dystrophy and has previously been administered to more than 3600 adult healthy volunteers and subjects including participants in a Phase 3 trial. Many of these trials were for chronic inflammatory indications for which the compound exhibited a favorable safety profile not significantly different from placebo. These trials have also indicated that losmapimod has good exposure after oral dosing, robust target engagement, and acutely reduces inflammatory biomarkers that have been associated with poor prognosis in COVID-19, including C-reactive protein (CRP) and interleukin-6 (IL-6). Additionally, a clinical study recently concluded that losmapimod restored the normal immune response of older subjects (median 69 years, range: 65, 77 years) following a viral challenge. Further information is available in the losmapimod Investigator Brochure.

Losmapimod is attractive as a potential therapeutic option for COVID-19:

- p38 inhibition improves survival in mouse SARS-CoV-1 models and other nonclinical viral models, suppressing the exaggerated immune response to acute infection.
- Losmapimod acutely has reduced exaggerated inflammatory responses in human trials for multiple inflammatory diseases, including IL-6 and CRP, and has normalized immune response to viral or other acute inflammatory challenges in older subjects.
- Losmapimod is a clinical-stage, potent, and selective p38 inhibitor with extensive human experience and extensive evidence of safety and tolerability, including in a Phase 3 clinical trial in acute myocardial infarction.
- p38 inhibition has the potential to reduce hypothesized deleterious effects of increased angiotensin II in COVID-19, such as vasoconstriction, increased inflammation, cardiac arrhythmias, and organ failure.

Objectives and Endpoints:

All study objectives will be evaluated in subjects diagnosed with COVID-19:

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale: • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation Total number of study days in ICU Total number of study days hospitalized Total number of respiratory failure-free study days Percentage of subjects discharged from the hospital
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive

Objectives	Endpoints
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

Design

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥50 years old who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.

Subjects who sign informed consent and meet all entry criteria (listed below) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg orally (PO) twice daily (BID); OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim "sentinel" safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter.

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site.

Investigational drug

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Comparative drug

Matching placebo tablets will be provided for oral administration.

Inclusion criteria

1. Able and willing to provide written informed consent.
2. Willing and able to comply with all study procedures.
3. Age ≥50 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. ≥90% oxygen saturation on room air and/or ≥94% oxygen saturation on oxygen administration at 2 L/min by nasal canula at the baseline visit.
8. Radiographic (X-ray or computed tomography scan, per local standard of care) evidence of pulmonary involvement consistent with COVID-19 at screening or baseline, per the judgment of the investigator.
    a. Note: If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator

10. CRP at screening >15 mg/L on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows:
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock) or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or HIV infection.
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Treatment with anti-IL 6, anti-IL-6R antibodies, Janus kinase (JAK) inhibitors, or other immune modulators (unless considered part of local standard of care) in the past 30 days or 5 half-lives (whichever is longer) or plan to receive these agents as part of investigational clinical trials any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.

11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

Sample size justification

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an interim analysis (IA) will be conducted after approximately 206 subjects (103 in each of the losmapimod and placebo arms) have completed the Day 28 visit, to assess futility.

Statistical methodology

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the IA. The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% confidence intervals.

Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

Primary endpoint

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables. An interim analysis to assess futility analysis—and potential sample size re estimation—will be conducted. All results will be summarized descriptively by treatment arm and

expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p values.

Secondary endpoints

Clinical status at Day 7 and Day 14: percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects for each of the items in the scale will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variable.

Total number of study days: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, with age group as a covariate with stratification factors as covariates. Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables.

Table 1: Visit and Assessment Schedule

	SCR	Treatment Period											FU[14]		ET
Time point / Assessment[1]	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Informed consent	X														
Demography	X														
Inclusion and exclusion criteria	X	X													
Medical history, including COVID-19 clinical diagnosis[2]	X														
Chest X-ray/CT scan	X[3]	X[3]													
Study drug administration:															
Randomization		X													
Losmapimod or placebo PO BID		X	X	X	X	X	X	X	X	X	X	X			
Pharmacodynamics:															
Drug levels/PK[4]		P, 4-5h	4-5h	4-5h	4-5h	4-5h	4-5h	4-5h				4-5h			X
[redacted]															
Clinical status and symptoms:															
Respiratory failure and survival assessment[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical status assessment per WHO 9-point scale[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral presence and viral load by central testing (nasopharyngeal [preferred] or oropharyngeal swab)[7]		X	X (sentinel only)[7]	X (sentinel only)[7]	X (sentinel only)[7]			X							X
Confirmation of COVID-19 diagnosis (nasopharyngeal [preferred] or oropharyngeal swab)	X[2]	X (PR)[2]													
Oxygenation and FiO_2[8]	X	X	X	X	X	X	X	X	X	X	X	X			X

	SCR	Treatment Period											FU[14]		ET
Time point / Assessment[1]	-3d to -1d	D1 (base-line)	D2	D3	D4	D5	D6	D7	D8	D10	D12	D14	D21 (± 3d)	D28 (± 3d)	
Safety assessments:															
Physical examination	X														X
Weight/height[9]	X												X		X
Hematology, chemistry safety labs[6]	X	X	X		X			X		X		X	X		X
CRP[6]	X														
Urinalysis[10]	X							X							
Urine or serum β-hCG (female subjects only)	X[11]												X		X
ECG[12]	X							X							
HR, BP, RR, temperature[8]	X	X	X	X	X	X	X	X	X	X	X	X			X
(S)AEs[13]	X														X
Concomitant medications (including SOC)	X														X

AE = adverse event; BP = blood pressure; COVID-19 = novel coronavirus; HR = heart rate; P = pre dose; PAO_2 = partial pressure of oxygen; PR – pre-randomization; RR = respiratory rate; sent = sentinel; SOC = standard of care; SCR = screening.

Note: All screening assessments are to be performed before dosing. If procedures required at any time point have already been performed as part of routine clinical care, these assessments do not need to be repeated, and information will be collected and entered on the eCRF from the subject's medical records. Unscheduled visits can take place at any time at the discretion of the site to check for new AEs/SAEs or to repeat key missed assessments or for other reasons.

[1] The order of assessments can be performed at the discretion of the investigator once informed consent is obtained.

[2] COVID-19 diagnosis to be confirmed by local testing (PCR) before randomization and first dosing.

[3] To be performed while hospitalized based on standard-of-care local assessment. Result required for eligibility assessment to confirm radiographic evidence of COVID-19. If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

[4] PK assessments will be performed as a substudy in all sentinel subjects. For those subjects requiring dialysis, a single pre- and post-dialysis PK should be obtained for review by the DMC to decide if dose adjustment is needed. PK should be measured weekly at C_{max} (4-5 hours post dose) for subjects with renal insufficiency when possible.

[redacted].

[6] Assessments for clinical/respiratory status, progression, and safety serum chemistry and hematology tests to be performed and samples to be collected while hospitalized based on standard-of-care local laboratory assessments and after discharge from the hospital by home visit or outpatient clinic visit or telemedicine call. For subjects who are discharged to home or other outpatient setting after initial hospitalization, the assessments and laboratory samples can be obtained less often but not less than at least once weekly. CRP result required to determine eligibility are based on local laboratory results at screening.

[7] Viral load testing will be collected daily for the first 4 days using local testing in the first 10 enrolled subjects as part of the sentinel safety assessment. For all subjects, including the sentinel subjects, swabs or other sample collection for central viral load testing will be collected on D1 pretreatment and on D7 or earlier if being discharged from the hospital prior to D7.

[8] Vital signs will be performed after subjects have been supine for at least 5 minutes when possible. Vital signs to include oxygen saturation; PaO_2 should be recorded if available from blood gases obtained as part of SOC; oxygen administration should also be recorded (eg, room air or oxygen flow by nasal canula or facial mask or endotracheal tube). For subjects who are discharged to home or other outpatient setting after initial hospitalization, assessments may be obtained less often but at least once per week in the outpatient clinic or at home.

[9] Height assessed at screening only; can be by self-report or from medical records. Weight is an actual recording.
[10] Urinalysis will be performed during the study period only on Day 7 and on any other day only if clinically indicated.
[11] Pregnancy testing to be conducted within 72 hours of the first dose of study treatment.
[12] Standard 12-lead ECGs will be performed after the subject has been supine for at least 5 minutes if possible. ECGs will be performed at Day 7 in all subjects and at any other time during the study if clinically indicated.
[13] Adverse events and SAEs will be assessed from the time the subject signs the ICF through the D28 follow-up visit.
[14] Outpatient assessments to be conducted via telemedicine or outpatient clinic. Outpatient laboratory assessments to be completed at outside local laboratory or home or outpatient visit.

1 BACKGROUND AND RATIONALE

1.1 Scientific rationale for investigation of losmapimod in COVID-19

COVID-19 is a severe pandemic disease with high mortality particularly in older individuals, due to infection with the SARS-CoV-2 coronavirus. The therapeutic hypothesis for the use of losmapimod in COVID-19 disease is that increased mortality and severe disease is caused by p38 mitogen-activated protein kinase (MAPK)-mediated exaggerated acute inflammatory response resulting from SARS-CoV-2 infection. The older population is especially at risk of severe disease and death upon infection with SARS-CoV-2. The hyperactivated immune response in COVID-19 shares features of the cytokine storm syndrome and appears to be responsible for the severe pulmonary edema, ARDS, and cardiac and renal disease responsible for most of the severe morbidity and mortality.

The proposal to develop losmapimod, a potent, specific, and bioavailable p38α/β inhibitor, for treatment of COVID-19 is based on the following rationale:

(1) Nonclinical work has shown that older mice infected with SARS-CoV-1 develop much more severe disease than younger ones, and that treatment with a p38 MAPK small molecule inhibitor greatly reduced their mortality when given after viral inoculation; similar survival benefit of p38 MAPK inhibition has been seen in animal models of severe H5N1 influenza and HSV-1.

(2) Nonclinical work has shown that p38 MAPK inhibition reduces viral load in several experimental models with coronaviruses, including mouse hepatitis virus, human CoV-229E, transmissible gastroenteritis virus, and Middle East respiratory syndrome virus.

(3) p38 MAPK is proposed to play a critical role in the development of ARDS, including regulating the expression and activity of inflammatory mediators such as ICAM-1, HMGB1, and ET-1, neutrophil chemotaxis and apoptosis, the balance of Treg/Th17 cells, and pulmonary endothelial cell apoptosis.

(4) Clinical investigation showing that excessive acute inflammation in response to external stressors in older individuals, including viral antigen challenges, hinders the specific immune response to infection; many of the excessive inflammatory mediators associated with this aberrant immune response in older individuals are associated with activation of the p38 MAPK pathway.

(5) Treatment with losmapimod in older subjects restored the normal immune response to viral antigen challenge and improved the resolution of acute inflammation.

(6) Treatment of various inflammatory diseases with losmapimod, including active rheumatoid arthritis (RA), acute myocardial infarction, and chronic obstructive pulmonary disease (COPD) resulted in significant reduction in markers of acute inflammation, including interleukin-6 (IL-6), C-reactive protein (CRP), chemokines such as CXCL13, and other markers (see Table 5 for further details).

(7) Losmapimod may be beneficial in COVID-19 treatment via reduction of the damaging effects of angiotensin II (Ang II). Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS-CoV viruses and is expressed in the lung and the heart. Upon infection with SARS-CoV-2, there is internalization of and depletion of ACE2. ACE2 converts Ang II into angiotensin 1-7 (Ang 1-7), which counterbalances the vasoconstrictive and pro-inflammatory effects of Ang II. Ang II is significantly elevated in COVID-19, and the levels are positively correlated with viral load and acute lung injury (Liu Y et al, 2020). Blocking the p38 MAPK pathway in nonclinical models has been

shown to reduce many of the adverse effects of elevated Ang II, resulting in lower frequency of cardiac arrhythmias, renal failure, and hypertension.

p38 inhibitors have been explored extensively in clinical trials for numerous chronic inflammatory indications, as summarized in the Investigator Brochure. Losmapimod has been extensively tested in humans and found to be generally well tolerated, including in over 3600 adult healthy volunteers and subjects in 11 different indications. The 15 mg oral (PO) twice per day (BID) dose proposed for the COVID-19 Phase 3 study has been shown to provide robust and sustained inhibition of the p38 MAPK pathway systemically and in tissues, specifically in skeletal muscle needle biopsies of subjects with facioscapulohumeral muscular dystrophy (FSHD). This dose of losmapimod was shown experimentally in older (median 69 years, range: 65, 77 years) human volunteers to restore the normal immune response to viral challenge and improve the resolution of acute inflammation. Furthermore, losmapimod has been shown to significantly reduce markers of hyperactive acute innate immune inflammation in the context of acute myocardial infection, RA, and COPD in clinical trials as listed below:

1- Single-dose study in 50 subjects with RA (RA 3103730). Treatment with losmapimod (N=38) reduced levels of IL-6 compared with placebo (N=12). Losmapimod was dosed as follows: 7.5 mg: 13 subjects; 20 mg: 12 subjects; 60 mg: 13 subjects. Analysis of serum IL-6 at 3 hours post dose showed significantly lower levels with losmapimod than with placebo (Table 2).

Table 2: Change from Baseline in IL-6 Serum Levels with Increasing Single Doses of Losmapimod in Subjects with Rheumatoid Arthritis

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to placebo	95% CI
Placebo	0.92	0.60, 1.41		
Losmapimod 7.5 mg	0.41	0.26, 0.63	0.45	0.24, 0.82
Losmapimod 20 mg	0.43	0.27, 0.68	0.47	0.25, 0.88
Losmapimod 60 mg	0.38	0.25, 0.57	0.41	0.23, 0.75

Abbreviations: CI = confidence interval.

2- Repeated-dose study in subjects with acute coronary syndrome (ACS; PM1111810). A total of 535 subjects with non-ST elevation myocardial infarction were randomized to an initial dose of 7.5 or 15 mg of losmapimod followed by 7.5 mg PO BID (N= 388) or matching placebo (N=138) for 12 weeks. Results showed that relative to placebo, losmapimod significantly suppressed CRP and IL-6 acutely at the 24- to 36-hour assessments (Table 3).

Table 3: Change from Baseline in hsCRP and IL-6 with 7.5mg PO BID Losmapimod Over Placebo in Subjects with Acute Coronary Syndrome

Parameter	Placebo (N=138)	All losmapimod (N=388)	P value
hsCRP at 72 hours or discharge (nmol/L)	110.8 (83.1-147.7)	64.1 (53.0-77.6)	<0.05
IL-6 at 24 hours (ng/L)	10.6 (8.6-13.1)	6.6 (5.8-7.4)	<0.05

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6.

3- Repeated-dose study in subjects with COPD (MKI113006). In this study, subjects with COPD were dosed with losmapimod 2.5 mg BID (N=149), losmapimod 7.5 mg BID (N=151), or placebo BID (N=154) for 24 weeks; or losmapimod 7.5 mg BID for 4 weeks followed by losmapimod 15 mg BID (N=150) for 20 weeks. Over the first 12 weeks of treatment, statistically significant reductions in serum high-sensitivity CRP (hsCRP) levels were observed in the losmapimod 7.5 mg and 15 mg groups compared with placebo. For hsCRP, Week 12, 7.5 mg dose versus placebo: ratio 0.73; 95% confidence interval [CI] 0.57, 0.93;

p=0.011; 15 mg dose versus placebo: ratio 0.64; 95% CI 0.50, 0.82; p<0.001. Table 4 shows the results for the subgroup with higher CRP at baseline.

Table 4: Change from Baseline in CRP Over 12 Weeks of Treatment with Different Doses of Losmapimod Compared with Placebo in Subjects with COPD and High Baseline CRP Levels (>6.4 mg/L)

Week 12 Baseline hsCRP >6.40 mg/L	Placebo BID (N=42)	Losmapimod 2.5 mg BID (N=33)	Losmapimod 7.5 mg BID (N=31)	Losmapimod 15 mg BID (N=31)
Geometric LS mean (SE of logs)	6.75 (0.153)	8.08 (0.180)	5.16 (0.180)	3.54 (0.186)
Geometric LS mean ratio to baseline (SE of logs)	0.49 (0.153)	0.59 (0.180)	0.38 (0.180)	0.26 (0.186)
Column vs placebo				
Ratio		1.20	0.77	0.53
95% CI		0.75, 1.92	0.48, 1.22	0.33, 0.85

Abbreviations: CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; LS = least square; SE = standard error.

Fulcrum Therapeutics is planning to conduct the initial clinical trial for the investigation of losmapimod for the treatment of COVID-19 in these high-risk subjects. Losmapimod is currently in Phase 2 clinical development for the treatment of the root cause of FSHD under an open IND in the United States and open clinical trial applications in Canada, Spain, France, and The Netherlands.

A summary of published literature supporting the therapeutic hypothesis for the clinical development of losmapimod for the treatment of COVID-19 is provided in Table 5.

Table 5: Listing of Evidence Supporting the Development of the p38 Inhibitor Losmapimod for Treatment of COVID-19

Evidence	References
Pneumonitis, acute respiratory distress syndrome, pulmonary edema, and cardiomyopathy drive COVID-19 mortality	• Siddiqi HK et al. J Heart Lung Transplant. 2020 • Ruan Q et al. Intensive Care Med. 2020 Mar 3
Older patients are at greatest risk of COVID-19 mortality	• Ruan Q et al. Intensive Care Med. 2020 Mar 3
Human SARS-CoV-2 pathology is recapitulated in SARS-CoV-1 mice	• Zhou F et al. Lancet. 2020 • Nagata N et al. Am J Pathol. 2008
Exaggerated acute inflammatory response and lymphopenia correlate with mortality in human with COVID-19 and older mice infected with SARS-CoV-1	• Nagata N et al. Am J Pathol. 2008 • Zhou F et al. Lancet. 2020
SARS-CoV-1 activates the p38 MAPK pathway in peripheral blood early in the infection	• Lee CH et al. J Immunol. 2004.
SARS-CoV envelope protein (E) activates the host's inflammatory response via p38 signaling	• Jimenez-Guardeño JM et al. PLOS Pathog. 2014

Evidence	References
Several nonclinical studies have shown evidence of p38 inhibition reducing viral replication including with coronavirus	• Kono M et al. Antiviral Res. 2008 • Dong Y et al. Antiviral Res. 2020 • Kindrachuk D et al. Anti Microb Agents & Chem. 2015
p38 inhibition reduces mortality in older mice infected with SARS-CoV-1	• Jimenez-Guardeño J et al. PLOS Pathog. 2014
Nonclinical efficacy of p38 inhibition also observed in other models of severe acute viral pneumonitis and other severe acute viral infections	• Shapiro L et al. PNAS. 1998 • Iordanov MS et al. Mol Cell Bio. 2000 • Salomon R et al. PNAS. 2007 • Griego SD et al. J Immunol. 2000 • Banerjee S et al. J Virology. 2002 • Börgeling Y et al. J Biol Chem. 2014 • Chen Y et al. J Exp Med. 2017 • He F et al. J Transl Med. 2019
p38 inhibition reduces lung mucous production in mice models of toxic airway injury	• Liu et al. Int Immunopharmacol. 2009
Losmapimod and other p38 inhibitors acutely reduce inflammatory markers in humans	• GSK data in Fulcrum Original IND 138739, Module 4 • Genovese M et al. J Rheumatol. 2011 • Christie J et al. Crit Care Med. 2015
Losmapimod reduces inflammatory markers associated with COVID-19 severity at currently utilized doses	• Fulcrum clinical data on file • GSK clinical data • Newby L et al. Lancet. 2014
Inhibition of p38 with 15 mg losmapimod BID dose in older subjects restored the adaptive immune response to viral challenge	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
Exaggerated acute inflammatory response in older subjects is driven to a large extent by p38 activation	• Vukmanovic-Stejic M et al. J Allergy Clin Immunol. 2018
In vivo data in Ferrets indicate SARS-Cov-2 induces profoundly lower immune response vs other virus	• Blanco-Melo D et al. bioRxiv. 2020
Evidence that p38 inhibition may treat the deleterious effects of elevated Ang II in COVID-19	• Grimes JM et al. J Mol Cell Cardiol. 2020
Losmapimod is a highly selective p38 inhibitor at advanced stage of clinical development with excellent safety data profile	• Losmapimod Investigator Brochure Fulcrum 2020 • Cadavid D et al. FSHD IRC Poster. 2019

Abbreviations: BID = twice daily; COVID-19 = disease caused by novel coronavirus; IND = investigational new drug application; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

2 STUDY OBJECTIVES AND ENDPOINTS

All study objectives will be evaluated in subjects diagnosed with COVID-19.

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale (WHO 2020): • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities • (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation Total number of study days in ICU Total number of study days hospitalized Total number of respiratory failure-free study days Percentage of subjects discharged from the hospital

Objectives	Endpoints
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

Abbreviations: AE = adverse event; [redacted] ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = disease caused by novel coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; [redacted]; ICU = intensive care unit; IL-6 = interleukin-6; [redacted]; PD = pharmacodynamics; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

3 STUDY IMPLEMENTATION

3.1 Overall study design and plan

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥50 years old, who have a C-reactive protein (CRP) >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.

Subjects who sign informed consent (refer to Section 9.1.3) and meet all entry criteria (see Section 4) may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg PO BID; OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects (5 placebo and 5 losmapimod) will be dosed and followed for at least 72 hours after their first dose for an interim “sentinel” safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter (see Section 8.10).

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

See Table 1 for the time points of the assessments.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site (refer to Section 6.7).

3.2 Start of study and end of study definitions

The start of the study is defined as the date the first enrolled subject signs an informed consent form (ICF). The end of the study is defined as the date of the last subject’s last assessment (scheduled or unscheduled).

3.3 Selection of doses in the study

In the Phase 1 study in healthy volunteers and FSHD subjects (Study FIS-001-2018), the dose levels of 7.5 mg and 15 mg given by mouth BID with food were based on predictive nonclinical efficacy and published clinical target engagement and safety data for losmapimod previously generated by GSK. This Phase 1 study was recently completed and demonstrated that the 15 mg PO BID dose gives higher plasma levels and greater and more sustained target engagement in blood and tissues than the 7.5 mg PO BID dose, while resulting in similar safety and tolerability. The 15 mg BID dose is used in the ongoing Phase 2 studies in FSHD (Study FIS-001-2019 and Study FIS-002-2019). Prior results indicated the favorable safety and tolerability of losmapimod for chronic administration in the clinic, including in the context of severe acute diseases, such as acute myocardial infarction, in older people.

Prior studies of biodistribution of radiolabeled losmapimod by GSK showed ample distribution to all tissues including the lungs and the heart. Our recent target engagement data in the FSHD Phase 1 Study FIS-001-2018 indicates that pHSP27 inhibition in blood, an assessment of p38 target engagement, is nearing a plateau at a losmapimod dose of 15 mg BID (see Investigator Brochure [Fulcrum Therapeutics 2020]), so doses of losmapimod higher than 15 mg PO BID are not warranted.

Additionally, at the proposed dose level of 15 mg PO BID, exposures are not expected to exceed those previously demonstrated to be safe in humans in multiple previous studies by GSK in healthy volunteers and various patient populations including older subjects (Cheriyan et al 2011; Barbour et al 2013; Watz et al 2014; Pascoe et al 2017).

In previous clinical studies performed by GSK, it was shown that losmapimod significantly reduced markers of acute inflammation, including IL-6, CRP, and the CXCL13 chemokine after a single dose. Additionally, losmapimod reduced IL-6 after 15 days of treatment (GSK study RA3103718) and CRP acutely in subjects with acute myocardial infarction treated with 7.5 mg PO BID (O'Donoghue et al 2016). In subjects with COPD, losmapimod at 15 mg PO BID significantly reduced CRP over 12 weeks compared with placebo (GSK Study MKI 113006). In one study in healthy older adult volunteers, it was shown that a 15 mg PO BID dose of losmapimod for 4 days restored the normal immune response to varicella-zoster virus antigen challenge (Vukmanovic-Stejic et al 2018). The same formulation used in these previous clinical studies is the one proposed for use in the present clinical study.

The rationale for the proposed study duration of up to 28 days is that in most cases of COVID-19 the disease has resolved or resulted in severe outcomes over the first month from onset of symptoms. COVID-19 is a severe and rapidly progressive infection, especially in the high-risk population selected for the proposed Phase 3 trial. Therefore, treatment for longer than 14 days and study duration for longer than 28 days is not justified.

3.4 Study drug modifications and withdrawal

3.4.1 Dose modifications

Before trial medication is administered, changes in the subject's health status, including laboratory results if applicable, since the previous visit or previous dose should be checked.

Study drug interruptions and reductions are not permitted; subjects who are on dialysis may require a dose adjustment.

Study treatment dose adjustment for subjects on dialysis

The elimination of losmapimod is almost exclusively by metabolism, with only 2% of the administered dose recovered as unchanged drug in urine and feces. The metabolite is clinically inactive and does not exert any toxic effects.

Losmapimod has not been studied in renal insufficiency or renal failure. There has been 1 study of losmapimod in 17 subjects with focal segmental glomerulosclerosis (FSGS; FSG117283). In this study, subjects were given losmapimod 7.5 mg BID for 2 weeks followed by losmapimod 15 mg BID for 22 weeks. The mean duration of exposure to investigational product in subjects with FSGS was approximately 21 weeks (range: 3.7, 25 weeks).

Creatine and GFR for the population enrolled is in the table below.

Parameter	Mean (SD)	Range
eGFR (mL/min/1.73m^2)	79.4 (34.9)	36, 155
Creatine (µmol/L)	1.1 (0.5)	0.48, 2.07

eGFR = estimated glomerular filtration rate.

Losmapimod plasma concentration data in subjects with FSGS were compared with historical data obtained in the Phase 3 clinical trial in subjects with ACS. In general, exposure in subjects with FSGS was similar to that in subjects with ACS over the 24-week treatment period.

Consistent with the safety database of over 3500 subjects, the 2 most frequently reported AEs in the FSGS trial were headache (5/17; 29%) and fatigue (4/17; 24%). Seven AEs (by preferred term: vomiting, dizziness, oropharyngeal pain, nausea, blood creatinine increased, muscle spasms, and rash) were reported in 3 subjects (18%) each. All other AEs (by preferred term) were reported in ≤2 subjects each. Four subjects had at least 1 AE that led to withdrawal from the study or from treatment. The AEs that led to discontinuation were increase in blood urea nitrogen (related), increase in creatinine (not related), increase in cystatin C (related), and joint stiffness (related). None of the AEs was serious or severe; 3 of the AEs in 2 subjects were reported as related to study treatment.

Based on the current safety and exposure information, dosing adjustment is likely not needed for subjects with renal insufficiency. However, close monitoring of pharmacokinetics (PK) for such cases will be implemented to ensure that therapeutic concentrations are maintained (refer to Section 6.2). For those subjects requiring dialysis, dose adjustment may be needed and will be determined by pre- and post-dialysis PK by the DMC. Adjustments may be recommended by the DMC also for subjects on placebo who develop acute renal failure to prevent unblinding at the sites.

Study treatment discontinuation

Discontinuation of study treatment should be considered if:

- ALT or AST >8 x the upper limit of normal (ULN)
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (total bilirubin >2 x ULN or international normalized ratio >1.5) in the absence of reasonable alternative etiology
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- QTcF prolongation with QTcF >500 msec or an increase in QTcF of >60 msec over baseline (confirmed by 2 successive repeat measurements)

In addition, the investigator must permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the subject. The premature discontinuation of study drug might be triggered by an adverse event (AE), a diagnostic or therapeutic procedure, an abnormal assessment (eg, ECG or laboratory abnormalities), or for

administrative reasons, in particular withdrawal of the subject's consent. The reason for study drug interruption or premature discontinuation must be clearly documented in the eCRF.

3.4.2 Subject withdrawal

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. The subject is noncompliant with the protocol.
2. The subject has a serious or intolerable adverse event(s) (AE[s]) that, in the investigator's opinion, require(s) withdrawal from the study.
3. The subject has laboratory safety results that reveal clinically significant hematological or biochemical worsening from the baseline values that could be attributed to the study medication.
4. The subject develops symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
5. The subject is lost to follow-up.
6. Other reasons (eg, pregnancy, development of contraindications of use of study drug as determined by the sponsor or the treating physician).
7. The study is discontinued by the sponsor or the study site.

For subjects to be considered as lost to follow-up, 2 attempts should be made to contact the subject to return for the scheduled study visit. After 2 attempts, a certified letter should be sent to the subject's address requesting the subject to contact the investigator to schedule a follow-up assessment. If no reply is provided by the subject within 30 days of receipt of the certified letter, the subject can then be considered lost to follow-up.

3.4.3 Replacement policy

Subjects who withdraw from the study will not be replaced.

3.4.4 Stopping criteria

Dosing will be stopped in case of an unacceptable tolerability profile based on the nature, frequency, and intensity of observed AEs judged jointly by the investigator and the sponsor or as recommended by the DMC.

In the event of a study hold due to unacceptable tolerability, the sponsor will conduct an extensive safety and PK analysis and will communicate to stakeholders, including the Investigators, institutional review boards (IRBs)/independent ethics committees (IEC), and health authorities any potentially emergent safety information as well as the timing of planned resumption of dosing. Dosing and enrollment will not resume unless it is considered safe to do so after consultation with Investigators and health authorities and approval by IRBs/IECs.

4 STUDY POPULATION

4.1 Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening.

1. Able and willing to provide written informed consent.
2. Willing and able to comply with all study procedures.
3. Age ≥50 years at time of screening.
4. Confirmed infection with SARS-CoV-2 virus at or before the baseline visit (by polymerase chain reaction [PCR] testing).
    a. Note: Refer to the Study Manual for details on PCR SARS-Cov-2 testing procedures.
5. ≤7 days to the time of randomization from the time of collection of the specimen that tested positive for the SARS-CoV-2 virus.
6. Hospitalization at the time of the baseline visit.
7. ≥90% oxygen saturation on room air and/or ≥94% oxygen saturation on oxygen administration at 2 L/min by nasal canula at the baseline visit.
8. Radiographic (X-ray or computed tomography scan, per local standard of care) evidence of pulmonary involvement consistent with COVID-19 at screening or baseline, per the judgment of the investigator.
    a. Note: If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.
9. Clinical syndrome consistent with COVID-19 at screening, per the judgment of the investigator (CDC 2020).
10. CRP at screening >15 mg/L on local laboratory testing.
11. Agrees to practice an approved method of birth control as follows:
    a. Females of childbearing potential: Using 1 of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap). This criterion must be followed from the time of the first dose of study medication until 90 days after last dose
    b. Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms. This criterion must be followed from the time of the first dose of study medication until 90 days after last dose.

       Note: Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

4.2 Exclusion criteria

1. Inability to take oral medication at screening or baseline visit.
2. Evidence at screening or baseline of critical COVID-19 disease (eg, cardiac failure, septic shock) or severe pulmonary involvement (eg, bilateral extensive involvement on chest X-ray or chest computed tomography, ARDS, immediate need for intubation or mechanical ventilation, anticipated need for intubation in the next 48 hours) per the judgment of the investigator.
3. Positive pregnancy test at screening for women of childbearing potential.
4. Lactating female at baseline for women of childbearing potential.
    a. Note: a female will be considered eligible who is lactating at screening if she agrees to discontinue breastfeeding for the duration of the trial plus 14 days post last dose.
5. ≥5 × upper limit of normal (ULN) for alanine or aspartate aminotransferases or total bilirubin >1.5 × ULN at screening or known history of Child-Pugh Class C, hepatitis B or C, or HIV infection.
6. Glomerular filtration rate <30 mL/min/1.73 m^2 at screening.
7. QTcF >450 msec for male or >470 msec for females or evidence of cardiac dysrhythmia at screening.
8. Significant history or evidence of clinically significant disorder, condition, current illness, illicit drug or other addiction, or disease that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
9. Treatment with anti-IL 6, anti-IL-6R antibodies, Janus kinase (JAK) inhibitors, or other immune modulators (unless considered part of local standard of care) in the past 30 days or 5 half-lives (whichever is longer) or plan to receive these agents as part of investigational clinical trials any time during the study period.
10. Treatment with hydroxychloroquine/ chloroquine in the past 30 days or plan to receive these agents as part of investigational clinical trials or SOC any time during the study period.
11. Recent (within 30 days) or current participation in other COVID-19 therapeutic trials or expanded access programs.
12. Prior or current participation in COVID-19 vaccine trials.

4.3 Concomitant medications

All medications (prescription and over-the-counter) taken at the time of study screening will be recorded, with indication, route of administration, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Subjects are allowed to use paracetamol (up to 3 g/day) and/or contraceptives (oral or parenteral), and any medications needed for SOC at the local institution. Use of hydroxychloroquine/ chloroquine is not permitted. Use of other experimental treatments for COVID-19 is not permitted unless it is part of SOC at the local institution. SOC for COVID-19 will be documented at each site during the site activation visit; additionally, it will be documented if any restrictions on standard of care treatment administration were encountered due to resource limitations. The use of antiviral medications is permitted.

Concomitant medications used to treat chronic comorbid conditions per SOC are permitted, including but not limited to metered dose inhalers, corticosteroids if on stable doses for at least 30 days prior to screening, or sedative or anesthetic agents.

Concomitant medications initiated or stopped for an AE will be recorded.

Both losmapimod and its major metabolite, GSK198602, are in vitro inhibitors of human BCRP. There is a low risk of interaction of losmapimod with orally administered BCRP substrates with a narrow therapeutic index (eg, methotrexate, topotecan, rosuvastatin). Therefore, such co-administration is indicated only if the medical benefit is considered to outweigh the risk for toxicity, and careful monitoring for adverse effects of these agents is advised.

Losmapimod is a relatively potent in vitro inhibitor of the renal transporters MATE1 and MATE2-K, and it is possible that a mild inhibition of tubular secretion may contribute to the small rise in (model-adjusted geometric mean) serum creatinine observed clinically. GSK198602 is a relatively potent in vitro inhibitor of OAT3 and co-administration of sensitive OAT3 substrates is indicated only if the medical benefit is considered to outweigh the risk for toxicity. Careful monitoring for adverse effects of these agents is advised, especially for those with narrow therapeutic margin (eg, methotrexate, metformin).

4.4 Lifestyle restrictions

Subjects should not donate blood, sperm, or ova from the screening visit through 90 days after the last dose of study treatment.

4.4.1 Contraception requirements

Teratogenicity and effects on embryofetal survival were noted in rat and rabbit reproductive toxicology studies with losmapimod. Therefore, losmapimod should not be taken by women of childbearing potential who are not utilizing adequate contraceptive methods.

All women of childbearing potential and all males must practice effective contraception during the study from the time of the first dose of study medication until 90 days after last dose.

Women of child-bearing potential are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks after surgical bilateral oophorectomy/bilateral salpingectomy with or without hysterectomy;
- Post hysterectomy.

For the purposes of the study, effective contraception is defined as follows:

- Females of childbearing potential: Using 1 or more of the following acceptable methods of contraception: surgical sterilization (eg, bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with diaphragm, sponge, or cervical cap).
- Males: Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms.

Abstinence can be considered an acceptable method of contraception at the discretion of the investigator. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not considered acceptable methods of contraception.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Investigational drug and matching placebo

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Matching placebo tablets will be provided for oral administration.

The tablets are plain white, round, biconvex, film-coated tablets. The proposed dosing regimen is as a twice daily dose of 15 mg (2 × 7.5 mg tablets/dose BID). The proposed duration of treatment is for up to 14 days.

Subjects should take their dose of losmapimod or placebo with food whenever possible and with 240 mL of room temperature water.

5.2 Study drug packaging and labelling

Losmapimod tablets for oral administration are available as white, round, biconvex, plain, film-coated tablets containing 7.5 mg of losmapimod as the micronized base, GW856553X.

Losmapimod tablets also contain the inactive excipients microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, povidone K30, hypromellose, titanium dioxide (E171), and polyethylene glycol.

Placebo tablets are identical in appearance to losmapimod and have the same excipient ingredients as losmapimod but do not have the active compound.

All tablets are packed in opaque, white, square, high-density polyethylene bottles with induction sealed child-resistant closures.

Losmapimod must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature not to exceed 30°C.

5.3 Drug accountability

The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

The Investigator (or designee) will maintain an accurate record of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures by the sponsor. Any unused assembled unit doses will be retained until completion of the study.

After completion of the study, all unused supplies will be returned to the sponsor or disposed of by the study site, per the sponsor's written instructions.

5.4 Treatment assignment and blinding

5.4.1 Randomization and treatment assignment

A total of up to 410 subjects will be recruited into this study and will be randomized in a 1:1 ratio to 15 mg losmapimod (BID) or placebo using an interactive/web voice response system (IxRS) for randomization. The randomization list will be produced by a qualified randomization vendor and will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no) at enrollment.

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug. Randomized subjects will be sequentially assigned a unique subject number from the randomization list per the IxRS. From the time of randomization and throughout the duration of the study, subjects will be identified by their unique randomization number.

The authorized site personnel will prepare the appropriate study drug for each subject based on the randomization schedule. Treatment codes should not be broken except in emergency situations, ie, when knowledge of the treatment is essential for the immediate further management of the subject.

5.4.2 Blinding

This study will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to subject-level treatment assignment until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way.

5.4.3 Treatment compliance

All doses will be administered either in the hospital (anticipated during the first week of study treatment) or taken by the study participants on an outpatient basis.

The subject will bring the study treatment bottle to each visit (clinic or home assessment) for review by the site staff.

The study treatment bottles will be collected at the Day 14 visit whether in the hospital or outpatient or at the ET visit if prior to Day 14.

6 STUDY ASSESSMENTS

See Table 1 for the time points of the assessments.

If additional visits or blood draws are required beyond the planned visits in any part of the study, these visits or samples should be recorded in the eCRF as unscheduled visits prior to the subject's completion of the study.

6.1 Medical history

A complete medical history will be taken at Screening and is to include demographic information, prior medical illnesses and conditions, and surgical procedures for at least 3 months prior to screening. The medical history may be collected from medical records, if available, or during the physical examination.

The history of SARS-CoV-2 infection and symptoms at screening should be recorded; the details of how infection history will be assessed and recorded can be found in the Study Manual.

A chest X-ray or CT will be performed while the patient is hospitalized based on standard-of-care local assessment. The results are required for eligibility assessment to confirm radiographic evidence of COVID 19. If radiography is not considered local standard of care for COVID-19 diagnosis, evidence of pulmonary involvement consistent with COVID-19 may also be obtained from clinical examination, per the judgment of the investigator. Evidence of pulmonary involvement obtained by clinical examination should be documented in the eCRF.

A pre-existing condition is one that is present prior to administration of study drug. Such conditions should be recorded as medical history. A pre-existing condition should be recorded as an AE or serious adverse event (SAE) only if the frequency, intensity, or nature of the condition worsens following administration of study drug.

6.2 Pharmacokinetic and pharmacodynamic assessments

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess PK. PK assessments will be performed as a substudy in all sentinel subjects to evaluate the PK of losmapimod in the population of subjects with COVID-19.

Blood samples will be collected as outlined in the Schedule of Assessments (Table 1) to assess plasma biomarkers of response to COVID-19, [redacted]

Procedures for collection, processing, and return of blood samples will be detailed in the Study Manual. Specifics of the analytical methods will be provided in separate documents.

Cytokines and chemokines will be evaluated using a multiplex assay. Details of the assay and specimen sampling will be provided in the Study Manual.

Viral load will be assessed by nasopharyngeal (preferred) or oropharyngeal swab or saliva assay as outlined in the Schedule of Assessments (Table 1). Diagnosis of COVID-19 should be confirmed by local PCR testing prior to randomization. Refer to the Study Manual for details on procedures and type(s) of diagnostic testing allowed.

PK should be measured weekly at C_{max} (4-5 hours) for subjects with renal insufficiency (eGFR ≤45 mL/min/ 1.73 m^2). For those subjects requiring dialysis, dose adjustment may be needed (see Section 3.4.1) and will be determined by pre- and post-dialysis PK by the DMC to prevent site unblinding.

6.3 Clinical status and symptoms

The investigator may consult with a relevant clinical or other specialist as appropriate per SOC.

6.3.1 Respiratory failure and survival assessment

Total number of study days free of oxygen supplementation and total number of study days free of respiratory failure will be evaluated. Refer to Section 6.5.1 for further details of vital sign collection.

- Note: Respiratory failure is defined as either need for mechanical ventilation (invasive or non-invasive) or high flow oxygen (defined by greater than 15 LPM flow of oxygen to maintain oxygen saturation between 90% and 95%, sustained for at least 48 hours, at any time during the study.

The reason for hospitalization and number of total study days of hospitalization and intensive care unit (ICU) utilization will be recorded.

Details of subject discharge (date of discharge and condition at discharge) from the hospital will be recorded.

Any significant deviation from standard of care due to limited resources will be documented.

Survival status at the end of the study period will be documented, including cause of death for any reason.

6.3.2 Clinical status assessment

Clinical status as outlined in the Schedule of Assessments (Table 1) will be measured on the following clinician-reported 9-point ranking scale (WHO):

- (8) death
- (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO)
- (6) intubation and mechanical ventilation
- (5) noninvasive ventilation or high-flow oxygen therapy
- (4) oxygen therapy but not requiring high-flow or non-invasive ventilation
- (3) hospitalized but not requiring oxygen therapy
- (2) discharged from the hospital but with limitation of activities
- (1) discharged from the hospital and without any limitation
- (0) no clinical evidence of the disease

Instructions for administration will be provided in the Study Manual.

6.4 Extended vital signs

Extended vital signs, including oxygen saturation and fraction of inspired oxygen (FiO_2) will be collected as specified in the schedule of assessments. Refer to Section 6.5.1 for further details of measurements.

6.5 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 7.

6.5.1 Vital signs

Evaluations of systolic and diastolic blood pressure, respiratory rate, and temperature will be performed throughout the study. In addition, oxygen saturation and FiO_2 will be assessed throughout the study. Oxygen administration (eg, room air or oxygen flow by nasal canula or facial mask) will be recorded. Vital signs will be performed after subjects have been supine for at least 5 minutes when possible.

Arterial blood gases may be performed if clinically indicated in some subjects but are not required for this study. If arterial blood gasses are measured, the results for arterial pressure of oxygen (PaO_2) should be reported at each measurement in the eCRF.

Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.2 Weight and height

Weight (kg) will be recorded at screening and the follow-up assessment (by alternative methods including outpatient visit). Height (cm) will be recorded and body mass index (BMI) calculated at screening.

BMI (kg/m^2) = weight (kg)/(height [cm]/100)^2

6.5.3 Physical examination

Physical examination (ie, inspection, percussion, palpation, and auscultation) is performed to determine eligibility and as clinically indicated during the study. Clinically relevant findings that are present prior to study drug initiation must be recorded with the subject's medical history. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.4 Electrocardiography

ECGs will be taken singly after 5 minutes in the supine position as specified in the schedule of assessments. The investigator will assess the ECG recording as 'normal', 'abnormal - not clinically significant', or 'abnormal - clinically significant' and include a description of the abnormality as required. The ECG parameters assessed will include heart rate, PR, QRS, QT, and QTcB and QTcF (calculated using Bazett's and Fridericia's method, respectively). ECGs will be performed to determine eligibility and during the study period only if clinically indicated. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded.

6.5.5 Laboratory assessments

Laboratory parameters

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data. Clinically relevant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded. Clinical relevance is defined as:

- Is accompanied by clinical symptoms
- Leads to dose modification of study treatment

- Requires significant changes, addition of, interruption of, discontinuation of a concomitant medication, therapy, or treatment
- Reflects a disease and/or organ toxicity

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria or those that is a result of an AE that has already been reported.

Blood and other biological samples will be collected for the following clinical laboratory tests; refer to the Study Manual for details of collection and analysis and information on the central clinical laboratory:

Lab	Tests
Hematology	Hemoglobin [including mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration], hematocrit, red cell count, total white cell count, and platelet count. Differential blood count, including: basophils, eosinophils, neutrophils, lymphocytes, and monocytes.
Chemistry and electrolytes	Sodium, potassium, calcium, inorganic phosphate, total protein, albumin, blood urea nitrogen, creatinine, uric acid, total bilirubin[1], alkaline phosphatase, AST, ALT, gamma-glutamyl transferase, and LDH.
Glucose	Glucose
Urinalysis	Leucocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose. If there is a clinically significant positive result, urine will be sent to the central laboratory facility for microscopy and/or culture.
Pregnancy[2]	hCG (urine or serum). If there is a clinically significant, positive result in urine, urine will be sent to the central laboratory facility for confirmation.
[1]Conjugated bilirubin will be reported only when total bilirubin is outside the reference range. [2]Pregnancy test for women of childbearing potential will be performed within 72 hours of first dose and if pregnancy is suspected during the study.	

6.6 Unscheduled visit

Unscheduled visits may be performed at any time at the subject's or the investigator's request and may include (but are not limited to) vital signs/focused physical examination, ECG, AE review, concomitant medications and procedures review, disease-related constitutional symptoms, and/or laboratory and biomarker assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

6.6.1 Early termination visit

When the investigator determines that study treatment will no longer be used, the investigator will perform the ET procedures and document the reason for discontinuation from study treatment in the eCRF. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the time of study treatment discontinuation, these tests need not be repeated. Every effort should be made to keep subjects in the study, including if a subject and/or their treating physician decides to prematurely discontinue study treatment.

6.7 Alternative follow-up methods to site visits

Trial participants may not be able to come to the investigational site for protocol-specified or unscheduled visits. The sponsor may use alternative methods for safety assessments, including

telemedicine visits, telephone visits, and/or an alternative location for visits depending on the local or institutional standards.

7 SAFETY REPORTING

7.1 Definitions of adverse events

An adverse event (AE) is any untoward medical occurrence in a subject who is participating in a clinical study performed. The AE does not necessarily have to follow the administration of a study drug, or to have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or vital sign finding), symptom, or disease temporally associated with the study participation whether or not it is related to the study drug.

7.1.1 Intensity of adverse events

The intensity of clinical AEs is graded 3-point scale as defined below:

- Mild: discomfort noticed but no disruption of normal daily activity;
- Moderate: discomfort sufficient to reduce or affect normal daily activity;
- Severe: inability to work or perform daily activity.

7.1.2 Relationship to study drug

For each AE, the relationship to drug as judged by the investigator:

- Probable;
- Possible;
- Unlikely;
- Unrelated.

7.1.3 Serious adverse events

A serious adverse event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatient hospitalization;
    - Note: COVID-19-related hospitalization or ICU admission is excluded from this definition, as SARS-CoV-2, COVID-19 infection, or pulmonary conditions attributable to COVID-19 infection are efficacy-related endpoints
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE.

7.1.4 Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is unexpected (nature or severity of which is not consistent with the applicable product information (eg, the Investigator Brochure for losmapimod) and suspected (a reasonable possibility of causal relationship with investigational drug, regardless of the administered dose).

7.1.5 Reporting of serious adverse events

The investigator must report any AE that meets the SAE criteria (Section 7.1.3) to PPD immediately (ie, within 24 hours after the site personnel first learn about the event) via electronic data capture (EDC). In the event that EDC entry is not possible (eg, system failure or access problems), the study site staff should complete the paper SAE report form and fax the form to PPD Pharmacovigilance within 24 hours of awareness or call the PPD safety hotline to report. The study site staff should update the EDC system as soon as it is available.

A full description of every SAE will need to be provided to PPD Pharmacovigilance.

[redacted]

7.1.6 Follow-up of adverse events

All AEs will be followed until they have abated, returned to baseline status or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.1.7 Adverse events of special interest

An AESI (serious or non-serious) is one of scientific and medical concern for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Adverse events of special interest for this study include QTc prolongation as well as liver tests that meet the criteria for potential drug-induced liver injury (DILI), in accordance with the US Food and Drug Administration “Guidance for Industry-Drug-Induced Liver Injury: Premarketing Clinical Evaluation”.

Adverse event of special interest: QTc prolongation

A thorough QT study (PM1116628) was conducted in healthy volunteers who received losmapimod at 7.5 mg BID or 20 mg daily or with placebo administered for 5 days. At the 20 mg dose of losmapimod, the upper bound of the 90% CI of the ΔΔQT interval (change from baseline in QTcF compared with that for placebo) exceeded the 10 msec threshold at the 24-hour post-dose time point. For the 7.5 mg BID dose, the upper bound of the 90% CI of ΔΔQTcF exceeded the 10 msec threshold at multiple time points. No subjects experienced QTcF values >480 msec or QTcF changes from baseline ≥60 msec at any time in the study. Although the upper bound of the 90% CI exceeded the 10 msec regulatory threshold of concern in the primary pharmacodynamic analysis, it was determined by GSK that there was no clinically relevant effect on the QT interval, as there was no clinically relevant concentration QTc effect using standard placebo/baseline subtracted measured QTc data. Additional information on the QTc interval and its behavior, as demonstrated in the large cohort of patients with ACS treated with losmapimod (PM1116197), supported the lack of a QT effect. PK/PD modeling using the raw QTcF and plasma concentration data showed that at plasma losmapimod concentrations 4 times the exposure at the therapeutic dose (7.5 mg BID) (ie, at exposures approximately 2-fold higher than 15 mg BID, the predicted upper bound of the 90% CI of ΔΔQTcF) did not exceed 10 msec, and the predicted median ΔΔQTcF was less than 5 msec. Further details are presented in the Investigator Brochure. No drug effect on QT prolongation of losmapimod over placebo has been documented in any of the phase 2 or the one phase 3 trial completed so far.

Study drug should be discontinued for subjects who meet the QTc prolongation criteria as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting

procedures (Section 7.1.5). Further safety steps should be taken to closely observe and follow-up the event until resolution and treatment initiated per local standard of care.

Adverse event of special interest: Drug-induced liver injury

The following 3 laboratory value criteria must be met for potential DILI, or "Hy's Law":

- An elevated alanine transaminase or aspartate transaminase laboratory value that is ≥3 × ULN
- An elevated total bilirubin laboratory value that is ≥2 × ULN
- An alkaline phosphatase laboratory value that is <2 × ULN

Study drug should be discontinued for subjects who meet the laboratory criteria for potential DILI as a result of within-protocol specific testing or unscheduled testing (see Section 3.4.4 stopping criteria). This AESI must be reported to the sponsor within 24 hours of awareness per the SAE reporting procedures (Section 7.1.5). Further safety steps should be taken to closely observe and follow-up the event until resolution. These steps include, but are not limited to:

- Making every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver tests
- Obtaining a more detailed history of symptoms and prior or concurrent disease, concomitant medication use, alcohol use, recreational drug use, and special diets
- Repeating liver enzyme and serum bilirubin tests twice weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic
- Obtaining viral hepatitis serology
- Considering liver imaging and/or hepatology consultation

7.2 Pregnancy

7.2.1 Teratogenicity

If a woman becomes pregnant when on study drug, study drug should be permanently discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known. In the event of pregnancy in the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

7.2.2 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during study drug administration or until follow-up, must be reported within 24 hours of the investigator's knowledge of the event to the sponsor. The Investigator must make every effort to follow the pregnant partner of a male subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the SAE form.

8 STATISTICAL METHODOLOGY AND ANALYSES

8.1 Statistical analysis plan

A statistical analysis plan (SAP) will be generated and approved prior to database snapshot for the interim analysis (IA). The SAP will detail the implementation of all planned statistical analysis. Any deviations from the planned analysis will be described and justified in the final clinical study report.

All safety and statistical programming will be conducted using SAS 9.4 for Windows or newer (SAS Institute Inc., Cary, NC, USA), and other statistical programming/sample size calculation software as necessary.

8.1.1 Determination of sample size

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of up to 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level. The sample size estimate assumes an IA will be conducted after approximately 206 subjects (103 in the losmapimod arm, and 103 in the placebo arm) have completed the Day 28 visit, to assess early futility, using the rules specified in Section 8.9.

8.1.2 Analysis methods

In general, all study endpoints will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, median, minimum, and maximum. Descriptive statistics for categorical data will include frequency and percentage.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% CI.

8.1.3 Analysis sets

Full Analysis Set (FAS): The FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS.

Per Protocol Set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria and do not have any significant protocol deviations. All analyses using the PPS will group subjects according to randomized treatment.

Safety Analysis Set: The safety analysis set is defined as all subjects who are randomized and receive study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The safety analysis set will be used for all safety and tolerability analyses.

8.2 Protocol violations/deviations

Protocol deviations will be identified based on conditions related to the categories below:

- Protocol entry criteria
- Forbidden concomitant medications
- Missing evaluations for relevant endpoints

- Other protocol deviations occurring during study conduct.

Major protocol deviations will be identified before study closure and listed where appropriate.

8.3 Missing, unused and spurious data

All missing or incomplete safety and PD data, including dates and times, are treated as such. Missing test results or assessments will not be imputed, and as such, are assumed missing-completely-at-random (MCAR).

For laboratory data, values below the limit of quantitation (recorded as "< LLQ") will be set to half that limit.

Censoring rules for time-to-event endpoints will be discussed in the SAP. Imputation rules for the primary endpoint will be discussed in the SAP. The handling of any missing, unused, and spurious data will be documented in the SAP or the clinical study report.

8.4 Subject disposition

Subject disposition will be listed by subject.

The following subject data will be summarized:

- number and percentage of subjects screened,
- number and percentage of subjects enrolled,
- number and percentage of subjects completed,
- number and percentage of subjects included in safety population

A subject who completed the study is defined as a subject where the last PD assessment was completed.

8.5 Baseline parameters and concomitant medications

8.5.1 Demographics and baseline variables

Demographic and other baseline characteristics will be summarized using descriptive statistics for the treatment group and overall.

8.5.2 Medical history

Medical history will be listed.

8.5.3 Prior and concomitant medications

Prior and concomitant medications will be listed by international nonproprietary names, dose, regimen, route and for which indication it was prescribed.

8.5.4 Treatment compliance/exposure

Exposure to study treatment is described in terms of duration of treatment.

8.5.5 Safety and tolerability endpoints

The safety data set is used to perform all safety analyses.

Baseline is defined as the last value prior to dosing. Change from baseline will be calculated for all continuous safety parameters.

8.5.6 Adverse events

The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used for the coding of AEs. The overall incidence of AEs will be displayed by MedDRA system organ class, preferred term, and treatment group.

All AEs will be displayed in listings. In addition, SAEs and treatment-emergent AEs (TEAEs) leading to discontinuation of study drug will be listed.

Treatment-emergent AEs will be defined as an event that occurs on or after the first dose of study drug or the worsening of a preexisting condition on or after the first dose of study drug. If a subject does experience an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (ie, it is reported with a new start date) after starting administration of the specific treatment, and prior to the start of another treatment, if any. All TEAEs collected during the investigational period will be summarized.

The number of TEAEs and the number of subjects with at least 1 TEAE will be summarized by treatment group for the following:

1. System organ class and preferred term;
2. System organ class, preferred term, and maximum severity
3. System organ class, preferred term, and maximum drug relatedness.

8.5.7 Vital signs

Reported values and change from baseline values of supine blood pressure and pulse rate and temperature will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will be presented by treatment group. Vital sign variables will be listed. Values outside the reference range will be flagged in the listing.

Vital sign results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.5.8 ECG

ECG values will be listed.

8.5.9 Clinical laboratory tests

Reported values and change from baseline values of clinical laboratory variables will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will also be presented by treatment group. Clinical laboratory values will be listed.

Clinical laboratory test results and change from baseline values will be summarized using descriptive statistics by treatment group and time point.

8.6 Primary endpoints

1) Assuming p_t is probability of outcome in the losmapimod arm; p_c is the probability of outcome in the control arm

Study hypothesis: H_0: $= p_t - p_c = 0$

H_1: $= p_t - p_c > 0$

Assuming p_t=0.18, p_c=0.30, we can restate the hypothesis as

H_0: $\theta = \theta_0 = 0$

H_1: $\theta = \theta_1 = -0.12$

For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables. An interim analysis to assess futility analysis—and potential sample size re-estimation—is discussed in Section 8.9. All results will be summarized descriptively by treatment arm and expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p-values.

8.7 Secondary endpoints

Clinical status at Day 7 and Day 14: percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects for each of the items in the scale will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variable.

Total number of study days: (a) free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive: For each endpoint (a) - (e), a Poisson regression model or a negative binomial model will be used to assess the relationship with treatment, with age group as a covariate with stratification factors as covariates. Details of the model, including censoring rules, if any, will be provided in the SAP.

Percentage of subjects discharged from the hospital: percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables.

All-cause mortality at Day 28: percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables.

Incidence of AEs/SAEs: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of clinically significant changes: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables.

[redacted]

8.9 Interim analysis for futility and sample size re-estimation

An interim analysis (IA) will be conducted after 206 subjects have been enrolled (approximately 103 in each of the losmapimod and placebo arms) and have been treated for 14 days with 28 days of follow-up. Only futility—and potential sample size-estimation—will be assessed by the DMC at the IA. The O'Brien-Fleming group sequential method will be used to adjust beta for interim testing. Table 7, Figure 1, Figure 2, and Figure 3 contain sample size requirements, boundary information, and stopping probabilities for testing futility on the primary endpoint at both the IA and final analysis. P-values are single-sided. Sample size estimation was done using SAS® (Proc SeqDesign, Version 4.0). The study will not be stopped for efficacy at the IA.

Table 6: Boundary Values for Interim Analysis Futility Assessment

Analysis Stage	Sample Size		Beta: Futility			Alpha: Efficacy		
	Losmapimod	Control	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under null hypothesis)	Standardized- Z (p-value)	MLE	Stopping Probability (accept null under alternative hypothesis)
Interim Analysis	103	103	-0.67873 (0.24865)	-0.04017	0.75135	Not applicable	--	0.08871
Final Analysis	205	205	-1.91358 (0.02784)	-0.08009	0.97500	--	--	0.20000

Overall alpha=0.025 (1-sided); overall power=80%.
Abbreviations: MLE: maximum likelihood estimate.

Figure 1: Acceptance Region (Standardized-Z Scale)

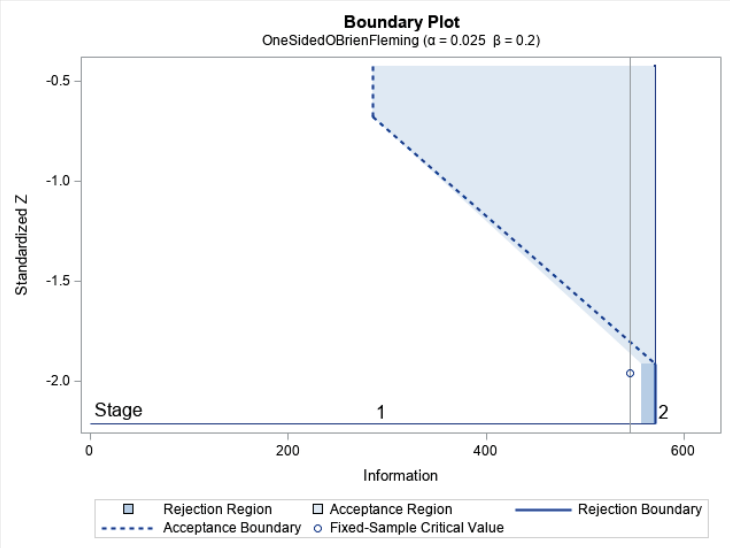


Figure 2: Acceptance Region (P-value)

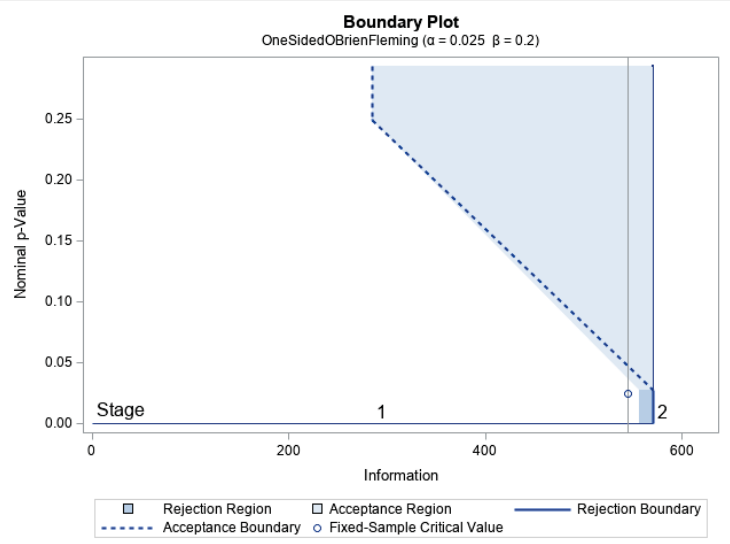
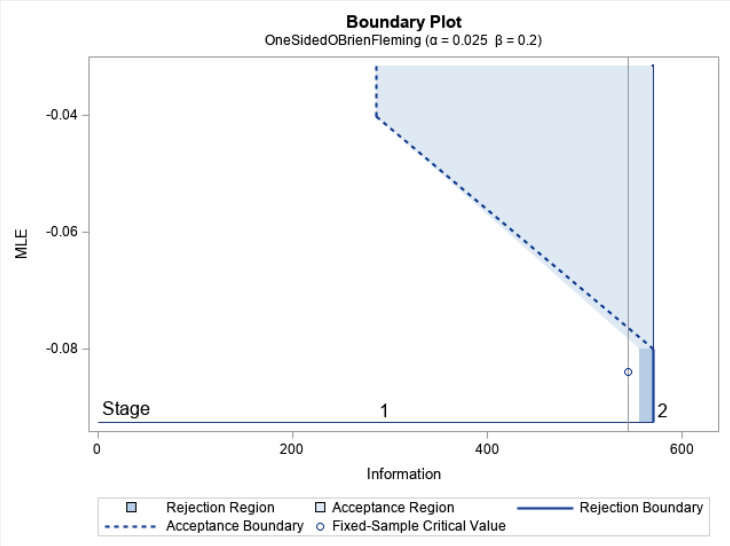


Figure 3: Acceptance Region (Maximum Likelihood Estimate)



8.9.1 Futility Testing

The process is as follows:

1. Futility at IA: If standardized z-value (MLE: maximum likelihood estimate) of $\mathbf{p_t - p_c}$ is ≥ -0.67873 (-0.04017), or p-value ≥0.24865, then stop for futility. Probability of stopping for futility under null hypothesis is ~0.75.
2. At Final Analysis: The final p-value is tested at an adjusted alpha of 0.02784.

8.9.2 Sample Size Re-estimation

The Chen-DeMets-Lan method (Chen et al 2004) will be used for unblinded sample size re-estimation, with IA futility stopping boundaries created using O'Brien-Fleming method, as described above. Wald conditional probabilities will be calculated using the actual observed proportion from both treatment arms.

The maximum sample size allowed is 820 subjects. Sample size will be increased only if the observed data at the IA are promising; that is, if the conditional power is ≥50% and <80%. Sample size will be increased to ensure a target conditional power of at least 80%.

There is only one IA, and conditional power at IA must lie between 50% and 80% for sample size re-estimation to be implemented. These 2 conditions ensure that the target Type I error of 2.5% is not exceeded by increasing sample size to meet the original target power (Chen et al 2004).

Sample size re-estimation will not be done in the following 2 instances:

- If conditional power is <50%, then sample size re-estimation will not be done, and decision on futility will be made based on boundary values from the O'Brien-Fleming method.

- If conditional power is ≥80%, then a sample size re-estimation will not be done, as the study will be considered sufficiently powered to detect the effect of interest at the final analysis.

A Wald Test statistic will be calculated and compared with the boundary value for futility (see Table 7). If the Wald Test statistic lies in the acceptance region, then the study will stop for futility.

All calculations for the IA and the unblinded sample size re-estimation will be conducted by an external, unblinded statistician. The DMC will review the results in a closed session and make appropriate recommendations to the Sponsor afterwards.

8.9.3 Possible Recommendations by the DMC

After reviewing the results of the IA, the DMC may select 3 or more possible recommendations, based on the test statistics obtained at the IA:

- Stop for Futility - Stop trial early due to strong evidence for futility due to test statistic being in the futility region.
- Continue without change - Continue until next look with no changes due to test statistic not being in the futility region or the conditional power being <50% or ≥80%.
- Add required additional sample size, n, without exceeding the maximum sample size of 820 and continue the trial.

At the final analysis, 2 recommendations can be made:

- Efficacy is demonstrated.
- Efficacy is NOT demonstrated.

8.10 Data monitoring committee

An independent DMC composed of experts external to the sponsor and investigators will monitor the safety of the trial participants and the conduct of the trial on an ongoing basis and will be responsible for the interim analysis and recommendations regarding sample size re-estimation. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will include at least 2 external clinician with expertise relevant to the evaluation of COVID-19, such as Critical Care, Pulmonology, or Infectious Disease, as well as at least 1 independent biostatistician with expertise in clinical trial design and statistical methods for clinical research and analysis of research data including interim analysis.

Details on the composition of the DMC and the schedule and format of DMC meetings and data outputs will be presented in the DMC charter. The DMC will review, at a minimum, data for the sentinel subjects prior to continued study drug dosing and cumulative safety data at regular intervals based on subject enrollment.

The safety evaluations will be detailed in the DMC charter and will include review of conventional safety variables, such as serious adverse events. Any safety event that requires unblinding will be immediately reported to the DMC and to the FDA. The DMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of subjects. The DMC will also review the efficacy data at the IA and make recommendations based on the futility criteria and for sample size re-estimation if needed (see Section 8.9). After reviewing study data, the DMC will make recommendations regarding continuation, termination, or modification of the study. The DMC may also perform ad hoc review PK of subjects who require dialysis.

9 GOOD CLINICAL PRACTICE, ETHICS AND ADMINISTRATIVE PROCEDURES

9.1 Good clinical practice

9.1.1 Ethics and good clinical practice

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice (GCP), the protocol, and all applicable regulations.

9.1.2 Ethics committee / institutional review board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date on which approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.1.3 Informed consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation. Following discussion of the study with site staff, subjects or their legally authorized representative will be required to provide one of the following:

1. Sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records; OR
2. If a subject is in isolation due to COVID-19 and institutional infection control policy would prevent removal of a document signed by the subject from their hospital room, then one of the following methods will be used to obtain informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable:
    - Obtain the informed consent electronically; OR
    - Obtain the informed consent by teleconference/video conference in alignment with local regulatory guidance.

    How the consent was obtained and reason why it was obtained using that particular method should be documented in the eCRF. The trial record at the investigational site should document how it was confirmed that the subject signed the consent form (ie, either using attestation by the witness and investigator or a photograph of the signed consent).

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

9.2 Data handling and record keeping

This study will be conducted according to ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

Study site personnel will enter subject data into the EDC program. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After final database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. PPD will maintain a duplicate CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9.3 Access to source data and documents

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.4 Investigator's obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with

limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.
To ensure privacy, directly identifying information of study subjects will not be attached to records or samples released to the sponsor and its service providers for research purposes.
The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties. Additional confidentiality requirements and obligations will be set forth in the clinical trial agreement to be entered into by the sponsor, the principal investigator, and the institution.

9.6 Financial disclosure and obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

9.7 Investigator documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- FDA Form 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- A curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required by applicable regulatory authorities. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site.

9.8 Study conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.9 Adherence to protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.10 Adverse events and study report requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.11 Investigator's final report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.12 Records retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.13 Publications

After completion of the study, the data will be submitted for reporting at a scientific meeting and for publication in a peer-reviewed scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld. Further terms concerning publication will be set forth in the clinical trial agreement entered into by the sponsor, the principal investigator, any vendors, and the institution.

10 STUDY MANAGEMENT

The administrative structure will include a DMC (see Section 8.10).

10.1 Monitoring

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor regularly monitors the trial remotely and will periodically visit the investigator based on local restrictions, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation remotely, and discussion of the conduct of the study with the investigator and personnel. All relevant source documents will be uploaded into the IBM electronic system or access to the electronic medical records will be provided for remote monitoring purposes.
All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.2 Inspection of records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.
The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.3 Management of protocol amendments and deviations

10.3.1 Modification of the protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

10.3.2 Protocol deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change of the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.
A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines and will lead to the subject being withdrawn from the study. A list of major protocol deviations will be compiled prior to the start of the study.
Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.4 Study termination

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

the study be required, the sponsor will promptly inform the investigator and the IRB/IEC and provide them with a detailed written explanation. Fulcrum and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The sponsor has no plans to provide study drug to subjects after study closure or termination. The obligations to provide study results for subjects and reports to IRB/IEC shall continue as required by applicable laws and regulations.

At any time, the sponsor, the investigators, or the IRBs/IECs may terminate this study for reasonable cause. Conditions that may lead to reasonable cause and warrant termination include, but are not limited to the following:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the regulatory authority

Written notification that includes the reason for the clinical study termination is required.

The end of the study is defined as the date on which the last subject completes the last visit (includes the safety follow-up visit).

10.5 Final report

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study reports. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study reports, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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