PROTOCOL

PRODUCT NAME/NUMBER:	Varespladib-methyl
PROTOCOL NUMBER:	OPX-PR-02
IND NUMBER:	IND 152230
NCT NUMBER:	04969991
DEVELOPMENT PHASE:	Phase 2
PROTOCOL TITLE:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Varespladib in Patients Hospitalized with Severe COVID-19 Caused by SARS-CoV-2 (STAIRS: **S**mall molecule **T**argeting **A**cute **I**nflammatory and **R**espiratory **S**ymptoms in SARS-CoV-2)
CURRENT VERSION DATE:	v3.0, 28-Feb-2022
SPONSORED BY:	Ophirex, Inc. 5643 Paradise Drive #2 Corte Madera, CA 94925 (415) 891-8682
CONTRACT RESEARCH ORGANIZATION (CRO):	[redacted]

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: OPX-PR-02

PROTOCOL TITLE: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Varespladib in Patients Hospitalized with Severe COVID-19 Caused by SARS-CoV-2

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

March 7, 2022

March 7, 2022

March 7, 2022

SIGNATURE **DATE:**

[redacted]

March 7, 2022

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Varespladib-methyl
PROTOCOL NUMBER	OPX-PR-02
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Varespladib in Patients Hospitalized with Severe COVID-19 Caused by SARS-CoV-2
INDICATION	Severe coronavirus disease 2019 (COVID-19)
STUDY POPULATION	Adult participants aged 18 to 80 years diagnosed with severe laboratory-confirmed COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
OBJECTIVES	The objectives of this study are as follows: <u>Primary:</u> • To evaluate the safety, tolerability, and efficacy of varespladib in patients hospitalized with severe COVID-19 when given in addition to the institutional standard of care <u>Secondary:</u> • To evaluate the efficacy of varespladib in reducing the need for respiratory support • To evaluate the efficacy of varespladib in reducing the duration of hospitalization • To evaluate the efficacy of varespladib in improving time to recovery • To evaluate time to resolution of symptoms • To evaluate the efficacy of varespladib in reducing the incidence of morbidity and mortality <u>Exploratory:</u> • To assess the pharmacokinetics (PK) of varespladib in COVID-19 patients • To evaluate the overall effect of varespladib in suppression of secretory phospholipase A2 (sPLA2) with SARS-CoV-2 infection • To assess pharmacoeconomic outcomes
STUDY DESIGN	This is a 2-part, multi-center, randomized, double-blind, placebo-controlled, phase 2 study designed to evaluate the safety, tolerability, and efficacy of oral varespladib, in addition to standard of care, in patients hospitalized with severe COVID-19 caused by SARS-CoV-2. The goals of this study are to define a safe dose for the population and to assess the safety, tolerability, and efficacy of orally dosed varespladib to improve survival without respiratory failure in patients hospitalized with severe COVID-19 when given in addition to the institutional standard of care therapy. The mortality rates of COVID-19 are strongly linked to acute respiratory distress syndrome (ARDS) which is correlated with elevations of sPLA2 and widespread loss of functioning lung tissue. Upregulation of sPLA2 has been shown to be involved in the dysregulated inflammatory cascade pathways (increased markers of immune activation, also known as cytokine release syndrome) and enzymatic degradation of lung surfactant linked to the development of ARDS. It is believed that treatment with

	varespladib, a potent inhibitor of sPLA2, will prevent or mitigate progression of pulmonary dysfunction in COVID-19 patients by two mechanisms: suppression of sPLA2-induced inflammation and, uniquely, preservation of pulmonary surfactant by direct inhibition of the enzyme responsible for surfactant phospholipid degradation: sPLA2. Data from previous phase 2 clinical trials of varespladib suggest it was capable of reducing mortality in severely septic patients with ARDS, particularly when treatment was initiated within 18 hours of identification of organ failure. The study will be conducted in 2 parts. Both parts will be randomized and double-blind. Part 1 will be dose-finding in 4 parallel treatment groups randomized to treatment with varespladib (at 250 mg once daily [QD], twice daily [BID], or three times daily [TID] [250, 500, or 750 mg/day]) or placebo in a 5:5:5:3 ratio. After all participants in Part 1 have completed Day 28, a data safety monitoring board (DSMB) will review results from Part 1, including all available safety data through Day 60, and will recommend the dose regimen to be used in Part 2. Part 2 will randomize an additional 72 participants to the dose regimen selected from Part 1 or placebo in a 1:1 ratio. In both parts of the study, eligible participants will be enrolled and randomized to receive active varespladib or placebo in addition to institutional standard of care for 7 days (7 complete days of study drug administration after randomization). Participants will be assessed daily per standard of care while hospitalized and on a regular basis after discharge. The Day 1, 4, 7, 14, and 28 visits will be performed in person (either at the hospital/site or via a home health provider) to assess safety, obtain blood and urine samples for laboratory tests, and obtain clinical outcome data. The Day 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 45, and 60 visits for discharged participants may be conducted by phone or via electronic patient-reported outcome (ePRO) devices. Efficacy will be assessed by respiratory failure-free survival at Day 28. Safety will be assessed by evaluating adverse events (AEs), vital sign measurements, use of oxygen therapies, changes in levels of biomarkers, clinical laboratory test results, electrocardiograms (ECGs), physical examination findings, and concomitant medications and therapies. A DSMB will evaluate safety data at specified intervals during both parts of the trial. Pharmacokinetic samples will be drawn from all participants in Part 1 and in a subset of approximately 14 participants in Part 2 in order to enable estimation of PK parameters in approximately 22 participants receiving active treatment with varespladib. The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis. Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}).

PLANNED NUMBER OF PARTICIPANTS	Approximately 90 participants will be enrolled. Part 1 of the study will enroll 18 participants; Part 2 of the study will enroll approximately 72 participants in a 1:1 ratio.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. Participant is hospitalized with severe COVID-19 illness, defined in accordance with the FDA Guidance for Industry – COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (May 2020): a. Severe illness: i. Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress ii. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or partial pressure of oxygen PaO_2/fraction of inspired oxygen $FiO_2 < 300$ 2. Participant has a positive virologic nucleic acid amplification test (NAAT) indicating SARS-CoV-2 infection in a sample collected < 72 hours prior to randomization. 3. Participant is between the ages of 18 and 80 years at the time of enrollment. 4. Participant (or legally authorized representative) provides informed consent prior to initiation of any study procedures. 5. Participant agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 28. 6. Participant has adequate hematologic status (in the absence of transfusion and growth factor support for at least 28 days), defined as follows: a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L b. Platelet count $\geq 75 \times 10^9$/L c. Hemoglobin ≥9 g/dL 7. Participant has an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2. Exclusion criteria: 1. Participant has mild, moderate, or critical COVID-19 defined in accordance with the FDA Guidance for Industry: a. Mild COVID-19: i. Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea ii. No clinical signs indicative of moderate, severe, or critical severity b. Moderate COVID-19: i. Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms) or shortness of breath with exertion ii. Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, peripheral oxygen saturation (SpO_2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute iii. No clinical signs indicative of severe or critical illness

	c. Critical COVID-19: i. Respiratory failure defined based on resource utilization requiring at least one of the following: • Endotracheal intubation and mechanical ventilation • Oxygen delivered by high-flow nasal cannula ([HFNC] heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5) • Noninvasive positive pressure ventilation • extracorporeal membrane oxygenation (ECMO), or • Clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) ii. Shock (defined by systolic blood pressure < 90 mmHg, or diastolic blood pressure < 60 mmHg or requiring vasopressors) iii. Multi-organ dysfunction/failure 2. Participant has taken investigational medications within 7 days or 5 half-lives prior to enrollment, whichever is shorter. 3. Participant has required any new form of sedation, anxiolysis or central nervous system (CNS) depressant within the 48 hours prior to enrollment that would interfere with neurologic assessments at enrollment. 4. Has history of cerebrovascular accident or intracranial bleeding of any kind, acute coronary syndrome, myocardial infarction, or severe pulmonary hypertension. 5. Participant has chronic respiratory failure not associated with COVID-19, defined as prior need for home oxygen, need for home noninvasive positive-pressure ventilation (NIPPV) for reasons other than isolated sleep apnea, or other signs of chronic respiratory failure, in the investigator's judgment. 6. Upper gastrointestinal (GI) bleed evidenced by hematemesis, "coffee-ground" emesis or nasogastric aspirate, or hematochezia thought to originate from upper GI tract. 7. Participant has abnormal liver function defined as any 2 of the following at screening: a. Total bilirubin ≥ 2 × ULN b. Alanine aminotransferase (ALT) ≥ 3 × ULN c. Aspartate aminotransferase (AST) ≥ 3 × ULN d. Alkaline phosphatase (ALP) > 3× ULN e. Gamma-glutamyl transferase (GGT) > 3 × ULN 8. Participant has an estimated glomerular filtration rate (eGFR) < 60 mL/min. 9. Participant has a known allergy or significant adverse reaction to varespladib-methyl or related compounds. 10. Participant is considered by the investigator to be unable to comply with protocol requirements due to geographic considerations, psychiatric disorders, or other compliance concerns; or has any serious medical condition or clinically significant laboratory, ECG, vital sign, or physical examination abnormality that would prevent study participation or place the participant at significant risk, as judged by the Investigator. 11. Participant is breast-feeding, pregnant, has a positive serum hCG pregnancy test, or is not willing to use a highly effective method of contraception for 14 days after treatment. Highly effective methods of contraception are as follows:

	a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable) c. Intrauterine device, intrauterine hormone-releasing system d. Bilateral tubal occlusion e. Vasectomized partner f. Sexual abstinence g. Double-barrier method (condoms, sponge, diaphragm, with spermicidal jellies, or cream)
INVESTIGATIONAL PRODUCTS (IP)	Test: varespladib-methyl (LY333013) 250 mg immediate-release, oblong, white, film-coated tablet for oral administration LY333013 contains the excipients anhydrous lactose USP/National Formulary (NF), lactose monohydrate USP/NF, hydroxypropyl cellulose USP/NF, polysorbate 80 (vegetable source) USP/NF, microcrystalline cellulose USP/NF, croscarmellose sodium USP/NF, magnesium stearate (vegetable source) USP/NF, and the film coat Opadry II 85F18422 White. Reference: placebo Oral formulation matched to the oral varespladib tablet.
TREATMENT REGIMENS	Varespladib or placebo will be administered in addition to institutional standard of care for 7 days. Part 1: Participants will be randomized to receive varespladib (250 mg QD, BID, or TID [250, 500, or 750 mg/day]) or placebo in a 5:5:5:3 ratio. Part 2: Participants will be randomized to receive varespladib or placebo in a 1:1 ratio. The varespladib dose for Part 2 will be the dose selected from Part 1. The written institutional standard of care at each site may change during the study. Other COVID-19 treatments currently approved or authorized for emergency use by the FDA are permitted if in the institution's written standard of care.
PLANNED STUDY SITES	Approximately 5 to 10 study sites in the United States.
CRITERIA FOR EVALUATION	**Efficacy endpoints:** Primary efficacy endpoint: • Proportion of participants alive and free of respiratory failure at Day 28 (respiratory failure is defined in exclusion criterion 1.c.i) Secondary efficacy endpoints: • Clinical improvement as measured by the World Health Organization (WHO) 9-point ordinal scale from baseline through Day 60 • Time to and proportion of subjects with all-cause mortality through Day 60 • Proportion of participants who experienced respiratory failure within the first 28 days after randomization • Among patients that never experience respiratory failure in the first 28 days, time to initiation, duration, and proportion of subjects receiving supplemental oxygen or other respiratory support within the first 28 days after randomization • Among patients that experience respiratory failure in the first 28 days, time to initiation and duration of the forms of respiratory support meeting criteria outlined in critical COVID criteria (exclusion criteria 1.c.i) within the first 28 days after randomization

	• Number of days of oxygen support through Day 28 after randomization • SpO_2 through Day 28 after randomization • Number of ventilator-free days through Day 28 after randomization • Number of hospitalization days through Day 28 after randomization • Number of days without renal stabilization and/or replacement through Day 28 after randomization • Number of organ failure-free days through Day 28 after randomization • Number of days at elevated level of care (intensive care unit [ICU]) through Day 28 after randomization • Number of healthcare encounters through Day 28 after randomization <u>Exploratory endpoints:</u> • sPLA2 within blood samples from treatment initiation to Day 28 after randomization **Safety and tolerability endpoints:** • Incidence and severity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0 grade) of AEs, serious AEs, and AEs leading to discontinuation of IP • Vital signs • Changes in levels of biomarkers: cardiac troponin, C-reactive protein, and ferritin • Clinical laboratory evaluations • 12-lead ECGs **PK endpoints (exploratory):** • PK parameters **Pharmacoeconomic endpoints (exploratory):** • Selected secondary endpoints to include number of healthcare encounters, number of hospitalization days, and number of days at elevated level of care (ICU), after randomization through Day 28.
STATISTICAL METHODS	Descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum for continuous data; frequencies and percentages for categorical data) will be used to summarize study data and details of analyses as outlined in the study Statistical Analysis Plan (SAP). Quantitative outcomes (i.e., durations of interventions or healthcare events, ordinal scales, SpO_2, and concentrations) will generally be analyzed via ANCOVA models for change from baseline. Dichotomous outcomes (i.e., occurrence of interventions or healthcare events) will generally be analyzed with logistic regression models, with risk differences presented and calculated via the delta method. Time-to-event outcomes (i.e., mortality, time till interventions or healthcare events) will generally be analyzed with Cox proportional hazards models. These analyses will control for covariates to be specified in the SAP. Pharmacokinetic and biomarker data will be summarized descriptively. Further details and specifications are provided in the SAP.
SAMPLE SIZE DETERMINATION	A total of approximately 90 participants will be randomized, 18 in Part 1 and 72 in Part 2. This is an exploratory proof of concept study and is not powered based on statistical assumptions.
STUDY AND TREATMENT DURATION	The overall study duration is expected to be approximately 18 months (6 months of active enrollment and 2 months of follow-up in Part 1; 2 to 4 weeks for DSMB review of Part 1 results at Day 28 and selection of the Part 2 dose; 6 months of active enrollment in Part 2; and 2 months of follow-up in Part 2). The sequence and approximate duration of the study periods will be as follows:

	1. Screening: up to 72 hours 2. Treatment: 7 days 3. Follow-up: 28 days after randomization 4. Safety follow-up: 45 and 60 days after randomization The maximum study duration for each participant is approximately 60 days. The treatment duration for each participant is 7 days from the point of randomization (7 complete days of study drug administration after randomization). Screening/enrollment and baseline (Day 1) of the Treatment Period can take place on the same day if the required screening test results are available.

2.2. Schedule of Events

Table 2-1: Schedule of Events

Assessment	Screening/ enrollment	Treatment Period							Follow-up Period											
Study Day	**-1[a]**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [±2]**	**15, 16, 17, 18, 19, 20**	**21 [±2]**	**28 [±2] or ET**	**45 [±3]**	**60 [±4]**
Written informed consent	X																			
Inclusion/exclusion criteria review	X																			
Medication history	X																			
Demographics	X																			
Medical history	X																			
Vital signs (hospitalized patients)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (outpatients)[b]					X			X							X			X		
Peripheral oxygen saturation (SpO_2) (hospitalized patients)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral oxygen saturation (SpO_2) (outpatients)[b]					X			X							X			X		
Height, weight[c]	X																	X		
12-lead electrocardiogram[d]	X		X		X			X							X			X		
Physical examination[e]	X	X			X			X										X		
Neurological assessment	X	X			X			X										X		
Nasopharyngeal swab[f]	X																			
Clinical laboratory tests • CBC • Blood chemistry • Coagulation profile • Biomarkers[g] • sPLA2 activity • Urinalysis	X				X			X							X			X		

Assessment	**Screening/ enrollment**	**Treatment Period**							**Follow-up Period**											
Study Day	**-1[a]**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [±2]**	**15, 16, 17, 18, 19, 20**	**21 [±2]**	**28 [±2] or ET**	**45 [±3]**	**60 [±4]**
Serum pregnancy test	X																	X		
PK blood sample[h]		X	X	X																
WHO 9-point ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer study intervention[i]		X	X	X	X	X	X	X												
Concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The Day 1, 4, 7, 14, and 28 visits will be performed **in person** (either at the hospital/site or via a home health provider).

The Day 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 45, and 60 visits for discharged participants **may be conducted by phone or via ePRO**.

Note: Participants will be assessed daily per standard of care while hospitalized.

Abbreviations: CBC = complete blood count; COVID-19 = coronavirus disease 2019; ePRO = electronic patient-reported outcome; ET = early termination; PK = pharmacokinetic; SAE = serious adverse event; sPLA2 = secretory phospholipase 2; SpO_2 = peripheral oxygen saturation; WHO = World Health Organization

a Screening, enrollment, and Day 1 of the Treatment Period can take place on the same day if the required screening test results are available.

b Vital signs and SpO_2 will be assessed per institutional practice and recorded daily through Day 28 while hospitalized. Vital signs collection is not required prior to collection of PK blood samples, and daily vital signs may be collected before or after PK blood samples as local procedures allow.

c Weight at all marked visits; height at screening only.

d Initial EKG screening should be performed within 24 hours of randomization

e Complete physical examination at Screening; targeted physical examination at subsequent visits.

f Nasopharyngeal swab for virologic testing, if not collected within the previous 72 hours. Nucleic acid amplification test (NAAT) confirmation of COVID-19 in a sample collected < 72 hours prior to randomization is required.

g Biomarkers will include cardiac troponin, C-reactive protein, and ferritin.

h Pharmacokinetic samples will be drawn from all participants in Part 1, and in a subset of approximately 14 participants in Part 2, at the following timepoints:
- Part 1 all participants: Days 1 and 3: pre-first dose and 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-first dose. Day 2: pre-morning dose.
- Part 2 PK participants: Day 3: pre-morning dose and 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-morning dose.
- PK samples may be drawn via a home health provider for participants who are not hospitalized.
- The 12-hour PK samples may be omitted for participants who are not hospitalized.
- Samples should be drawn within windows for each timepoint: ± 15 minutes for 0.5 hour timepoint, ± 30 minutes for 1, 2, 3 and 4 hour timepoints, and ± 1 hour for 6, 8 and 12 hour timepoints.

i There are 7 complete days of treatment. Depending on initial dose administration time, the final dose may conclude on calendar day 8.

3. TABLE OF CONTENTS

3.1. List of In-text Tables

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ACS	acute coronary syndrome
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area-under-the-curve
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
DSMB	data safety monitoring board
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ePRO	electronic patient-reported outcome
ET	early termination
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal

ABBREVIATION	EXPLANATION
hCG	human chorionic gonadotropin
HFNC	high-flow nasal cannula
HRPO	Human Research Protection Office
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
MI	myocardial infarction
MMRM	mixed-model repeated measures
NAAT	nucleic acid amplification test
NCI	National Cancer Institute (United States)
NF	national formulary
NIPPV	noninvasive positive-pressure ventilation
PaO_2	partial pressure of oxygen
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol
Q12H	every 12 hours
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sPLA2	secretory phospholipase 2
SpO_2	peripheral oxygen saturation
TEAE	treatment-emergent adverse event
TID	three times daily
T_{max}	time of maximum concentration
ULN	upper limit of normal

ABBREVIATION	EXPLANATION
USP	United States Pharmacopeia
WHO	World Health Organization

5. INTRODUCTION

5.1. Background and Rationale

Evaluation and management of coronavirus disease 2019 (COVID-19) depends on the severity of the disease; patients with mild disease typically recover at home. Patients with severe or critical COVID-19 are usually hospitalized for observation and supportive care. While most people with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that requires oxygen support, and 5% develop critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury.[1] Despite decades of research and therapeutic development, mortality due to ARDS remains high, at approximately 25% to 40% in most studies.[2] There is significant comorbidity and reduced quality of life in patients who survive.[2] ARDS is a life-threatening, clinical complex of signs and symptoms resulting in respiratory failure. The most common clinical disorders associated with the development of ARDS are pneumonias of bacterial or viral origin. Among other reasons, ARDS is also commonly associated with sepsis due to non-pulmonary sources, trauma (including iatrogenic), and aspiration of gastric contents, and less commonly with pancreatitis and drug reactions. ARDS is characterized by rapid-onset pulmonary failure, often preceded by a dysregulated inflammatory response, with preceding or resulting pulmonary surfactant destruction resulting in a need for supplemental oxygen, extracorporeal membrane oxygenation, or varying degrees of mechanical respiratory support.[3] These cycles of inflammation and surfactant destruction act synergistically to the point at which the innate immune response to insult becomes lethally maladaptive. Once pulmonary edema fluid accumulates in the interstitium and air spaces of the lungs, it causes difficulty in the mechanical work of breathing and impaired gas exchange, causing the sensation of impending doom associated with oxygen starvation. This can result in hypoxemia, reduced carbon dioxide excretion, and ultimately, respiratory failure.[4] The reduction of the inflammation cascade that leads to deteriorating pulmonary function is crucial to the prevention of worsening disease and the development of ARDS.

Several therapeutic agents have failed to improve ARDS outcomes; the current treatment strategy is largely supportive and based on optimized ventilator settings (defined by the ratio of arterial oxygen tension [partial pressure of oxygen] to fraction of inspired oxygen [PaO_2/FiO_2]).[5] It is, therefore, critical to identify novel targeted therapies for ARDS that is related to, or induced by, COVID-19.

Mild and moderate COVID-19 cases are usually defined as those without pneumonia, ARDS, or intensive care unit (ICU) admission.[6] Data suggest that patients with moderate disease may have dyspnea, but the peripheral oxygen saturation (SpO_2) saturation is often, paradoxically, within normal range on ambient air.[7,8,9] Indicators of severe disease are marked tachypnea (respiratory rate $\geq$ 30 breaths per minute), hypoxemia ($SpO_2 \leq 93\%$), $PaO_2/FiO_2 < 300$), and lung infiltrates (> 50% of the lung field involved within 24 to 48 hours).[10] Among patients with severe disease, the median time to dyspnea from the onset of illness or symptoms ranges from 5 to 8 days and the median time to ARDS from the onset of illness or symptoms ranges from 8 to 12 days.[11]

The mortality rates of COVID-19 are strongly linked to deteriorating pulmonary function, which, in turn, is also strongly correlated with the elevation of secretory phospholipase A2 (sPLA2) and widespread loss of functioning lung tissue. Upregulation of sPLA2 has been shown to be involved in the dysregulated inflammatory cascade pathways and enzymatic degradation of lung surfactant,

both of which are linked to ARDS. It is believed that treatment with varespladib, a potent inhibitor of sPLA2, will prevent or mitigate progression of ARDS in COVID-19 patients by two mechanisms: suppression of sPLA2-induced inflammation and, uniquely, preservation of pulmonary surfactant by direct inhibition of the enzyme responsible for surfactant phospholipid degradation: sPLA2.

Data from previous phase 2 clinical trials suggest varespladib could be capable of reducing mortality in severely septic patients with ARDS, particularly when treatment was given within 18 hours of identification of organ failure.[12] This population corresponds with COVID-19 patients with severe disease as defined by the FDA.[13]

The goal of treatment with varespladib in COVID-19 patients is to improve survival without respiratory failure from COVID-19. The goals of this study are to define a safe dose for the population and to assess the safety, tolerability, and efficacy of orally dosed varespladib to improve survival without respiratory failure in patients hospitalized with severe COVID-19, when given in addition to the institutional standard of care therapy.

5.2. Clinical Experience

Multiple clinical studies were previously performed by Eli Lilly and Anthera to characterize the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of varespladib. The inflammatory conditions studied clinically by the previous sponsors for varespladib include sepsis, rheumatoid arthritis, ulcerative colitis, asthma, atherosclerosis, acute chest syndrome in at-risk patients with sickle cell disease, and psoriasis. Previous clinical studies are summarized in the current version of the varespladib investigator's brochure (IB).

5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are improvement in survival and respiratory signs and symptoms. Study participants may experience fewer hospitalizations, fewer hospitalization days, and a more rapid recovery. It is hoped that this study will demonstrate oral varespladib to be a cost-effective and procedurally simplified treatment for patients with COVID-19.

All subjects, regardless of arm randomized, will benefit from participation in this study through safety monitoring beyond the standard of care. Other benefits include added clinical oversight from local study physician(s), providers, nurses, and research staff, as well as medical personnel at the Sponsor and the Contract Research Organization. Continued monitoring/oversight starting with the subject entering the study, through day 60, from health professionals as part of the Post-Treatment Observation Period will provide subjects clinical monitoring well beyond hospital discharge and normal follow up. Vital sign monitoring is a key aspect of this study, and due to the increased frequency of monitoring any trending of the subject status decreasing will potentially be identified earlier. All subjects will receive a total of six 12-lead electrocardiograms. Additional laboratory tests to monitor liver function, cardiac function, renal function, coagulation, and hematology in addition to standard of care will increase safety monitoring of all subjects. Because of the high-level of monitoring and oversight for patients within the study, these patients, including those randomized to placebo, will likely have more timely access to resources including clinician evaluation, procedures, and escalation of care if warranted.

The doses proposed for this study are anticipated to be safe and tolerable for adult participants. The potential risks of study participation include those associated with varespladib, including adverse events (AEs) and serious adverse events (SAEs) as well as the risks of medical evaluation and treatment, including the minimal possibility of allergic reaction from the study drug. Across clinical studies, varespladib was tolerated well and generally did not induce AEs beyond those observed in placebo treatment groups, even in severely ill participants. A total of seven Phase 1 and three phase 2 studies were performed with varespladib, with a total of 733 participants receiving study drug by intravenous (IV) infusion. A total of twelve phase 1 and five phase 2 studies were performed with varespladib-methyl, with a total of 3,679 participants receiving study drug as an oral tablet formulation. Common AEs observed included rhinitis, nausea, and diarrhea. No clinically meaningful varespladib or varespladib-methyl treatment-related effects were noted for biochemical and hematologic parameters other than modest transient increases in liver enzymes that occurred in a number of participants. Treatment with varespladib or varespladib-methyl was not associated with changes in heart rate or blood pressure and there was no evidence of an effect on ventricular repolarization (QT interval). SAEs including cerebrovascular accident (CVA) and myocardial infarction (MI) have been observed in some acutely ill participants in clinical trials for indications such as severe sepsis and acute coronary syndrome. Patients with conditions such as these are excluded from participation in the trial.

In participants receiving varespladib (LY315920) by continuous IV infusion, plasma drug concentrations up to 800 ng/mL for 6 hours were tolerated well and treatment-related AEs were not prevalent. Short-term dosing with varespladib by IV infusion, resulting in plasma concentrations of up to 1,200 ng/mL for 30 minutes, did not induce any AEs; similarly, infusion of varespladib at doses up to 0.323 mg/kg/hour for 4 hours was well-tolerated with no treatment-emergent adverse events (TEAEs) observed. Multiple oral doses of varespladib-methyl tablets (LY333013) up to 500 mg once every 12 hours (Q12H) were tolerated well. Thus, short-term treatment with varespladib or varespladib-methyl (e.g., up to 1 hour) at doses exceeding 0.2 mg/kg/hr (IV) or 500 mg Q12H (oral) is not anticipated to induce AEs, TEAEs, or SAEs. In healthy participants, dosing with varespladib or varespladib-methyl for up to 7 days and at doses up to 77 mg/kg (over 7 days IV) or 500 mg Q12H (orally for up to 12 weeks) did not induce SAEs. In participants with severe sepsis, continuous IV dosing with varespladib for up to 7 days at plasma concentrations of up to 800 ng/mL did not induce substantially more SAEs than were observed with placebo. Thus, administration of varespladib at the proposed doses for this protocol is not anticipated to induce AEs, even in severely ill participants such as those with severe COVID-19.

A summary of the pharmaceutical properties and known potential risks of varespladib and varespladib-methyl is provided in the current version of the varespladib IB. The Investigator must become familiar with all sections of the varespladib IB before the start of the study.

6. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective	**Primary Efficacy Endpoint**
To evaluate the safety, tolerability, and efficacy of varespladib in patients hospitalized with severe COVID-19 when given in addition to the institutional standard of care	Proportion of participants alive and free of respiratory failure at Day 28 (respiratory failure is defined in exclusion criterion 1.c.i)
	Safety and Tolerability Endpoints
	Incidence and severity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0 grade) of AEs, serious AEs, and AEs leading to discontinuation of IP Vital signs Changes in levels of biomarkers: cardiac troponin, C-reactive protein, and ferritin Clinical laboratory evaluations 12-lead ECGs
Secondary Objectives	**Secondary Efficacy Endpoints**
To evaluate the efficacy of varespladib in reducing the need for respiratory support	• Proportion of participants who experienced respiratory failure within the first 28 days after randomization • Among patients that never experience respiratory failure in the first 28 days, time to initiation, duration, and proportion of subjects receiving supplemental oxygen or other respiratory support within the first 28 days after randomization • Among patients that experience respiratory failure in the first 28 days, time to initiation, duration, and proportion of the forms of respiratory support meeting criteria outlined in critical COVID criteria within the first 28 days after randomization • Number of days of oxygen support through Day 28 after randomization • SpO_2 through Day 28 after randomization • Number of ventilator-free days through Day 28 after randomization
To evaluate the efficacy of varespladib in reducing the duration of hospitalization	Number of hospitalization days through Day 28 after randomization

To evaluate the efficacy of varespladib in improving time to recovery To evaluate time to resolution of symptoms	• Clinical improvement as measured by the World Health Organization (WHO) 9-point ordinal scale from baseline through Day 60 • Number of days at elevated level of care (ICU) through Day 28 after randomization • Number of healthcare encounters through Day 28 after randomization
To evaluate the efficacy of varespladib in reducing the incidence of morbidity and mortality	• Time to and proportion of subjects with all-cause mortality through Day 60 • Number of days without renal stabilization and/or replacement through Day 28 after randomization • Number of organ failure-free days through Day 28 after randomization
Exploratory Objectives	**Exploratory Endpoints**
To assess the pharmacokinetics of varespladib in COVID-19 patients	PK parameters
To evaluate the overall effect of varespladib in suppression of sPLA2 with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection	sPLA2 within blood samples from treatment initiation to Day 28 after randomization
To assess pharmacoeconomic endpoints	Selected secondary endpoints, to include number of healthcare encounters, number of hospitalization days, and number of days at elevated level of care (ICU), all through Day 28

7. STUDY DESIGN

7.1. Overall Study Design and Plan

This is a 2-part, multi-center, randomized, double-blind, placebo-controlled, phase 2 study designed to evaluate the safety, tolerability, and efficacy of oral varespladib, in addition to standard of care, in patients hospitalized with severe COVID-19 caused by SARS-CoV-2.

Approximately 90 participants will be randomized, 18 in Part 1 and 72 in Part 2. Participants must be 18 to 80 years of age and have severe laboratory-confirmed COVID-19.

The study will be conducted in 2 parts. Both parts will be randomized and double-blind. Part 1 will be dose-finding in 4 parallel treatment groups randomized to treatment with varespladib (at 250 mg once daily [QD], twice daily [BID], or three times daily [TID] [total doses of 250, 500, or 750 mg/day]) or placebo in a 5:5:5:3 ratio. After all participants in Part 1 have completed Day 28, a data safety monitoring board (DSMB) will review results from Part 1 and will recommend the dose regimen to be used in Part 2. Part 2 will randomize an additional 72 participants to the dose regimen selected from Part 1 or placebo in a 1:1 ratio.

In both parts of the study, eligible participants will be enrolled and randomized to receive either varespladib or placebo in addition to institutional standard of care for 7 days (7 complete days of study drug administration after randomization).

Participants will be assessed daily per standard of care while hospitalized and on a regular basis after discharge. The Day 1, 4, 7, 14, and 28 visits will be performed in person (either at the hospital/site or via a home health provider) to assess safety, obtain blood and urine samples for laboratory tests, and obtain clinical outcome data. The Day 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 45, and 60 visits for discharged participants may be conducted by phone or via electronic patient-reported outcome (ePRO) devices.

Efficacy will be assessed by respiratory failure-free survival at Day 28. For the purposes of this protocol, respiratory failure is defined as a subject requiring:

- Endotracheal intubation and mechanical ventilation
- Oxygen delivered by high-flow nasal cannula ([HFNC] heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5)
- Noninvasive positive pressure ventilation
- extracorporeal membrane oxygenation (ECMO), or
- Clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)

Safety will be assessed by evaluating AEs, vital sign measurements, use of oxygen therapies, changes in levels of biomarkers, clinical laboratory test results, ECGs, physical examination findings, and concomitant medications and therapies. A DSMB will evaluate safety data at specified intervals during both parts of the trial.

All AEs observed by the study personnel or reported by the participant during the study (from the time of the signing of the informed consent through Day 60) will be documented.

PK samples will be drawn from all participants in Part 1 and in a subset of approximately 14 participants in Part 2 in order to enable estimation of PK parameters in approximately 22 participants receiving active treatment with varespladib.

7.2. Rationale and Discussion of Study Design

The available nonclinical and clinical data are sufficient to support a small, phase 2, proof-of-concept trial in adult participants with COVID-19. The initial dose-ranging part of the study will be used to select the safest dose that is likely to demonstrate clinical efficacy in Part 2 of the study and later trials. Safety reviews of data from Part 1 and interim data from Part 2 are designed to ensure participant safety prior to enrollment and treatment of a substantial number of participants.

The use of a placebo control will enable interpretation of safety and efficacy data. The study design requires that both treatment arms (varespladib and placebo) receive standard of care concurrently. Thus, participants will receive treatment in a timely manner while being evaluated for the potential clinical benefit of varespladib.

This study is designed to exclude as few potentially critically ill COVID-19 patients as possible. However, restricting the study population to severe patients and excluding the critical population will better enable interpretation of safety and toxicity data. In addition, excluding patients who already meet clinical criteria of chronic respiratory failure or who already require oxygen support will allow for clearer measurement of progression of acute respiratory failure and consistency with our underlying hypothesis.

Given the safety concern for cerebrovascular accidents (CVA) and myocardial infarction (MI) due to COVID-19, patients at risk of CVA and acute coronary syndrome (ACS) are excluded, and patients requiring any form of sedation, anxiolysis, or central nervous system (CNS) depressant within the 48 hours prior to enrollment that would interfere with neurologic assessments at enrollment are excluded. Given the known modest, transient increases in liver enzymes with varespladib, patients with liver abnormalities are excluded. Given the predominantly renal clearance of varespladib, patients with renal insufficiency are excluded.

The efficacy endpoints for this study were selected to demonstrate superiority of varespladib over placebo. The primary endpoint was selected to evaluate clear clinical benefit based on survival without respiratory failure, whereas secondary and exploratory endpoints were selected to evaluate a range of potential effects of varespladib over the course of treatment that may inform later trials.

7.3. Selection of Doses in the Study

The proposed dosing regimens of LY333013 (varespladib methyl) for the treatment of COVID-19 infection are based on the available PK/PD from previous clinical studies.

LY333013, which is administered orally, is the prodrug of LY315920, which is administered intravenously. LY333013 is rapidly absorbed and hydrolyzed to LY315920; therefore, only LY315920 is detected in the systemic circulation and LY333013 pharmacokinetics are based solely on concentrations of LY315920. Both formulations have been investigated in clinical studies in healthy participants and participants with various disease states.

The pharmacokinetics of LY315920 and LY333013 was investigated in 3 studies in participants with rheumatoid arthritis (Studies J4A-LC-EZZC, J4A-LC-EZZG, and H5P-MC-BWWC). Plasma clearance, steady-state volume of distribution, and drug elimination rates for LY315920 in participants with active rheumatoid arthritis are essentially similar to those observed in healthy participants.

The dose regimens in this study are supported by efficacy and safety data from clinical studies conducted by Eli Lilly in severe sepsis, including multiple organ failure. Two of the studies (J4A-LC-EZZE and J4A-LC-EZZF) support a specific dosing strategy in patients with severe sepsis. This strategy is based on a target plasma concentration of 800 ng/mL using the IV formulation of varespladib (LY315920), which was shown to be an effective concentration for inhibition of sPLA2. Studies in various indications indicated that this target concentration may be achieved with a dosing regimen of 500 to 1000 mg per day when given with food (Studies H5P-LC-BWWC, H5P-LC-BWXC, H5P-LC-BWWE, NCT00533039 [SPIDER-PCI], NCT00455546 [PLASMA 1], NCT00525954 [PLASMA 2], NCT01130246 [VISTA-16], and NCT00743925 [FRANCIS-ACS]).

The dose regimen for participants in Part 2 will be selected based on Part 1 of this study.

7.4. Study Sites

The study will take place at approximately 5 to 10 sites in the United States. Each site is anticipated to screen a sufficient number of participants to randomize approximately 5 to 15 participants. Sites will be selected to ensure access to a representative cross-section of the US population. A study site with a high recruitment rate may be allowed to recruit more participants if other sites have slow enrollment.

7.5. End of Study Definition

The clinical trial is considered completed when the last participant’s final study visit has occurred.

8. PARTICIPANT POPULATION

8.1. Selection of Study Population

Investigators or their designees will maintain a screening log of all candidates who are considered for participation in this study, including reasons for ineligibility or refusal to participate. Consent, screening, randomization, and dosing may occur on the same day if test results are available. Participants who do not meet all of the eligibility criteria will not be enrolled. Approximately 90 participants will be randomized.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A participant will be eligible for study participation if he or she meets all of the following criteria:

1. Participant is hospitalized with severe COVID-19 illness, defined in accordance with the FDA Guidance for Industry – COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (May 2020):
    a. Severe illness:
        i. Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
        ii. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or partial pressure of oxygen PaO_2/fraction of inspired oxygen $FiO_2 < 300$
2. Participant has a positive virologic nucleic acid amplification test (NAAT) indicating SARS-CoV-2 infection in a sample collected < 72 hours prior to randomization.
3. Participant is between the ages of 18 and 80 years at the time of enrollment.
4. Participant (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
5. Participant agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 28.
6. Participant has adequate hematologic status (in the absence of transfusion and growth factor support for at least 28 days), defined as follows:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Platelet count $\geq 75 \times 10^9$/L
    c. Hemoglobin ≥ 9 g/dL
7. Participant has an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2.

8.2.2 Exclusion Criteria

A participant will be excluded from the study if he or she meets any of the following criteria:

1. Participant has mild, moderate, or critical COVID-19 defined in accordance with the FDA Guidance for Industry:

a. Mild COVID-19:
   i. Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
   ii. No clinical signs indicative of moderate, severe, or critical severity

b. Moderate COVID-19:
   i. Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms) or shortness of breath with exertion
   ii. Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, peripheral oxygen saturation (SpO_2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
   iii. No clinical signs indicative of severe or critical illness

c. Critical COVID-19:
   i. Respiratory failure defined based on resource utilization requiring at least one of the following:
      - Endotracheal intubation and mechanical ventilation
      - Oxygen delivered by high-flow nasal cannula ([HFNC] heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5)
      - Noninvasive positive pressure ventilation
      - ECMO, or
      - Clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
   ii. Shock (defined by systolic blood pressure < 90 mmHg, or diastolic blood pressure < 60 mmHg or requiring vasopressors)
   iii. Multi-organ dysfunction/failure

2. Participant has taken investigational medications within 7 days or 5 half-lives prior to enrollment, whichever is shorter.
3. Participant has required any new form of sedation, anxiolysis or central nervous system (CNS) depressant within the 48 hours prior to enrollment that would interfere with neurologic assessments at enrollment.
4. Has history of cerebrovascular accident or intracranial bleeding of any kind, acute coronary syndrome, myocardial infarction, or severe pulmonary hypertension.
5. Participant has chronic respiratory failure not associated with COVID-19, defined as prior need for home oxygen, need for home noninvasive positive-pressure ventilation (NIPPV) for reasons other than isolated sleep apnea, or other signs of chronic respiratory failure, in the investigator's judgment.
6. Upper gastrointestinal (GI) bleed evidenced by hematemesis, "coffee-ground" emesis or nasogastric aspirate, or hematochezia thought to originate from upper GI tract.

7. Participant has abnormal liver function defined as any 2 of the following at screening:
   a. Total bilirubin ≥ 2 × ULN
   b. Alanine aminotransferase (ALT) ≥ 3 × ULN
   c. Aspartate aminotransferase (AST) ≥ 3 × ULN
   d. Alkaline phosphatase (ALP) > 3× ULN
   e. Gamma-glutamyl transferase (GGT) > 3 × ULN
8. Participant has an estimated glomerular filtration rate (eGFR) < 60 mL/min.
9. Participant has a known allergy or significant adverse reaction to varespladib-methyl or related compounds.
10. Participant is considered by the investigator to be unable to comply with protocol requirements due to geographic considerations, psychiatric disorders, or other compliance concerns; or has any serious medical condition or clinically significant laboratory, ECG, vital sign, or physical examination abnormality that would prevent study participation or place the participant at significant risk, as judged by the Investigator.
11. Participant is breast-feeding, pregnant, has a positive serum hCG pregnancy test, or is not willing to use a highly effective method of contraception for 14 days after treatment. Highly effective methods of contraception are as follows:
    a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
    c. Intrauterine device, intrauterine hormone-releasing system
    d. Bilateral tubal occlusion
    e. Vasectomized partner
    f. Sexual abstinence
    g. Double-barrier method (condoms, sponge, diaphragm, with spermicidal jellies, or cream)

8.3. Participant Replacement

Withdrawn participants will not be replaced.

Randomized participants withdrawn from the study may not reenter. The participant number for a withdrawn participant will not be reassigned to another participant.

9. TREATMENTS

9.1. Identification of Investigational Products

The investigational products (IPs) in this study are varespladib and matching placebo.

- Varespladib-methyl (LY333013)
  - 250 mg immediate-release oblong, white, film-coated tablet for oral administration
- Placebo
  - Oral formulation matched to the oral varespladib tablet

LY333013 contains the excipients anhydrous lactose United States pharmacopeia (USP)/National Formulary (NF), lactose monohydrate USP/NF, hydroxypropyl cellulose USP/NF, polysorbate 80 (vegetable source) USP/NF, microcrystalline cellulose USP/NF, croscarmellose sodium USP/NF, magnesium stearate (vegetable source) USP/NF, and the film coat Opadry II 85F18422 White.

9.2. Timing of Dose for Each Participant

In Part 1, varespladib or placebo will be administered in addition to institutional standard of care for 7 days at a dosage of 250 mg QD, BID, or TID (total doses of 250, 500, or 750 mg/day). The doses should be taken at the same times each day (+/- 2 hours for medication scheduling); ideally at least 5 hours apart. In Part 1, each participant will take 3 tablets per day with food. If IP is administered via nasogastric tube, it should be taken with food if possible.

Part 1 Randomized Treatment	**Morning**	**Afternoon**	**Bedtime**
250 mg QD	250 mg	placebo	placebo
250 mg BID	250 mg	placebo	250 mg
250 mg TID	250 mg	250 mg	250 mg
placebo	placebo	placebo	placebo

In Part 1, any dose that is missed should not be taken later that day. This includes Day 1; if a participant is enrolled in the afternoon or evening, only the afternoon and/or evening doses should be taken. If 7 complete days of dosing have not been completed by the end of Day 7, then the remaining doses will be administered on the appropriate schedule on Day 8. Examples:

- On Day 1, a participant who is enrolled in the morning should take the morning dose in the morning, the afternoon dose in the afternoon, and the bedtime dose at bedtime. No doses will be taken on Day 8.
- On Day 1, a participant who is enrolled in the afternoon should take the afternoon dose in the afternoon and the bedtime dose at bedtime. The last morning dose will be taken in the morning on Day 8, completing study treatment.
- On Day 1, a participant who is enrolled in the evening should take the bedtime dose at bedtime. The last morning and afternoon doses will be taken in the morning and afternoon, respectively, on Day 8, completing study treatment.

In Part 2, varespladib or placebo will be administered in addition to institutional standard of care for 7 days using the dose regimen selected from Part 1. For Part 2, the dose regimen for placebo will match the treatment regimen. The dose regimen selected for Part 2 will not include placebo doses used to maintain the blinding in Part 1. For example, if BID dosing is selected for Part 2, then the afternoon dose will be eliminated, and only morning and evening doses will be given for 7 days. If QD dosing is selected for Part 2, then only one dose will be administered per day for 7 days.

The doses should be taken at the same times each day (+/- 2 hours for medication scheduling), with food. As in Part 1, if IP is administered via nasogastric tube, it should be taken with food if possible. For Part 2, missed doses should be taken as soon as possible. Doses should be spaced evenly, but if a dose is missed, an interval of at least 5 hours between doses is recommended. If 7 complete days of dosing have not been completed by the end of Day 7 for Part 2 patients, then the remaining doses will be administered on the appropriate schedule on Day 8.

9.3. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

9.4. Premature Participant Withdrawal

All participants will be advised that they are free to withdraw consent from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep participants in the study, even if IP is discontinued; however, participants must be withdrawn from the study if they withdraw consent to participate. Participants should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the investigators to make efforts to continue to obtain their outcome data. Investigators must attempt to contact participants who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

If a participant withdraws consent before completing the study, the reason for withdrawal of consent and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study (see Section 10.2.3.5) should be performed at the time of premature discontinuation from the study, regardless of whether the participant has received study drug or not.

9.5. Discontinuation of Study Intervention

9.5.1 Individual Participant Halting Criteria

If a clinically significant finding is identified (including, but not limited to, deterioration from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Every effort should be made to administer the planned doses. Dosing should be held for a participant who experiences any of the following toxicities:

- Any Grade ≥ 2 creatinine increase (> 1.5 × baseline or ULN)
- Any new, treatment-emergent occurrence of any of the following adverse events of special interest:

- Cerebrovascular accident
- Acute coronary syndrome
- Supraventricular arrhythmia requiring urgent medical intervention
- Any ventricular tachycardia/fibrillation including Torsade de Pointes
- Hepatic toxicity with AST and/or ALT ≥ 3 × ULN for 2 days or > 5 × ULN on one occasion

If a participant becomes unable to swallow the IP due to worsening of their condition, nasogastric administration or a dose delay may be considered in consultation with the medical monitor. In general, treatment with IP should continue for the full 7 days unless the participant is unable to continue treatment or if it is the participant's best interest to discontinue treatment. If a participant must discontinue IP, every effort will be made to continue the participant in the study through Day 60. If a participant experiences an SAE judged to be related to the IP, the treatment for that participant will be permanently discontinued from the IP, but every effort will be made to continue the participant in the study through Day 60.

Any new clinically relevant adverse finding will be reported as an adverse event (AE) as defined in Section 11.1.

Discontinuation from IP does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.

9.5.2 Management of Acute Kidney or Liver Injury

Acute kidney/liver injury has been reported as a possible complication during the disease progression of COVID-19.

Extra caution and monitoring will be exercised when treating patients with COVID-19-induced hepatic dysfunction. Given the relatively short duration of treatment (7 days) compared to previous studies with varespladib and the transient nature of hepatic enzyme elevation, subjects with acute liver injury will continue IP and be closely monitored with clinic visits and repeated blood work including liver function tests on Days 14 and 28. If hepatic enzymes exceed the hepatic toxicity limits specified in Section 9.5.1, IP should be discontinued. However, every effort will be made to continue the participant in the study through Day 60.

In the event of acute kidney injury secondary to COVID-19, the subsequent dose of the study drug will be withheld and will be recommenced once renal parameters become normal and an interval of at least 5 hours is available before the next dose. Once recommenced, IP will be given through the original 7-day treatment period and the missed dose will not be taken. If renal function is persistently abnormal and the participant misses study drug more than 24 hours, their IP treatment should be discontinued.

9.5.3 Study Halting Criteria

Any of the following criteria will trigger a review by the DSMB and a potential halt in IP administration or enrollment of new participants:

- Any participant death or SAE in which there a reasonable possibility that the IP caused the death or SAE, as judged by the investigator.

Section 14.6 describes procedures in the event of suspension or termination of the study for all participants. The DSMB charter will include details of the procedures they will follow when reviewing study data (see Section 12).

9.6. Treatment Compliance

While hospitalized, participants will receive the IP at the study site under the surveillance of appropriate study personnel. Tablet administration details will be recorded by the site. Participants who are discharged during the 7-day treatment period will be provided with the remainder of their assigned study drug and asked to record the date and time of each dose and whether it was taken with food.

9.7. Method of Assigning Participants to Treatment Groups

In Part 1, 18 participants will be randomized in a double-blind manner in 4 parallel treatment groups to treatment with varespladib (at 250 mg QD, BID, or TID [total doses of 250, 500, or 750 mg/day]) or placebo in a 5:5:5:3 ratio. After all participants in Part 1 have completed Day 28, a DSMB will review the results from Part 1, including all available safety data through Day 60, and will recommend the dose regimen to be used in Part 2.

Part 2 will randomize up to an additional 72 participants to the dose regimen selected from Part 1 versus placebo in a 1:1 ratio.

The randomization schedules will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as participants are entered into the study. Study center will be a blocking factor in the randomization schedules.

The randomization schedules will be prepared by the CRO before the start of the study. No one involved in the study performance will have access to the randomization schedules before official unblinding of treatment assignment. No participant will be randomized into this study more than once.

9.8. Blinding and Unblinding Treatment Assignment

All participants, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from the CRO who will have access to the randomization code, and the DSMB. One secondary pharmacist at each site participating in Part 1 only will be unblinded to ensure the correct cartons are assigned to morning, noon, and evening. This unblinded pharmacist will have no other study participation or activities. Details are provided in the Pharmacist Manual. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel upon database lock. The unblinded personnel who are not otherwise involved in the study will prepare the data for DSMB review. The DSMB charter will include procedures to prevent unblinding of the other study-related personnel.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the

participant's treatment assignment. Study personnel will not be unblinded to determine if an event is related to IP.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS. If the investigator is not able to discuss treatment unblinding in advance, they must notify the medical monitor as soon as possible about the unblinding incident without revealing the participant's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate CRF for that participant.

Unblinding for an individual participant will not result in unblinding the treatment assignments for the remaining participants in the study. Thus, the overall study blind will not be compromised. If a participant's treatment assignment is unblinded, he/she may be discontinued from IP administration, and every effort will be made to continue the participant in the study through Day 60. The investigator will make this decision after consultation with the medical monitor.

9.9. Prohibited and Permitted Therapies

All concomitant medications (including over-the-counter medications and herbal supplements) and concomitant therapies used will be recorded in the source document and on the appropriate eCRF.

No potential drug interactions or overlapping toxicities with current standard-of-care treatments for COVID-19 have been identified. In vitro cytochrome P450 enzyme interaction studies showed that varespladib would not cause clinically significant inhibition of the metabolic clearance of drugs metabolized by CYP3A (such as dexamethasone), and no effect of varespladib on p-glycoprotein.

Participants may receive supportive care according to the written standard of care policy or guidance for the trial site hospital. The written institutional standard of care at each site may change during the study.

9.9.1 Prohibited Therapies

Experimental treatment or off-label use of marketed medications intended as specific treatment for COVID-19 is prohibited from Day 1 through Day 28 unless such treatments are outlined by the institution's written standard of care. Dialysis before the study is prohibited. Prospective participants on mechanical ventilation or ECMO at the time of enrollment are not eligible, but these therapies may be started during the study.

9.9.2 Permitted Therapies

All concomitant medications and therapies not prohibited in Section 9.9.1 are allowed.

Other COVID-19 treatments currently approved or authorized for emergency use by the FDA are permitted **if in the institution's written standard of care**.

9.10. Treatment After End of Study

After the end of the study, each participant will be treated according to standard clinical practice.

9.11. Dispensing and Storage

The IP (varespladib and placebo) supplied by Ophirex, Inc. is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the products.

Until the IP is dispensed to the participants, it must be stored in a securely locked area that is not generally accessible. The IP may be stored at room temperature. The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the products.

Detailed instructions for selecting and dispensing each dose of IP are in the study manual.

9.12. Drug Accountability

The investigator or designee must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Ophirex, Inc. or designee.

The investigator or designee must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of participants who received the IPs. The investigator will not supply the IP to any person except those named as subinvestigators on the FDA form 1572, designated study personnel, and participants in this study. The investigator will not dispense the IPs from any study sites other than those listed on the FDA form 1572. Investigational product may not be relabeled or reassigned for use by other participants. If any of the IP is not dispensed, or is lost, stolen, spilled, unusable, or received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, the IP (including unused, partly used, and empty packaging) must be left in the original packaging and retained in a securely locked area until instructed by the sponsor.

9.13. Labeling

Investigational product supplies will have labels that meet the applicable regulatory requirements including the protocol number, a caution statement, storage, and sponsor identification.

10. STUDY PROCEDURES

Participants must provide written informed consent and/or assent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each participant. If a participant misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

The overall study duration is expected to be approximately 18 months (6 months of active enrollment and 2 months of follow-up in Part 1; 2 to 4 weeks for DSMB review of Part 1 results at Day 28 and selection of the Part 2 dose; 6 months of active enrollment in Part 2; and 2 months of follow-up in Part 2).

The sequence and approximate duration of the study periods will be as follows:

1. Screening: up to 72 hours
2. Treatment: 7 days
3. Follow-up: 28 days after randomization
4. Safety follow-up: 45 and 60 days after randomization

The maximum study duration for each participant is approximately 60 days.

The treatment duration for each participant is 7 days from the point of randomization (7 complete days of study drug administration after randomization). Screening/enrollment and baseline (Day 1) of the Treatment Period can take place on the same day if the required screening test results are available.

10.2. Study Periods and Visits

Participants will be assessed daily per standard of care while hospitalized and on a regular basis after discharge. The Day 1, 4, 7, 14, and 28 visits will be performed in person (either at the hospital/site or via a home health provider) to assess safety, obtain blood and urine samples for laboratory tests, and obtain clinical outcome data. The Day 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 45, and 60 visits for discharged participants may be conducted by phone or via ePRO devices.

10.2.1 Screening

The participant should be screened within 1 day before enrollment in the study; screening and enrollment could occur on the same day. Procedures and local laboratory results collected within 72 hours of signed consent may be used for screening, although it is preferential to conduct screening activities within 24 hours, as long as they are collected within allowable study windows and meet all other study criteria.

The following procedures will be performed at screening:

- Obtain informed consent in writing

- Review inclusion/exclusion criteria
- Collect demographic information
- Record medical history, including current medications and therapies (e.g., prescription and nonprescription medications)
- Measure vital signs and SpO_2 per institutional practice
- Measure weight and height
- 12-lead ECG
- Physical examination
- Neurological assessment
- Nasopharyngeal swab for virologic testing, if not collected within the previous 72 hours; NAAT confirmation of COVID-19 in a sample collected < 72 hours prior to randomization is required
- Collect blood and urine for the following tests (see Section 10.3.3.1 for details on the components included in CBC, chemistry, coagulation, urinalysis and biomarker testing):
    - clinical laboratory tests including complete blood count (CBC), blood chemistry, coagulation tests, and urinalysis
    - sPLA2 enzyme activity
    - serum pregnancy test (participants of childbearing potential only)
    - biomarkers (cardiac troponin, CRP, and ferritin)
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record any AEs occurring after informed consent was signed

Procedures for rescreening prospective participants who initially fail to meet study entry criteria are described in Section 14.3.

10.2.2 Treatment Period

The treatment period is defined as baseline (Day 1) through the completion of 7 days of study drug dosing which is expected on Day 7, but which may occur on calendar day 8, depending on the dosing regimen and timing of first dose of study drug.

10.2.2.1 Day 1

Following completion of all assessments and confirmation of eligibility, the participant will be randomized via the IWRS. The following procedures will be performed on Day 1 of the Treatment Period:

- Measure vital signs and SpO_2 per institutional practice

- Part 1 participants only: collect a PK blood sample prior to the first dose of IP (NOTE: Vital signs collection is not required prior to collection of PK blood samples, and daily vital signs may be collected before or after PK blood samples as local procedures allow.)
- Initiate IP dosing

After initiating treatment with the IP:

- Physical examination
- Part 1 participants only: collect a PK blood sample at the following times after the first dose: 30 minutes and 1, 2, 3, 4, 6, 8, and 12 hours
- Neurological assessment
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.2.2 Day 2

- Part 1 participants only: collect a PK blood sample prior to the morning dose of IP
- Continue IP dosing
- If hospitalized, measure vital signs and SpO_2 per institutional practice
- 12-lead ECG
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.2.3 Day 3

- Continue IP dosing
- If hospitalized, measure vital signs and SpO_2 per institutional practice
- Part 1 (all participants) and Part 2 (PK participants): collect a PK blood sample prior to the morning dose of IP and at the following times after the morning dose: 30 minutes and 1, 2, 3, 4, 6, 8, and 12 hours
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.2.4 Day 4

- Continue IP dosing
- If hospitalized, measure vital signs and SpO_2 per institutional practice
- 12-lead ECG

- Physical examination
- Neurological assessment
- Collect blood and urine for the following tests:
    - clinical laboratory tests including CBC, blood chemistry, coagulation tests, and urinalysis
    - sPLA2 enzyme activity
    - biomarkers (cardiac troponin level, CRP, and ferritin)
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.2.5 Day 5

- Continue IP dosing
- Measure vital signs and SpO_2 per institutional practice
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.2.6 Day 6

- Continue IP dosing
- If hospitalized, measure vital signs and SpO_2 per institutional practice
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.2.7 Day 7

- Continue IP dosing through the end of 7 complete days of study drug dosing (this may end on calendar Day 8)
- Measure vital signs and SpO_2 per institutional practice
- 12-lead ECG
- Physical examination
- Neurological assessment
- Collect blood and urine for the following tests:
    - clinical laboratory tests including CBC, blood chemistry, coagulation tests, and urinalysis

- sPLA2 enzyme activity
- biomarkers (cardiac troponin level, CRP, and ferritin)

- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.3 Follow-up Period

10.2.3.1 Days 8, 9, 10, 11, 12, and 13

- If hospitalized, measure vital signs and SpO_2 per institutional practice
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.3.2 Day 14 (±2)

At 14 (±2) days after randomization, the following procedures will be performed:

- Measure vital signs and SpO_2 per institutional practice
- 12-lead ECG
- Collect blood and urine for the following tests:
  - clinical laboratory tests including CBC, blood chemistry, coagulation tests, and urinalysis
  - sPLA2 enzyme activity
  - biomarkers (cardiac troponin level, CRP, and ferritin)
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.3.3 Days 15, 16, 17, 18, 19, and 20

- If hospitalized, measure vital signs and SpO_2 per institutional practice
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.3.4 Day 21 (±2)

At 21 (±2) days after randomization, the following procedures will be performed:

- If hospitalized, measure vital signs and SpO_2 per institutional practice

- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.3.5 Day 28 (±2) or at time of Early Termination

- Measure vital signs and SpO_2 per institutional practice
- Measure weight
- 12-lead ECG
- Physical examination
- Neurological assessment
- Collect blood and urine for the following tests:
    - clinical laboratory tests including CBC, blood chemistry, coagulation tests, and urinalysis
    - sPLA2 enzyme activity
    - serum pregnancy test (participants of childbearing potential only)
    - biomarkers (cardiac troponin level, CRP, and ferritin)
- Evaluate the participant using the WHO 9-point ordinal scale
- Record concomitant medications and concomitant therapies
- Assess and record AEs

10.2.3.6 Day 45 (±3)

- If hospitalized, measure vital signs and SpO_2 per institutional practice
- Evaluate the participant using the WHO 9-point ordinal scale
- Assess and record AEs

10.2.3.7 Day 60 (±4)

- If hospitalized, measure vital signs and SpO_2 per institutional practice
- Evaluate the participant using the WHO 9-point ordinal scale
- Assess and record AEs

10.3. Assessments

10.3.1 Efficacy Assessments

10.3.1.1 Oxygen Support

The investigator will assess the participant's need for oxygen support throughout the study per institutional practice. Endpoints pertaining to oxygenation, non-invasive ventilation/high flow oxygen, and invasive mechanical ventilation/ECMO will be assessed using these data.

10.3.1.2 WHO 9-point Ordinal Scale

The investigator will assess the participant's clinical status using the WHO 9-point ordinal scale.

Table 10-1: WHO 9-point Ordinal Scale

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitations on activities	1
	Limitation on activities	2
Hospitalized; mild disease	No oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized; severe disease	Noninvasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation plus additional organ support (pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)	7
Dead	Death	8

The timepoints are indicated in the Schedule of Events (Table 2-1).

Endpoints pertaining to hospitalization and mortality will be assessed using these data and post-discharge eCRF questions.

10.3.1.3 Healthcare Encounters

All healthcare encounters through Day 60 will be documented for each participant using participant reports and medical records. A healthcare encounter is defined as an interaction between a participant and a healthcare provider for the purpose of providing healthcare services or assessing the health status of a patient. An escalation in level of care for a hospitalized patient will also be included as a healthcare encounter for purposes of analysis.

10.3.2 Pharmacokinetics

10.3.2.1 Pharmacokinetic Analysis Methods

Pharmacokinetic samples will be drawn in all participants in Part 1 and in a subset of approximately 14 participants in Part 2 in order to enable estimation of PK parameters in approximately 22 participants receiving active treatment with varespladib. Samples should be drawn within windows for each timepoint: ± 15 minutes for 0.5 hour timepoint, ± 30 minutes for 1, 2, 3 and 4 hour timepoints, and ± 1 hour for 6, 8 and 12 hour timepoints. The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis. Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the PK analysis plan.

10.3.2.2 Pharmacokinetic Parameters

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation). Actual sampling times will be used for all parameter estimation.

10.3.2.3 Pharmacokinetic Sample Collection

Blood samples for PK analysis will be collected at the time points specified in the Schedule of Events (Section 2.2). Blood sample collection, processing, and shipping instructions will be provided in the study laboratory manual. Samples should be drawn within windows for each timepoint: ± 15 minutes for 0.5 hour timepoint, ± 30 minutes for 1, 2, 3 and 4 hour timepoints, and ± 1 hour for 6, 8 and 12 hour timepoints.

10.3.3 Safety Variables

Safety will be assessed by evaluating AEs, vital sign measurements, pulse oximetry, use of oxygen therapies, changes in levels of biomarkers, clinical laboratory test results, ECGs, physical examination findings, and concomitant medications and therapies.

10.3.3.1 Clinical Laboratory Safety Assessments

10.3.3.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points indicated in the Schedule of Events (Table 2-1).

Complete blood count:	hemoglobin, hematocrit, red blood cell (RBC) count, red cell distribution width (RDW), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count (or estimate), white blood cell count including differential (percentage and absolute: basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood chemistry:	albumin, creatinine, blood urea nitrogen (BUN), eGFR, total bilirubin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate

	aminotransferase, lactate dehydrogenase, gamma-glutamyl transferase, lipase, lactate, blood glucose
Coagulation:	international normalized ratio (INR), prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Other:	sPLA2 enzyme activity and biomarkers (cardiac troponin, C-reactive protein [CRP], and ferritin)
Serum pregnancy test:	for participants of childbearing potential only

Routine laboratory specimens will be analyzed at local laboratories, PK and sPLA2 samples will be analyzed by a central laboratory. Specimens must be prepared for analysis according to the instructions provided in the study laboratory manual before shipment to the central laboratory.

10.3.3.1.2 Evaluation of Clinical Laboratory Values

Each local laboratory will provide the normal ranges of values for the clinical laboratory assessments in this study, and the local ranges will be regarded as the reference ranges on which decisions will be made by each investigator.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.

10.3.3.2 Clinical Examinations

10.3.3.2.1 Vital Signs and Peripheral Oxygen Saturation (SpO_2)

Vital signs (including body temperature) and peripheral oxygen saturation (SpO_2) will be assessed at the timepoints indicated in the Schedule of Events (Table 2-1) per institutional practice.

If the participant has multiple vital sign or SpO_2 assessments on a given day, an assessment measured between 6 am-noon should be recorded in the eCRF, if possible, for consistency.

10.3.3.2.2 Twelve-lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at the timepoints indicated in the Schedule of Events (Table 2-1) per institutional practice. All ECG recordings will be identified with the participant identification, date, and time of the recording and will be attached to the participant's eCRF.

10.3.3.2.3 Physical Examination

A physical examination will be performed at the timepoints indicated in the Schedule of Events (Table 2-1) per institutional practice.

10.3.3.2.4 Neurological Assessment

A neurological assessment will be performed at the timepoints indicated in the Schedule of Events (Table 2-1) per institutional practice.

10.3.3.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, physical examination finding, or neurological finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity or a change in the quality of the disease or condition. Worsening of a pre-existing condition is considered an AE. Worsening or progression of the COVID-19 disease under study will not automatically be considered an AE unless the investigator believes that the progression is related to study drug. In that case, the worsening or progression of COVID-19 disease under study will be reported as an AE / SAE as appropriate.

Events that occur in participants treated with placebo, or during treatment-free periods of the study, are also considered AEs.

11.1.2 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a pre-approval test product, the known information is contained in the IB. An unexpected adverse event is one for which the nature or severity is not consistent with the IB. All AEs whether expected or unexpected will be recorded.

11.1.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy (a newly diagnosed pregnancy in a participant that received IP is not considered an SAE unless it is suspected that the IP interacted with a contraceptive method and led to the pregnancy)

- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions.

11.1.4 Treatment-emergent Adverse Events

An AE is defined as treatment-emergent if the first onset or worsening is after the first administration of IP and within the study's AE reporting period.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during hospitalization and at outpatient visits or via telephone.

All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to IP (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Site staff will record all reportable events with start dates occurring any time after informed consent is obtained through Day 60. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. During hospitalization and at each outpatient visit or telephone visit, the participant will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified by the investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Specific conditions and symptoms have values or descriptive comments for each grade. The CTCAE grades are based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Changes in the severity of an AE will be documented.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.3.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.3.

11.2.2.3 Action(s) Taken

Action(s) taken may consist of:

IP interrupted	IP schedule was modified by temporarily terminating the prescribed regimen of IP.
IP withdrawn	IP schedule was modified through termination of IP.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the participant's death, the outcome of death should be indicated for each such AE.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must assess each AE's relationship to the IP. Infection with SARS-CoV-2 resulting in severe COVID-19 is associated with broad, complex, and significant pathophysiology. The Investigator should carefully consider the list of possible manifestations of COVID-19 when assigning a relationship of specific AEs to the study drug. The categories for classifying the investigator's opinion of the relationship are as follows:

The investigator must assess each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Definitely	A definite probability exists of a relationship between the AE and IP.
Probably	A reasonable probability exists of a relationship between the AE and IP.
Possibly	A possibility exists of a relationship between the AE and IP.
Unrelated	No reasonable possibility exists of a relationship between the AE and IP.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the CRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the decision about whether the participant may continue treatment with IP will be made by the sponsor after consultation with the investigator and/or medical monitor.

For double-blinded studies, it is not necessary to unblind a participant's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.8 for a description of the unblinding procedures.

11.2.5 Reporting

11.2.5.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event by completing, signing and dating the SAE Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to [redacted] by one of the following methods:

Email: [redacted]

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Participant's identification number
- Participant's year of birth
- Participant's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable
- AE term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the participant's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, AEs, date of occurrence, participant identification number, study number, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the [redacted] Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor can assist with this.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

Investigators should specifically monitor several AEs potentially associated with varespladib treatment, including cerebrovascular accident (CVA; stroke), myocardial infarction (MI), and malignant cardiac arrhythmias. These AEs may also be associated with COVID-19. Investigators should carefully determine whether these AEs are potentially related to study drug.

11.3.2 Pregnancy

All participants of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Participants should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every participant of childbearing potential. A participant who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A participant who becomes pregnant during IP treatment will be immediately discontinued from IP, but every effort will be made to continue the participant in the study through Day 60. The investigator must report the pregnancy within 72 hours of learning of the pregnancy, to [redacted] Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on a pregnancy form provided by the sponsor or its designee.

Safety assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on a pregnancy form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

11.3.3 Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. Any AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE CRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Medical Monitor immediately (i.e., within 24 hours of learning of the event).

No specific antidote to LY333013 exists, so treatment should be directed at supportive care. As with any overdose, participants should be monitored closely and observed for expected and unexpected clinical and laboratory effects.

12. DATA SAFETY MONITORING BOARD

The DSMB will operate under a charter that will be finalized prior to the start of the study. After all participants in Part 1 have completed Day 28, the DSMB will review the safety results from Part 1, including all available safety data through Day 60, and will recommend the dose regimen to be used in Part 2. During Part 2, the DSMB will evaluate unblinded safety data, including data by group, at the intervals specified in the DSMB charter. In case of significant toxicity, the DSMB may choose to review the available safety data and recommend pausing or stopping recruitment in a particular dose group or the study as a whole. Efforts will be made to collect all follow-up and safety data through Day 60 for all patients enrolled in the study.

13. STATISTICS

13.1. Statistical Analysis

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. The statistical analysis plan (SAP) with final planned analyses will be developed and finalized before database lock.

Descriptive statistical methods will be used to summarize the data from this study with confidence intervals calculated for the primary and secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to the number of participants (n), mean, median, standard deviation, minimum, and maximum for continuous data; and frequencies and proportions for categorical data. All data collected during the study will be included in data listings.

Participants who die will have their data after death assigned as the worst possible value within a specific scale or with regard to duration or proportion as defined by the particular outcome. Participants who do not experience a particular event will not be excluded from the analysis of duration or time-to-event endpoints and will have an appropriate value assigned. Missing data for reasons other than death will, when possible, be derived from contemporaneous clinical data. If other clinical data are not available or not determinative of the outcome, data will be imputed based on the last available value (last observation carried forward).

Unless otherwise indicated, comparative statistics between treatment and control group will report point estimates, p-values, and 95% confidence intervals with the goal of understanding the clinical importance of observed effects.

This study is considered an exploratory study. Statistical tests will be interpreted in an exploratory sense only and will not be considered formal hypothesis tests.

All efficacy variables will be summarized descriptively. Primary and secondary efficacy endpoints will be tabulated according to the "Observed Cases" approach. Exploratory hypothesis testing will also be conducted for the majority of endpoints.

Part 2 efficacy summaries will be done by randomized treatment. Part 1 efficacy data will be listed only. Hypothesis testing will be evaluated in an exploratory manner in order to inform decisions about future trials.

All statistical analyses will be conducted with the SAS® System, version 9.3 or higher.

13.1.1 Analysis Populations

The following 5 analysis populations are planned for this study:

- **Intent-to-treat (ITT)**: All randomized participants.
- **Safety:** All participants who receive at least 1 dose of IP.
- **Per-protocol (PP):** All randomized participants with at least 1 dose of IP with no key protocol deviations during the study that would affect the interpretation of the primary efficacy assessments. Inclusion in the PP population will be determined prior to database lock and unblinding of treatment assignment.
- **Pharmacokinetic (PK):** All randomized participants who receive at least 1 dose of IP and provide at least 1 evaluable post-dose PK measurement.

- **Combined Population**: All participants in Part 2 and all participants in Part 1 assigned to the dose regimen selected for Part 2, who receive at least 1 dose of IP at the dose regimen used in Part 2.

Assignment of participants to populations will be determined prior to database lock.

The Safety Population will be used to analyze the safety endpoints, the ITT Population will be used to analyze the efficacy endpoints, and the PK population will be used to analyze the PK endpoints. In addition to the ITT Population, the PP and Combined Populations will be used to analyze the primary efficacy endpoint.

Part 1 efficacy data will be listed. Part 1 participants receiving placebo or the dose regimen used in Part 2 will be included in the Combined Population. Safety and PK analyses will be based on actual treatment received. For the efficacy analyses, in the event that a participant is randomized incorrectly or is given the incorrect IP, analyses of the ITT, PP, and Combined populations will be based on the randomized treatment.

13.1.2 Study Participants and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of participants randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of participants in each analysis population will be reported.

13.1.2.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major for statistical analysis purposes before unblinding and will be summarized or listed as appropriate. Key protocol deviations will be used to exclude participants from the PP population.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the safety and ITT populations.

Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the IP, in accordance with local regulatory requirements. Baseline participant characteristics will include medical history and disease characteristics.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of participants taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

13.1.3 Exposure and Compliance

IP exposure and dosing information including the number of doses and amount of IP received will be listed for each participant.

13.1.4 Efficacy Analysis

Withdrawn participants will not be replaced. Randomized participants withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

Missing data for reasons other than death will, when possible, be derived from contemporaneous clinical data. If other clinical data are not available or not determinative of the outcome, data will be imputed based on the last available value (last observation carried forward).

Participants in the ITT population with missing data due to death will have their missing data imputed as the worst possible value within a specific scale or in regard to duration or proportion as defined by the particular outcome. Participants who do not experience a particular event will not be excluded from the analysis of duration or time-to-event endpoints and will have an appropriate value assigned. Specific assignments for death are provided in the SAP.

Efficacy data for Part 1 participants will be listed only. All statistical testing for endpoints will be 2-sided and will be evaluated in an exploratory manner to inform decisions about future trials.

13.1.4.1 Efficacy Endpoints

The primary endpoint is the proportion of participants alive and free of respiratory failure at Day 28 (respiratory failure is defined in exclusion criterion 1.c.i).

The secondary efficacy endpoints are:

- Clinical improvement, as measured by the World Health Organization (WHO) 9-point ordinal scale through Day 60
- Time to and proportion of subjects with all-cause mortality through Day 60
- Proportion of participants who experienced respiratory failure in the first 28 days
- Among patients that never experience respiratory failure in the first 28 days, time to initiation, duration, and proportion of subjects receiving supplemental oxygen or other respiratory support within the first 28 days after randomization
- Among patients that experience respiratory failure in the first 28 days, time to initiation and duration of the forms of respiratory support meeting criteria outlined in critical COVID criteria (exclusion criteria 1.c.i) within the first 28 days after randomization
- Number of days of oxygen support through Day 28 after randomization
- SpO_2 through Day 28 after randomization
- Number of ventilator-free days through Day 28 after randomization
- Number of hospitalization days through Day 28 after randomization
- Number of days without renal stabilization and/or replacement through Day 28 after randomization
- Number of organ failure-free days through Day 28 after randomization
- Number of days at elevated level of care (ICU) through Day 28 after randomization
- Number of healthcare encounters through Day 28 after randomization

The exploratory efficacy endpoints are:

- sPLA2 within blood samples from treatment initiation to Day 28 after randomization

13.1.4.2 Primary Analysis

The ITT, PP, and Combined populations will be used to analyze the primary efficacy endpoint. The ITT population will be considered to be the primary population for the efficacy analyses.

The proportion of respiratory failure-free surviving participants in each Part 2 treatment group at Day 28 will be analyzed using logistic regression with treatment as a factor. Age, diabetes, body mass index, and baseline sPLA2 activity will be included as covariates. Risk differences between varespladib and placebo, the 95% CI for the risk difference, and p-values for differences in treatment will be presented and calculated via the delta method. Additional details will be provided in the SAP which will be finalized before unblinding of the data.

The primary endpoint will be analyzed using the ITT, PP, and Combined Populations.

13.1.4.3 Secondary Analyses

Analysis of the secondary endpoints will be carried out for the ITT and Combined populations.

Mean change from baseline in the WHO 9-point scale will be analyzed using an analysis of covariance model (ANCOVA); the model will include treatment and age, diabetes, body mass index, and baseline sPLA2 as covariates. Distribution of outcomes on the WHO ordinal scale will also be described via plots in supplemental analyses..

Ventilator-free days; hospitalization days; organ failure-free days; days at elevated level of care [ICU]; number of days without renal stabilization; days of oxygen support; and number of healthcare encounters) during the 28-day study period will be analyzed using an analysis of covariance model (ANCOVA); the model will include treatment as a covariate. Additional covariates may be added to the model and full details will be given in the final SAP.

Secondary time to event endpoints (all-cause mortality and respiratory support (in patients with and without respiratory failure)) will be analyzed using a Cox-Proportional hazard model. The number of participants who experience the event, median time to the event and 95% CI, and rate ratio and 95% CI will be presented. The p-value to test if the rate ratio between treatments differs from 1 will be presented. Additional covariates will be considered; full details will be given in the SAP.

Additionally, the duration respiratory support in patients with and without respiratory failure will be analyzed using the same ANCOVA model as previously described.

The absolute values and change from baseline of SpO_2 will be tabulated by treatment arm and visit. An ANCOVA approach will be used to assess the treatment effect for SpO_2 through Day 28. Additional details will be provided in the SAP.

The proportion of participants who die, the proportion of participants with and without respiratory failure that receive respiratory support will be summarized using the same logistic regression method as the primary endpoint. In general, the proportions of subjects with an event on or before Day 28 will be analyzed unless otherwise specified in the SAP.

No adjustment will be made for multiple comparisons. This is an exploratory pilot study that will be used to inform decisions about possible future trials.

Additional details of the efficacy analyses can be found in the SAP.

13.1.4.4 Exploratory Analyses

Change in sPLA2 from baseline through Day 28 will be analyzed using the same ANCOVA model as previously described for SpO_2. The pharmacoeconomic impacts of varespladib treatment will be reviewed in an exploratory manner using results from secondary endpoints to include number of healthcare encounters, number of hospitalization days, and number of days at elevated level of care (ICU), all through Day 28.

13.1.4.5 Clinical Pharmacology Analyses

13.1.4.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics; graphical representations will also be provided. The PK parameters will be summarized by dose using descriptive statistics. Testing of PK parameters will be outlined in the SAP.

13.1.5 Safety and Tolerability Analyses

All safety analyses will be performed on the Safety population.

The variables for safety endpoints are TEAEs, vital signs, oxygen therapies, changes in biomarker levels, laboratory evaluations, 12-lead ECGs, physical examinations, and concomitant medications and therapies.

Safety and tolerability will be evaluated by examining the occurrence of AEs, including treatment-emergent AEs that begin with treatment. Adverse events leading to discontinuation from IP, causality, and severity (based on NCI CTCAE v5.0 grade) will be summarized by treatment group. Adverse events will also be presented in listings. Summary statistics of clinical laboratory measures will be presented by treatment group for each assessment. The number and percentage of participants with at least 1 post-baseline potentially clinically significant abnormality will be presented by treatment group for selected parameters. The same approach will be used for vital signs, ECGs, and pulse oximetry. Separate safety outputs will be produced for Part 1 and Part 2 participants.

An additional analysis will be done for Part 2 participants for AEs with a greater severity than mild as well as for AEs related to study treatment. The frequency and percentage of participants experiencing each type of event by Day 60 will be presented in each treatment arm. The difference in proportions, 95% CI derived, and p-value comparing varespladib and placebo from a 2-proportion Z-test will also be presented.

Additional details will be given in the SAP.

13.1.5.1 Adverse Events

Treatment-emergent AEs are defined as AEs that first occur or worsen in severity (based on NCI CTCAE v5.0 grade) after the first dose of IP and prior to the 30 days after last administration of IP. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each treatment group, the number of TEAEs and incidence rates will be tabulated by preferred term and System Organ Class.

Treatment-emergent AEs leading to discontinuation from IP, causality, and severity will be summarized by treatment group. An additional analysis will be done for Part 2 participants for AEs with a greater severity than mild as well as for AEs related to study treatment. The frequency and percentage of participants experiencing each type of event by Day 60 will be presented in each treatment arm. The difference in proportions, 95% CI derived, and p-value comparing varespladib and placebo from a 2-proportion Z-test will also be presented.

13.1.5.2 Clinical Laboratory Evaluations, Vital Signs, Electrocardiograms, and Pulse Oximetry

Summary statistics of clinical laboratory measures will be presented by treatment group for each assessment. The number and percentage of participants with at least 1 post-baseline potentially clinically significant abnormality will be presented by treatment group for selected parameters.

The same approach will be used for vital signs, ECGs, and pulse oximetry.

13.1.5.3 Biomarkers

Observed values and changes from baseline in biomarkers such as cardiac troponin level, CRP, and ferritin will be summarized using descriptive statistics by visit.

13.1.6 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Approximately 90 participants are planned for this study. Eighteen participants will be randomized into Part 1 of the study in a 5:5:5:3 ratio with 3 varespladib arms and a placebo arm. In Part 2 of the study, 72 participants will be randomized in a 1:1 ratio with the selected varespladib arm from Part 1 of the study and a placebo arm. No stratification variables will be used.

This is a pilot study and exploratory in nature. The sample size is not based on a formal power calculation.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a participant from the study (Section 9.4), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Ophirex, Inc. agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP and applicable United States Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IPs, and their specific duties within the context of the study. Investigators are responsible for providing Ophirex, Inc. with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

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

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to,

medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the CRO. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study participant number. The study data entry and study management systems used by clinical sites and [redacted] staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

14.2. Site Initiation

Study personnel may not screen or enroll participants into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate informed consent form (ICF).
2. The study site Federal Wide Assurance has been verified.
3. All regulatory documents have been submitted to and approved by the sponsor or its designee. (Department of Defense-supported research sites will require Human Research Protection Office (HRPO) review prior to initiation.)
4. The study site has a Clinical Trial Agreement in place.
5. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an initially negative virologic test for COVID-19 can be rescreened upon new symptoms/new admission. Rescreened participants will be assigned a new participant number; the participant number from the initial screening will be recorded in the eCRF.

14.4. Study Documents

All documentation and material provided by Ophirex, Inc. for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant, and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the ICF prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory Documents

The regulatory documents are listed in the study manual.

The regulatory documents must be received from the investigator and reviewed and approved by Ophirex, Inc. or its designee before the study site can initiate the study and before Ophirex, Inc. will authorize shipment of IP to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the varespladib IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records will also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 17.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all participants who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual participant visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a designated sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. Source data permits not only reporting and analysis but also verification throughout the study for the purposes of confirmation, quality control, audit, or inspection. It is important that source data and the records that hold those data are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when needed

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the study manual. Any protocol data that will be permitted to be entered directly into the eCRFs (i.e., with no prior written or electronic record of the data) will be specified.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

14.5. Data Quality Control

Ophirex, Inc. and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Ophirex, Inc. and/or its designee will conduct site visits remotely or onsite to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and

other authorized Ophirex, Inc. personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Ophirex, Inc. or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan.

14.5.2 Data Management

Ophirex, Inc. or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the CRO's standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated CRF, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Ophirex, Inc. or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- Site audits
- Trial Master File audits
- Database audits
- Document audits (e.g., protocol and/or clinical study report)
- Specific protocol training documents

Ophirex, Inc. or its designee may conduct additional audits on a selection of study sites, requiring access to participant notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Ophirex, Inc. immediately.

14.6. Study Termination

The study may be terminated at Ophirex, Inc.'s discretion at any time and for any reason.

14.6.1 Premature Study Termination

The study may be temporarily suspended or terminated prematurely is there is sufficient reasonable cause at any time by Ophirex, Inc., IRBs, regulatory authorities, respective steering committees, or the coordinating investigator.

Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study sites may be asked to have all participants currently participating in the study complete all of the assessments for the Early Termination Visit.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Ophirex, Inc. may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate participant enrollment

14.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 3 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 3 years have elapsed since the formal discontinuation of clinical development of the IP

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

14.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the participant.

Data collected for this study will be analyzed and stored at the CRO. After the study is completed, the de-identified, archived data will be transmitted to and stored at the CRO for use by other researchers, including those outside of the study. Permission to transmit data to the CRO will be included in the informed consent.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Ophirex, Inc. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study. Any changes to the protocol will have written approval prior to implementation.

14.9. Use of Information and Publication

All information concerning varespladib, Ophirex, Inc.'s operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Ophirex, Inc. or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Ophirex, Inc. Case report forms also remain the property of Ophirex, Inc. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Ophirex, Inc. in connection with the continued development of varespladib and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Ophirex, Inc. Publication or other public presentation of varespladib data resulting from this study requires prior review and written

approval of Ophirex, Inc. Abstracts, manuscripts, and presentation materials should be provided to Ophirex, Inc. for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Ophirex, Inc. has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results from this study will be submitted to ClinicalTrials.gov.

14.10. Impact of COVID-19 on Current Conduct of Clinical Trials

To mitigate the possible risks associated with study conduct during the COVID-19 pandemic, measures and procedures based on the advice issued by local authorities should be followed by study participants and site staff (e.g., social distancing, use of personal protective equipment and disinfectants). Investigators should use medical judgment and current evidence as well as consultation with their IRB/IEC, as appropriate, to determine the risks and benefits of participation in the study, and investigators are encouraged to communicate with participants to ensure safety.

The sponsor, its designees, and investigators will conduct the appropriate study monitoring activities to ensure study integrity; if on-site monitoring visits are not possible, alternative procedures will be established.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, and the applicable regulations of the country in which the study is conducted.

15.2. Participant Information and Informed Consent and/or Assent

A properly constituted, valid IRB must review and approve the protocol, the investigator's ICF, and related participant information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the participant before any activity or procedure is undertaken that is not part of routine care.

If any enrolled participant becomes a prisoner and thus a vulnerable subject, the investigator must promptly report this information to their IRB and to the sponsor, who will report the information to the HRPO of the US Army Medical Research and Development Command.

15.3. Approval by Institutional Review Board

For Investigational New Drug studies, the minimum standards of conduct and requirements for informed consent and/or assent are defined in the FDA regulations.

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's designated contact before shipment of IP supplies, and will include the date of the committee's approval and the chairperson's signature.

Until written approval by the IRB has been received by the investigator, no participant may undergo any procedure not part of routine care for the participant's condition.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB or a designee must be received by Ophirex, Inc. before implementation.

Prior to implementation of any actions, HRPO approval is required. In addition, any amendments will also require HRPO approval prior to implementation.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCES

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17. ATTACHMENTS

17.1. Investigator's Agreement

PROTOCOL NUMBER:	OPX-PR-02
PROTOCOL TITLE:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Varespladib in Patients Hospitalized with Severe COVID-19 Caused by SARS-CoV-2
CURRENT VERSION DATE:	v3.0, 28-Feb-2022

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Ophirex, Inc. during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on an IP during and after study completion.

Principal Investigator:

Printed Name:

_____

Signature:

_____

Date:

_____

APPENDICES

A. Study-specific Requirements

- WHO 9-point Ordinal Scale
- WHO guideline for the clinical management of COVID-19 (living guidance: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1)

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf