# Statistical Analysis Plan

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| Sponsor | Ophirex, Inc. |
| 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<br>(STAIRS: **S**mall molecule **T**argeting **A**cute **I**nflammatory and **R**espiratory **S**ymptoms in SARS-CoV-2) |
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## Approvals

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# Document History

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| 1.0 | 28-Feb-2022 | [redacted] | Finalized version |
| 2.0 | 13-Jun-2022 | [redacted] | Addressing comments from FDA response IND 152230 IR 042522 received 06May2022. Updated changes to planned analysis section to account for analysis of Part 1 subjects. |

# Table of Contents

# List of Abbreviations

| ABBREVIATION | EXPLANATION |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance model |
| AUC | area-under-the-curve |
| BID | twice daily |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| ECMO | extracorporeal membrane oxygenation |
| eCRF | electronic case report form |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HFNC | high-flow nasal cannula |
| 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 |
| PD | pharmacodynamic |

| ABBREVIATION | EXPLANATION |
|---|---|
| PK | pharmacokinetic |
| PP | per protocol |
| QD | once daily |
| 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 |
| WHO | World Health Organization |

# 1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Ophirex, Inc. protocol number OPX-PR-02 (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: Small molecule Targeting Acute Inflammatory and Respiratory Symptoms in SARS-CoV-2)), Version 3.0, dated 28-Feb-2022. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved before any unblinded inferential or descriptive analysis of data pertaining to Ophirex, Inc.'s study OPX-PR-02.

# 2. Study Objectives and Endpoints

## 2.1. Study Objectives

### 2.1.1. Primary Objective

The primary objective is 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.

### 2.1.2. Secondary Objectives

The secondary objectives are:

- 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.

### 2.1.3. Exploratory Objectives

The exploratory objectives are:

- To assess the pharmacokinetics of varespladib in COVID-19 patients
- To evaluate the overall effect of varespladib in suppression of sPLA2 with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
- To assess pharmacoeconomic endpoints

## 2.2. Study Endpoints

### 2.2.1. Efficacy Endpoints

#### 2.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is a proportion of participants alive and free of respiratory failure at Day 28.

The primary estimand for the primary efficacy endpoint of this study is a proportion of participants alive and free of respiratory failure at Day 28.

#### 2.2.1.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- Clinical improvement as measured by the World Health Organization (WHO) 9-point ordinal scale from baseline through Day 60
- Time to and proportion of participants 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 (ICU) through Day 28 after randomization
- Number of healthcare encounters through Day 28 after randomization

#### 2.2.1.3. Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoints of this study include the following:

- sPLA2 within blood samples from baseline through Day 28 after randomization

### 2.2.2. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence and severity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0 grade) of AEs, SAEs, and AEs leading to discontinuation of IP
- Vital signs
- Changes in levels of biomarkers: cardiac troponin, C-reactive protein (CRP), and ferritin
- Clinical laboratory evaluations
- 12-lead electrocardiograms (ECGs)

### 2.2.3. Pharmacokinetic Variables (Exploratory)

The PK endpoints for the study include PK parameters for varespladib:

- PK Parameters

### 2.2.4. Pharmacokinetic Variables (Exploratory)

- 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

# 3. Overall Study Design and Plan

## 3.1. Overall 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.

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 the safety 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.

## 3.2. Sample Size and Power

Approximately 90 evaluable 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.

## 3.3. Study Population

Participants will be adults aged 18 to 80 years diagnosed with severe laboratory-confirmed COVID-19 requiring hospitalization caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

## 3.4. Treatments Administered

Varespladib or placebo will be administered in addition to institutional standard of care. The written institutional standard of care at each site may change during the study.

## 3.5. Method of Assigning Participants to Treatment Groups

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).

**Table 1: Treatment groups in 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 |

Any dose that is missed should not be taken later that day.

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.

### 3.6. Blinding and Unblinding

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 who will have access to the randomization code, and the DSMB. In Part 1 only, secondary pharmacists, separate from other study staff, will be unblinded to ensure the correct cartons are assigned to morning, noon, and evening. Unblinded pharmacists will have no other study participation or activities.

Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

### 3.7. Schedule of Events

Please see the protocol Table 2-1 for a detailed schedule of events.

## 4. Statistical Analysis and Reporting

### 4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations except for PK parameter estimation will primarily use SAS (release 9.3 or later). All PK parameter estimations will use WinNonlin® version 6.4 or later. If the use of other software is warranted, the final CSR will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of participants (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the particular category for each possible value. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population for the treatment groups, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

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.

### 4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

An independent Data Safety Monitoring Board (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 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 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.

## 5. Analysis Populations

The following 5 analysis populations are planned for this study:

- **Intent-to-treat Population (ITT)**: All randomized participants.
- **Safety Population (SAF)**: All participants who receive at least 1 dose of IP.
- **Per-protocol Population (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 Population (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 who receive at least 1 dose of placebo or at least 1 dose of IP at the dose regimen used in Part 2.

Assignment of participants to populations will be determined prior to the study 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. Secondary endpoints will also be analyzed using the Combined Population.

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 subject is randomized incorrectly or is given the incorrect IP, analyses of the ITT, PP, and Combined Populations will be based on the randomized treatment.

# 6. General Issues for Statistical Analysis

## 6.1. Statistical Definitions and Algorithms

### 6.1.1. Baseline

The last observation recorded before the first administration of IP will be used as the baseline observation for all calculations of change from baseline.

### 6.1.2. Adjustments for Covariates

The adjustments for covariates will be performed for analyses of data from Part 2 and for analyses of the Combined Population.

An analysis of covariance (ANCOVA) with the treatment as covariate will be used. When the analysis is based on a continuous endpoint, the baseline value of the endpoint will be included as a covariate. Endpoint analyses will also be adjusted for the following, *a priori* specified covariates: diabetes (dichotomous), age (continuous), body mass index (continuous), baseline sPLA2 activity (continuous). Each of these variables is known to be associated with outcomes in patients with severe COVID-19 infection. Each of these variables will be assessed at baseline, prior to randomization. Additional covariates will be considered for inclusion in the adjusted models if there is significant imbalance between the two arms of the trial.

### 6.1.3. Multiple Comparisons

This is an exploratory pilot study that will be used to inform decisions about possible future

trials. No adjustments for multiple comparisons are planned.

### 6.1.4. Handling of Dropouts or Missing Data

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 clincal 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 who experience death will have their data after death assigned 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.

### 6.1.5. Analysis Visit Windows

Visits will be analyzed as scheduled. The windows follow the Schedule of Events in the Protocol. Screening, enrollment, and Day 1 of the Treatment Period can take place on the same day if the required screening test results are available.

### 6.1.6. Pooling of Sites

There will be no pooling of sites for this study.

### 6.1.7. Derived Variables

- Respiratory failure is defined as the requirement for use of intubation/mechanical ventilation, an oxygen rate with high flow nasal cannula greater than 20 L/min, non-invasive positive pressure respiratory support, or ECMO, or clinical diagnosis of respiratory failure.
- Respiratory failure-free survival is defined as the combination of no respiratory failure (defined above) and no report of mortality from any cause.
- Mortality from any cause is defined as death listed on the Study Completion CRF or WHO 9-point ordinal scale assessment of death.
- Non-invasive positive pressure respiratory support is defined as the use of continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP).
- Ventilator use is defined as the use of mechanical ventilation, CPAP, or BiPAP.
- Organ failure is defined as a reported AE indicating a ‘failure’ of respiratory, cardiovascular, hepatic, renal, coagulation, or neurological reported at the PT level or

'insufficiency' reported as the lowest level term.

- Renal stabilization or replacement is defined as reported use of any type of dialysis in concomitant medications with a route recorded as ("HEMODIALYSIS", "PERITONEAL DIALYSIS", or "DIALYSIS").
- Time to initiation of supplemental oxygen or other respiratory support in the first 28 days after randomization = (the earliest of Day 28 or date/time of the first use – date/time of randomization) + 1.
- Duration of supplemental oxygen or other respiratory support in the first 28 days after randomization = (the earliest of Day 28 of the study or date/time of the last use – the latest of date/time of the first supplemental oxygen or other respiratory support or date/time of randomization) + 1.
- Time to initiation of intubation/mechanical ventilation, an oxygen rate with high flow nasal cannula greater than 20 L/min, non-invasive positive pressure respiratory support, ECMO in the first 28 days after randomization = (the earliest of Day 28 or date/time of the first support – date/time of randomization) + 1.
- Duration of intubation/mechanical ventilation, an oxygen rate with high flow nasal cannula greater than 20 L/min, non-invasive positive pressure respiratory support, or ECMO in the first 28 days after randomization = (the earliest of Day 28 of the study or date/time of the last specified respiratory support – the latest of date/time of the first specified respiratory support or randomization) + 1.
- For the time till all-cause mortality Cox proportional hazards model, time to all-cause mortality or censoring will be calculated as follows
    - If mortality occurs within 60 days post-randomization; then Time to all-cause mortality or censoring = date/time of death – date/time baseline + 1.
    - If mortality occurs on or after 60 days post-randomization; then Time to all-cause mortality or censoring = 60 days.
    - If mortality does not occur, and last follow-up is prior to 60 days; then Time to all-cause mortality or censoring = date/time of last follow-up – date/time baseline + 1.
    - If mortality does not occur, and last follow-up is on or after 60 days; then Time to all-cause mortality or censoring = 60 days.
- Change from baseline = value at current time point – value at baseline.
- TEAE = any adverse event with an onset or worsening date/time after the date/time of the first administration of IP and prior to the 30 days after last dose of IP.

### 6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as < 0.0001.

Adverse events will be coded using the MedDRA version 24.0 thesaurus.

A treatment related AE is any AE with a relationship to the study drug assessed by the investigator. The investigator should carefully consider the list of possible manifestations of COVID-19 when assigning a relationship of specific AEs to the study drug.

For partial start dates:

- If the year is unknown, then do not impute the date but instead assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, or the AE/medication is ongoing, then impute as the month and day of the randomization date. If this produces a date after the end date, assign 01 January.
    - Otherwise, assign 01 January.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the randomization date. If this produces a date after the AE/medication end date, assign 01.
    - Otherwise, assign 01.

For partial end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known but the month or month and day is unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
    - Otherwise, assign the last day of the month.

In general, for quantitative laboratory values reported as '<X' or '≤X', the lower limit of quantitation (LLOQ) will be used for analysis (i.e., the value of X will be used in the analysis for lab values reported as '<X' or '≤X'). Similarly, for quantitative laboratory values reported as '>X' or '≥X', the upper limit of quantitation (ULOQ) will be used for analysis (i.e., the value of X will be used in the analysis for lab values reported as '>X' or '≥X').

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeated laboratory value will be used for data analysis.

# 7. Study Participants and Demographics

## 7.1. Disposition of Patients/Participants and Withdrawals

Disposition will include tabulations of the number of participants randomized into each treatment group, the number of participants completing the study, and the number of participants withdrawing, along with the reasons for withdrawal, by treatment group and overall within each study part.

A listing will be presented to describe whether the subject completed the study, date of completion or early withdrawal, and the reason for discontinuation, if applicable. A listing will be provided to describe the date when informed consent was obtained and if the subject meets all inclusion/exclusion criteria.

## 7.2. Protocol Violations and Deviations

Protocol deviations will be identified and classified as important or non-important for statistical analysis purposes before unblinding. Important protocol deviations will be used to exclude participants from the PP population.

The protocol deviation data with the verbatim description, the date of deviation and whether the deviation is classified as minor or major will be listed.

## 7.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the Safety and ITT populations and will be presented by treatment group and study part.

Demographics will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history and disease characteristics.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated. For the categorical variables, the counts and proportions of each value will be tabulated. These summaries will be performed for the safety population overall, and by treatment.

The number and percent of participants reporting various medical histories will be grouped by MedDRA system organ class and preferred term (coded using MedDRA v24.0).

Medical history details as collected on the CRF such as verbatim description, dictionary terms, onset date, and stop date will be presented as a subject data listing.

## 7.4. Exposure and Compliance

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

# 8. Efficacy Analysis

Efficacy data for Part 1 participants will be listed only, except for data from Part 1 participants that are included in the Combined Population.

For Part 2 and the Combined Population, all statistical testing for endpoints will be 2-sided and will be evaluated in an exploratory manner to inform decisions about future trials. Tests comparing treatment and control group will report point estimates, p-values, and 95% confidence intervals. In Part 2 and the Combined Population, all efficacy variables will be summarized descriptively. The primary analytic method will include adjustment for *a priori* selected covariates as described in Section 6.1.2.

## 8.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of participants alive and free of respiratory failure at Day 28.

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 and age, diabetes, body mass index, and baseline sPLA2 activity included as covariates. Dummy/refence coding will be used in all logistic regression implementations. The risk difference between varespladib and placebo along with the 95% CI and p-value will be presented. Note that logistic regression typically involves calculation and testing of odds ratios, however, this analysis will focus on presenting and testing the risk difference via the delta method (Ge et al, 2011).

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

### 8.1.1. Sensitivity Analyses of the Primary and Key Secondary Efficacy Endpoints

Two types of sensivity analyses will be conducted for the primary efficacy endpoint and key secondary efficacy endpoints using the ITT population. The following sensitivity analysis will be conducted in Part 2 subjects only.

One sensitivity analysis will be to examine the effect of covariate selection. This work will include estimating (1) the effect of treatment on the outcome adjusted for only the *a priori* specified model covariates (see section 6.2.1), and (2) and if significant imbalance is observed in other important covariates, then adjustment for the *a priori* specified covariates as well as other variables that are imbalanced between the treatment arms.

A second sensitivity analysis will be stratified estimates of the effect of treatment. The following strata will be examined: 1) high or low sPLA2 activity, with high defined as the median sPLA2 value or greater, 2) male or female gender, 3) high or low SpO2 at baseline dichotomized based on median value; 4) baseline WHO ordinal scale score dichotomized based on the median value; and 5) use of remdesivir or dexamethasone at baseline. Stratified estimates for a given variable will not be conducted if the number of patients within a stratum are insufficient to support the analysis.

Sensitivity analyses are exploratory and will be interpreted as evidence to inform additional research. The above listed sensitivity analyses will be applied to the primary efficacy endpoint and the following key secondary endpoints: days of oxygen support through day 28, ICU days through day 28, 9-point WHO clinical status scale, and mortality through Day 60.

## 8.2. Secondary Efficacy Analysis

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 participants 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
- SpO2 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 ITT and Combined populations will be used to analyze the secondary efficacy endpoints. The ITT population will be considered to be the primary population for the efficacy analyses.

### 8.2.1. World Health Organization (WHO) 9-point Ordinal Scale

The investigators will assess participants' clinical status using the 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 |

Descriptive summaries of observed values and changes from baseline in the WHO 9-point scale will be presented for each scheduled visit within treatment group. Distribution of outcomes on the WHO ordinal scale will also be described via plots in supplemental analyses.

Mean change from baseline in the WHO 9-point scale for each assessment will be analyzed using ANCOVA at each scheduled post-baseline visit. The model will include treatment, age, diabetes, body mass index, and baseline value as covariates. The least squares (LS) mean change from baseline will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences in change from baseline between treatments will be presented along with associated 95% CIs and p-values. Participants that die will have a score of 8 assigned to all scheduled visits on and after the date of death.

### 8.2.2. All-Cause Mortality

All-cause mortality from randomization through Day 60 will be analyzed using a Cox-Proportional hazard model. The number of participants who experience the event and rate ratio with 95% CI will be presented. The p-value to test if the rate ratio between treatments differs from 1 will be evaluated. Kaplan-Meier methodology will be used to estimate the median time to the event and 95% CI. Time to all-cause mortality will be calculated according to Section 6.1.7.

Censoring events include loss to follow-up prior to Day 60. Covariates will include those a priori specified in Section 6.1.2, and Efron's method for handling tied time-to-events will be used. The p-value testing for non-zero treatment effect will be obtained from a Wald chi-square test, and

the 95% CI associated with the treatment effect will be a Wald-type CI.

Additionally, the proportion of participants who die will be analyzed using the same logistic regression and risk difference method with dummy coding as the primary endpoint (Ge et al, 2011). In general, the proportions of participants with an event on or before Day 60 will be analyzed.

### 8.2.3 Proportion of participants who experienced respiratory failure within the first 28 days after randomization

The proportion of participants experiencing respiratory failure from randomization through Day 28 will be analyzed using the same logistic regression and risk difference method with dummy coding as the primary endpoint. Respiratory failure is defined as defined by requiring HFNC >20 L/min, non-invasive positive pressure ventilation, mechanical ventilation, or ECMO, or clinical diagnosis of respiratory failure (exclusion criteria 1.c.i) at any time during the 28 days after randomization. Note that those who experience mortality after respiratory failure are still counted towards this analysis. Those who experience mortality without prior respiratory failure will not be counted towards this analysis.

### 8.2.4 Among patients that do not experience respiratory failure in the first 28 days, time to initiation and duration of supplemental oxygen or other respiratory support within the first 28 days

The number of days of supplemental oxygen or other respiratory support in patients not meeting the criteria for respiratory failure from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. For Part 1 analysis, this endpoint will be reported in all patients in the ITT population.

The time to start of supplemental oxygen or other respiratory support from randomization through Day 28 will be analyzed using a Cox-Proportional hazard model. The number of participants who experience the event and rate ratio with 95% CI will be presented. The p-value to test if the rate ratio between treatments differs from 1 will be evaluated. Kaplan-Meier methodology will be used to estimate the median time to the event and 95% CI. Censoring events include loss to follow-up prior to Day 28. Mortality will not be considered a censoring event and instead will be analyzed as if this patient was on supplemental oxygen or other respiratory support for all days between randomization and Day 28. If mortality or the event of interest does not occur; all subjects will be censored at Day 28. Covariates will include those a priori specified in Section 6.1.2, and Efron's method for handling tied time-to-events will be used. The p-value testing for non-zero treatment effect will be obtained from a Wald chi-square test, and the 95% CI associated with the treatment effect will be a Wald-type CI.

Duration and time to supplemental oxygen or other respiratory support through Day 28 will be calculated according to Section 6.1.7

### 8.2.5. 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

The number of days of respiratory support meeting criteria outline in the critical COVID criteria among patients that experience respiratory failure in the first 28 days from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values.

For study Part 1 analysis, this endpoint will be reported in all patients in the ITT population.

The time to start of respiratory support through Day 28 will be analyzed using a Cox-Proportional hazard model. The number of participants who experience the event and rate ratio with 95% CI will be presented. The p-value to test if the rate ratio between treatments differs from 1 will be evaluated. Kaplan-Meier methodology will be used to estimate the median time to the event and 95% CI. Censoring events include loss to follow-up prior to Day 28. Mortality will not be considered a censoring event and instead will be analyzed as if the patient was on the forms of supplemental oxygen for all days between randomization and Day 28. If mortality or the event of interest does not occur; all subjects will be censored at Day 28. Covariates will include those a priori specified in Section 6.1.2, and Efron's method for handling tied time-to-events will be used. The p-value testing for non-zero treatment effect will be obtained from a Wald chi-square test, and the 95% CI associated with the treatment effect will be a Wald-type CI.

Duration and time to the forms of respiratory support through Day 28 will be calculated according to Section 6.1.7.

In order to assign the worst total score for death, participants that die will have all days from randomization through Day 28 treated as if they were receiving critical COVID-level respiratory support (i.e., analyzed as having 28 days of COVID-level respiratory support) for these analyses. Participants that do not die but have missing data will not be excluded from the analysis of duration or time-to-event endpoints and will have an appropriate value assigned.

### 8.2.6. SpO2

Observed SpO2 values at each scheduled visit from randomization through Day 28 and changes from baseline will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences in change from baseline between treatments will be presented along with associated 95% CIs and p-values. Results will be presented in tabular and graphical formats. In the event of death within 28 days, participants will have $SpO_2$ imputed as the lowest clinically plausible value (60%) for analysis purposes for the time period between death and 28 days.

### 8.2.7. Ventilator-Free Days

The number of ventilator-free days from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they had been on a ventilator.

### 8.2.8. Hospitalization Days

The number of hospitalization days from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they had been in the hospital.

### 8.2.9. Organ Failure-Free Days

The number of organ failure-free days from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they had organ failure.

### 8.2.10. Days at Elevated Level of Care [ICU]

The number of days spent in the ICU from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they had been spent in the ICU.

### 8.2.11. Days Without Renal Stabilization

The number of days without renal stabilization from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they were on renal stabilization.

### 8.2.12. Days of Oxygen Support

The number of days of oxygen support from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they were on oxygen support.

### 8.2.13. Number of Healthcare Encounters

The number of healthcare encounters from randomization through Day 28 will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences between treatments will be presented along with associated 95% CIs and p-values. In order to assign the worst total score for death, participants that die will have all days from randomization through day 28 treated as if they had a healthcare encounter on each day.

## 8.3. Exploratory Efficacy Analysis

### 8.3.1. sPLA2

Observed sPLA2 values from randomization through Day 28 changes from baseline will be summarized descriptively and analyzed using ANCOVA. The LS means will be presented along with the associated 95% CI within each treatment group. In comparing treatments, LS mean differences in change from baseline between treatments will be presented along with associated 95% CIs and p-values.

### 8.3.2. Pharmacoeconomic Impacts

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), after randomization through Day 28.

## 8.4. Subgroup Analyses of Efficacy Variables

Subgroup analyses of efficacy variables are specified in Section 8.1.1.

# 9. Safety and Tolerability Analysis

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.

All safety analyses will be performed on the Safety Population. Separate outputs will be produced for Part 1 and Part 2 of the study.

## 9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v24.0.

Treatment-emergent AEs are defined as AEs that first occur or worsen in severity after the first dose of IP and prior to the 30 days after last administration of IP.

An overall summary of number and percentage of participants with at least one TEAE, severe TEAE, treatment-related TEAE, AE leading to discontinuation, AE leading to death, at least one SAE, and treatment-related SAE will be presented.

The number and percent of participants reporting treatment emergent TEAEs, grouped by MedDRA SOC and preferred term (coded using MedDRA v24.0) will be tabulated for the overall safety population and by treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

Causality, and severity of TEAEs (by CTCAE v5.0 grade) will be tabulated. In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported. Although not anticipated, if a particular event is missing the severity and/or relationship, missing severities will be imputed as CTCAE Grade 3 and missing relationships will be imputed as related. CTCAE Grade 3 (i.e., Severe or medically significant but not immediately life-threatening) is chosen since higher grades (i.e., Grade 4 [life-threatening] or Grade 5 [death]) are most unlikely to be unobserved and Grade 3 is considered sufficiently deleterious when the severity is in question. Related is chosen for missing relationships as it is the most conservative option. Missing data for severities and relationships will be reported with counts and percentages prior to this imputation.

An additional analysis will be done for Part 2 participants for AEs with a greater severity than mild and 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, p-value comparing varespladib and placebo from a 2-proportion Z-test will also be presented.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

### 9.1.1. Adverse Events Leading to Withdrawal of the Study Drug

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug by system organ class, and preferred term will be prepared for the safety population overall and treatment.

A data listing of TEAEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

### 9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

SAEs will be listed and also tabulated by system organ class and preferred term and presented by treatment.

## 9.2. Clinical Laboratory Evaluations

Laboratory test results for chemistry, coagulation, hematology and urinalysis will be summarized descriptively by treatment and visit as both observed values and change from baseline values.

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 number of participants with clinical laboratory values below, within, or above the normal range by visit and in relation to baseline will be tabulated for each clinical laboratory analyte by treatment group (shift table).

Individual data listings of laboratory results will be presented for each subject. Flags will be displayed for values outside of the laboratory's normal reference limits.

## 9.3. 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. The safety biomarkers data will be provided in a listing.

## 9.4. Vital Signs and Pulse Oximetry

Descriptive summaries of actual values and changes from baseline will be calculated systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, and $SpO_2$.

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.

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject.

## 9.5. 12-Lead Electrocardiogram

Descriptive summaries of observed values and changes from baseline will be calculated for heart rate, PR interval, QRS interval, QT interval and QTcF by visit and treatment group.

Frequencies and percentages of investigator interpretation of ECG results (normal, abnormal clinically significant, and abnormal not clinically significant) will be presented by visit and treatment group.

The safety ECG data will be provided in a listing.

### 9.6. Physical Examination

Frequencies and percentages of physical examination results (normal, abnormal clinically significant, and abnormal not clinically significant) will be presented by visit and treatment group.

All physical examination data will be listed, abnormal findings will be flagged.

### 9.7. Concomitant Medication

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of participants taking each medication, classified using WHO Drug Dictionary (vB3 Mar2021) Anatomical Therapeutic Chemical classes (level 3) and preferred terms.

Prior medications will be presented separately from concomitant medications. Medications that started before the first administration of IP will be considered prior medications whether or not they were stopped before the first administration of IP. Any medications continuing or starting after the first administration of IP will be considered to be concomitant. If a medication starts before the first administration of IP and continues after the first administration of IP it will be considered both prior and concomitant.

## 10. Changes from Planned Analysis

Recruitment was paused 03May2022 due to slow enrollment following low infection rates and hospitalizations with severe severe COVID-19. At the time of this pause, Part 1 was concluded with N=18 subjects, and only one subject was recruited for Part 2. In the interest of providing results in a timely manner and informing broader medical knowledge, the decision was made to report unblinded results on Part 1 participants (N=18). It was originally specified that efficacy data for Part 1 subjects would be listed only; however, summary statistics and confidence intervals will now be reported for primary and secondary outcomes in addition to the originally specified listings. Subgroup analyses for the primary and secondary efficacy analyses will not be performed due to limited sample size. Exploratory outcomes will be listed only. Means, standard deviations, and quantiles will be reported for continuous outcomes; while counts and percentages will be reported for categorical or dichotomous outcomes. No hypothesis tests will be performed, and no P values will be reported for efficacy data of Part 1 subjects. The Part 1 ITT Population will be used for all efficacy analyses; and the Part 1 Safety Population will be used for all safety analyses. There will be no changes to the originally planned analysis of safety outcomes for Part 1 subjects. These changes are specified prior to database lock for the Part 1 subjects. Subsetting on the secondary outcomes described in 8.2.4 and 8.2.5 will be removed in this analysis of Part 1

subjects; Part 1 analysis for these endpoints will be performed in the ITT population. For Part 2 analysis, as FDA comments were received on 06 May 2022 (after study pause on 03 May 2022), a protocol and SAP amendment will be performed to ensure consistent reporting of these secondary endpoints.

## 11. Other Planned Analysis

### 11.1. Pharmacokinetic Analysis

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA). NCA methods are model-independent, they do not rely upon assumptions about body compartments, and they tend to provide more analyst-to-analyst consistency.

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 $C_{max}$ ($T_{max}$). Other parameters maybe included in the final summaries.

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. Blood specimens for PK analyses will be collected at the following time points:

- 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.
- The 12-hour PK sample may be omitted for a participants who are not hospitalized.

For noncompartmental analysis, plasma concentrations will be listed and summarized at each scheduled time point using descriptive statistics. Graphical representations for linear plasma-concentration-time curves by treatment will also be provided.

The PK parameters will estimated from the plasma concentration-time data using Actual PK sampling time-points. The PK parameters will be summarized by dose using descriptive statistics.

## 12. References

ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. http://www.amstat.org/about/ethicalguidelines.cfm

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