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STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CD12_COVID-19

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Protocol Number:	**CD12_COVID-19**
Protocol Title:	A Phase 2b/3, Randomized, Double Blind, Placebo Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety of Leronlimab for Patients with Severe or Critical Coronavirus Disease 2019 (COVID-19)
Protocol Version / Date:	Version 6.0 / 28-Dec-2020

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Plan Version:	SAP - Final Version 7.0
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I have read and approve the Statistical Analysis Plan specified above and agree with its content:

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Transaminase
ASA	American Statistical Association
AST	Aspartate Aminotransferase
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CS	Clinically Significant
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EOT	End of Treatment
eCRF	Electronic Case Report Form
FDA	U.S. Food and Drug Administration
FU	Follow-Up
HEENT	Head, Ears, Eyes, Nose, Throat
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IP	Investigational Product
ITT	Intent-to-treat
LOA	Letter of Amendment
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SpO_2	Peripheral Capillary Oxygen Saturation

SV	Screening Visit
TEAE	Treatment Emergent Adverse Events
TV	Treatment Visit
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol CD12_COVID-19, sponsored by CytoDyn Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objective of this plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this Statistical Analysis Plan are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents and references [1-6], were reviewed in preparation of this Statistical Analysis Plan:

- Protocol Version 6.0 / 28-Dec-2020
- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

2. PROTOCOL DESIGN AND OBJECTIVES

2.1 Study Objectives

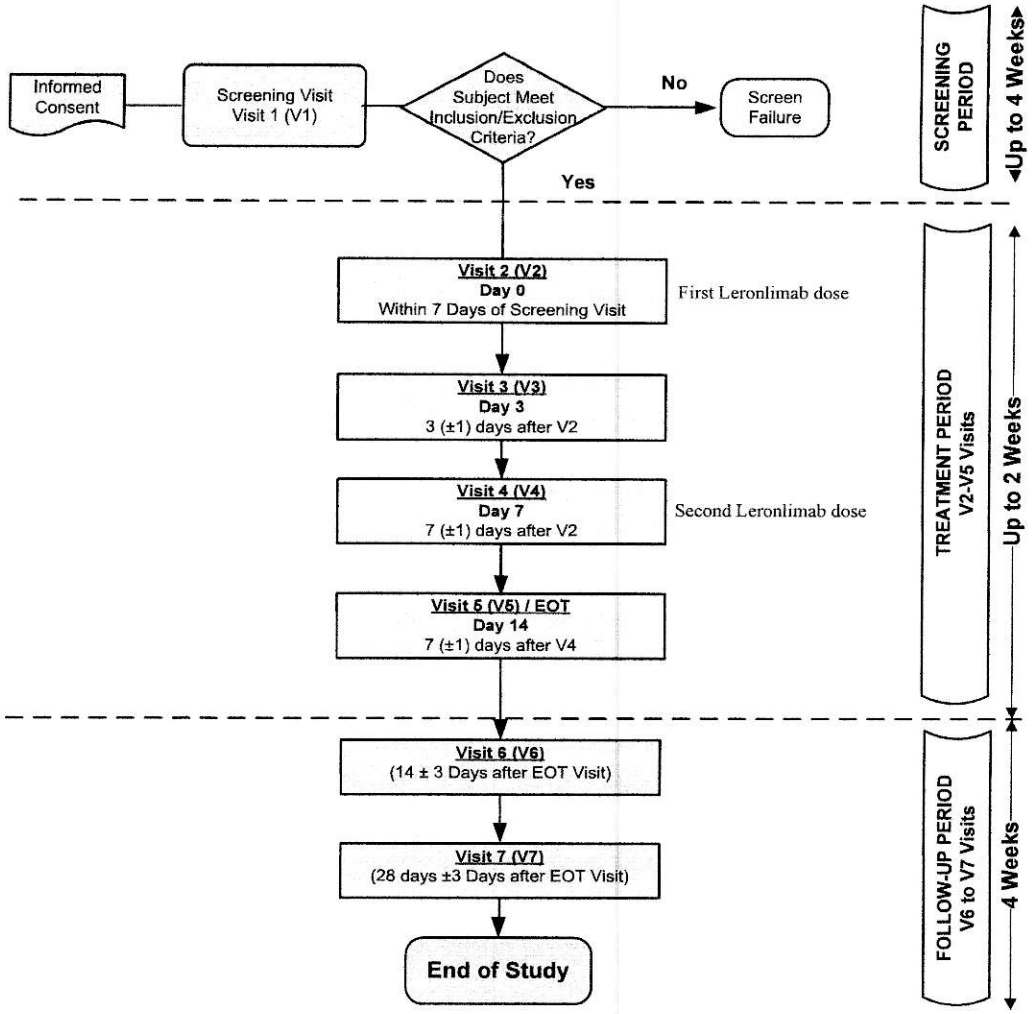
The purpose of this study is to assess the safety and efficacy of leronlimab (PRO 140) administered as weekly subcutaneous injection in subjects with severe or critical Coronavirus disease 2019 (COVID-19).

2.2 Design Overview

This study is a Phase 2b/3, two arm, randomized, double blind, placebo controlled, adaptive design study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with severe or critical symptoms of respiratory illness caused by Coronavirus disease 2019 (COVID-19). Patients will be randomized 2:1 to receive leronlimab (PRO 140) or placebo. Subjects will receive weekly 700 mg leronlimab (PRO 140) or placebo via subcutaneous injection for two weeks. The study will enroll 390 subjects. The study flow diagram is presented in Figure 2-1.

A single arm, non-randomized, open-label phase is added to the protocol after completion of enrollment in the Randomized Phase of the study. The study flow diagram presented in Figure 2-1 is same for randomized and non-randomized (open-label phase) of the study.

Figure 2-1: Study Schematic



The randomized portion of the study will have three phases: Screening Period, Treatment Period, and Follow-Up Period. The study Schedule of Assessments in presented in Table 2-1.

Screening Period (up to 1 week):

Screening assessments will commence at Visit 1 (V1) after obtaining signed informed consent, and will include review of medical and medication history, eligibility evaluation, subject demographics, physical examination, vital signs, clinical status – ordinal scale assessment, PaO2/FiO2 measurement, pulse oxygen saturation (SpO2), positive end-expiratory pressure (PEEP) (for intubated subjects), National Early Warning Score 2 (NEWS2) assessment, electrocardiogram (ECG), nasopharyngeal swab sample collection, chest radiograph or CT (if clinically indicated), assessment for the requirement of: mechanical ventilation, non-invasive ventilation, supplemental oxygen, vasopressors use, renal replacement therapy, ICU admission and hospital stay and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, and serum/urine pregnancy (if applicable). These assessments must be conducted within 7 days of the First Treatment Visit (V2).

All subjects who fail to meet eligibility criteria are considered screen failures, and are exited from the study without further evaluation.

Treatment Period (2 weeks ± allowed windows):

The schedule of visits during Treatment Period is as follows:

- Visit 2 (V2) [first treatment]: Within 1 week of the Screening Visit
- Visit 3 (V3): 3 (±1) day after V2
- Visit 4 (V4) [second treatment]: 7 (±1) days after V2
- Visit 5 (V5) / End of Treatment (EOT) Visit: 7 (±1) days after V4.

Subjects who meet the eligibility criteria will have completed the following evaluations and assessments at V2 prior to treatment: review of any changes in medical and medication history, physical examination, vital signs, clinical status – ordinal scale assessment, PaO2/FiO2 measurement, pulse oxygen saturation (SpO2), positive end-expiratory pressure (PEEP) (for intubated subjects), sequential Organ Failure Assessment (SOFA) score, National Early Warning Score 2 (NEWS2) assessment, nasopharyngeal swab sample collection, baseline assessment for the requirement of: mechanical ventilation, non-invasive ventilation, supplemental oxygen, vasopressors use, renal replacement therapy, ICU admission and hospital stay, assessment for any new infections, blood sample collection for CD3+, CD4+ and CD8+ T cell count, CCR5 receptor occupancy for Treg and macrophages, serum cytokine and chemokine levels, and CCR5 gene polymorphisms. After administration of leronlimab subjects will be assessed for vital sign, adverse event and concomitant medications. If Visit 2 (V2) takes place on the same day as the Screening Visit (V1), scheduled assessments performed under screening (V1) do not need to be repeated at V2.

At V2, subjects will be randomized to receive leronlimab (PRO 140) or placebo which will be administered subcutaneously weekly at Visit 2 (Day 0) and Visit 4 (Day 7) by a qualified medical professional at clinic. If the subject is discharged from the hospital prior to Visit 7 (Day 42), the visit can be completed at the subject's home.

The following assessments will be performed at V3, V4, and V5/EOT: physical examination, vital signs, clinical status – ordinal scale assessment, PaO2/FiO2 measurement, pulse oxygen saturation (SpO2), positive end-expiratory pressure (PEEP) (for intubated subjects), sequential Organ Failure Assessment (SOFA) score, NEWS2 assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, assessment for the requirement of: mechanical ventilation, non-invasive ventilation, supplemental oxygen, vasopressors use, renal replacement therapy, ICU admission and hospital stay, assessment for any new infections, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, serum/urine pregnancy test (V5/EOT), urinalysis, CD3+, CD4+ and CD8+ T cell count, CCR5 receptor occupancy for Treg and macrophage, serum cytokine and chemokine levels, and CCR5 gene polymorphisms.

Additionally, a chest radiograph or CT (if clinically indicated), mortality assessment, and ECG will be performed at V5/EOT visit. Adverse events and medications will be monitored throughout the study.

Follow Up Period (2 and 4 weeks after EOT± allowed windows)

Follow-up visits will be performed at 2 weeks (V6) and 4 weeks (V7) after the End of Treatment (EOT) visit. In order to ensure the safety of subjects and site staff, follow-up visits can be conducted as telephone or video contact visits. The following assessments will be performed at V6 and V7 visit: review of adverse events and concomitant medications, physical examination, vital signs, clinical status – ordinal scale assessment (V6 only), nasopharyngeal swab sample collection, mortality status, and blood collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V7 only). If V7 is a telephone/video visit, the scheduled blood sample collection will not be performed. In such cases, missed blood sample collection will not be captured as protocol deviation.

Note: During visits conducted at the study clinic, subjects and site personnel will use appropriate protective gear (e.g., masks, gloves) to prevent the spread of the infection. If the subject is discharged from the hospital prior to Visit 7 (Day 42), scheduled study visits can be conducted by a visiting nurse (or trained site staff) at the subject's home to mitigate the risk of spreading COVID-19.

During visits conducted at the subject's home, the visiting nurse (or trained site staff) will administer study drug (if applicable), monitor subjects for safety, perform blood draw, and all other assessments related to study outcomes measures. All procedures (except chest radiograph or CT scan) listed under the schedule of assessments can be performed by visiting nurse at visits taking place in the subject's home.

Table 2-1: Schedule of Assessments

Table 4-2: Schedule of Assessments

Procedure/Assessments	Screening Visit	Treatment Phase					Follow-Up	
Visit	V1	V2 [17] (Pre-Rx)	V2 [17] (Post-Rx)	V3	V4	V5 (EOT)	V6	V7
Day		Day 0		Day 3	Day 7	Day 14	Day 28	Day 42
Window Period		Within 7 days of the Screening Visit		±1 days after V2	±1 days after V2	±1 days after V4	14(±3) days after EOT Visit	28(±3) days after EOT Visit
Informed Consent [1]	X							
Eligibility Evaluation [2]	X							
Subject Demographics	X							
Medical History [3]	X							
Physical Examination	X	X		X[4]	X[4]	X	X[4]	X [4]
Vital Signs [5]	X	X	X	X	X	X	X	X
Clinical Status - Ordinal Scale Assessment	X	X		X	X	X	X	
PaO2/FiO2, if intubated	X	X		X	X	X		
Pulse oxygen saturation (SpO2)	X	X		X	X	X		
Positive End-Expiratory Pressure (PEEP), if intubated	X	X		X	X	X		
Sequential Organ Failure Assessment (SOFA) score, if intubated [6]		X		X	X	X		
National Early Warning Score 2 (NEWS2) Assessment [7] [19]	X	X		X	X	X		
Assessment of clinical recovery [8]				X	X	X		
ECG	X					X		
Laboratory tests:								
Complete Blood Count [9]	X			X	X	X		X
Biochemistry [10]	X			X	X	X		X
Coagulation Indices [11]	X			X	X	X		X

Procedure/Assessment:	Screening Visit	Treatment Phase					Follow-Up	
Visit	V1	V2 [17] (Pre-Rx)	V2 [17] (Post-Rx)	V3	V4	V5 (EOT)	V6	V7
Day		Day 0		Day 3	Day 7	Day 14	Day 28	Day +2
Window Period		Within 7 days of the Screening Visit		3(±2) days after V2	7(±1) days after V2	7(±1) days after V4	1-(±3) days after EOT Visit	28(±3) days after EOT Visit
Serum/Urine Pregnancy Test [12]	X					X		
Urinalysis [15]	X			X	X	X		X
CD3+, CD4+ and CD8+ T cell count		X		X	X	X		
CCR5 receptor occupancy for Treg and macrophage [19]		X		X	X	X		
Serum cytokine and chemokine levels [19]		X		X	X	X		
CCR5 Gene Polymorphisms [14] [19]		X		X	X	X		
Nasopharyngeal Swab Sample Collection [15] [19]	X	X		X	X	X	X	X
Chest radiograph or CT (if clinically indicated) [16]	X					X		
Randomization [18] [19]		X						
PRO 140 (700 mg) [or Placebo[19]] Administration		X			X			
Assessment for the requirement of: Mechanical Ventilation, Non-Invasive Ventilation, Supplemental Oxygen, Vasopressors Use, Renal Replacement Therapy, ICU Admission and Hospital Stay	X	X		X	X	X		
Assessment for any new infections		X		X	X	X		
Mortality Status						X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X

[1] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.
[2] Initial evaluation of patient eligibility will be performed by Investigator
[3] Medical history and current therapies (medications and non-medications)
[4] Symptom-directed physical examination
[5] Post treatment vital signs will be recorded at V2, V4, V5 (EOT) and will include blood pressure, heart rate, respiration rate, and temperature.

[6] The SOFA score assessment will be based on PaO2/FiO2, platelets, Glasgow coma scale (GCS), bilirubin, Mean arterial pressure OR administration of vasoactive agents required, and creatine.

[7] National Early Warning Score 2 (NEWS2) Assessment is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness)

[8] Based on hospital discharge or normalization of fever, respiratory rate, alleviation of cough, and resolution of hypoxia.

[9] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.

[10] Biochemistry

Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin Lactate dehydrogenase (LDH)

Renal function indicators: Serum creatinine, creatinine clearance, or eGFR

Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random), cholesterol (total), Creatine kinase, C-reactive protein, serum ferritin, d-dimer

[11] Prothrombin time (PT) and International Normalized Ratio (INR)

[12] ONLY performed on women of childbearing potential.

[13] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.

[14] Blood samples collected for receptor occupancy testing will also be used for CCR5 gene polymorphism for PRO 140 susceptibility

[15] Assessment is recommended but not required. Swabs will be used for quantitative virologic testing. Samples are to be stored at -70°C.

[16] Chest radiograph or CT will be performed if clinically indicated by the treating physician.

[17] If Visit 2 (V2) takes place on the same day as the Screening Visit (V1), scheduled assessments performed under screening (V1) do not need to be repeated at V2.

[18] Randomization via WebView CTMS system

[19] Not applicable for the single arm, non-randomized, open-label phase of the study.

2.3 Study Treatments

There will be two treatment groups in the study as detailed in Table 2-2 below:

Table 2-2: Treatment Groups

Study Drug	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
Leronlimab (PRO 140 700 mg)	Parenteral solution	175 mg/mL	2 injections of leronlimab (PRO 140 2 X 2 mL/inj.) per week on opposite sides of abdomen	SC injection
Placebo	Parenteral solution	0 mg/mL	2 injections of placebo (2 X 2 mL/inj.) per week on opposite sides of abdomen	SC injection

2.4 RANDOMIZATION

This is a multi-center randomized clinical trial. The randomization will use block size of 3 with a 2:1 ratio of leronlimab group and placebo group to ensure balanced distribution of leronlimab group and placebo subjects. An individual, independent of the clinical trial team, will develop the randomization schedules. The actual randomization assignment will be made through an Interactive Web Based Response System (IWRS) called WebView®. Subjects who have provided written informed consent and have met all the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment groups.

2.5 STRATIFICATION

Randomization will be stratified into one of the three categories based on clinical status of the patient at baseline:

- Hospitalized, not in intensive care unit (ICU)
- Hospitalized, in ICU, on mechanical ventilation, not on vasopressors
- Hospitalized, in ICU, on mechanical ventilation, on vasopressors

For the purpose of stratification, on vasoporessors dose is defined as: norepinephrine >20μg/min and/or vasopressin>0.04 units/kg/min.

Subjects will also be stratified for the prior use of off-label immunomodulatory treatments for COVID-19.

2.6 BLINDING

All subjects, Investigators and their staff (except unblinded pharmacist or designated site staff), and all Sponsor/CRO personnel involved in the management of the study will be blinded to treatment assignments.

The [redacted] Information Technology department will be unblinded to treatment. As noted above, the [redacted] Technology department is not otherwise involved with the study.

Treatment unblinding for the study will occur after all clinical data have been received, data inconsistencies have been resolved, and the database is locked, except for safety reasons on a case-by-case basis (i.e., emergency unblinding).

The process for emergency unblinding will be outlined in details in the Randomization Plan. In addition, any subject that is unblinded for any reason will be identified and discussed in the final clinical study report.

2.7 Time to UNBLINDING

2.7.1 Interim Analysis

Unblinded treatment assignments for the interim analysis will only be given to an independent statistician who will conduct the analysis. For this analysis there will be no subject specific unblinding to any other personnel in the study.

2.7.2 Emergency Unblinding

Breaking the blind prematurely will be allowed only if the subject's well-being requires knowledge of the subject's treatment allocation. Every attempt will be made to maintain the blind throughout the study.

In the event of an urgent safety issue where the randomized treatment of a subject is necessary to manage and treat the affected study subject (e.g., unblinding subjects because of SAEs that meet "expedited criteria" and requires reporting to FDA and other global regulatory authority), the Investigator will contact the Medical Monitor. The Medical Monitor, in consultation with sponsor, will make a decision to unblind. If the decision has been made to unblind, a prompt written notification will be provided to the Investigator. The reason for unblinding must be recorded; however the investigator must not record the subject's treatment assignment in study documentation and must not reveal the subject's treatment assignment to the clinical monitor.

If reporting of an adverse event is to be performed unblinded as per regulatory authority guidelines, study-unrelated personnel will unblind the individual subject's treatment group and will perform the unblinded reporting. No treatment group information would be shared with study personnel.

2.7.3 Final Analysis

Treatment unblinding and release of the randomization codes of the investigational product assignments for the study will occur immediately following database lock when all randomized subjects have completed the study or discontinued from the study and after all clinical data have been received and data inconsistencies have been resolved.

3. STUDY OUTCOME MEASURES (ENDPOINTS)

3.1 Primary Endpoint

The primary endpoint for the study is:

- All-cause mortality at Day 28

  Note: Day 0 refers to the date of randomization/first treatment.

3.2 Secondary Endpoints

The secondary efficacy endpoints for the study are:

- Proportion of patients achieving a category of 6 or higher at Days 14 and 28 (on a 7 point ordinal scale).
- All-cause mortality at Day 14
- Change in clinical status of subject at Days 14 and 28 (on a 7 point ordinal scale)

  A 7-category ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.
- Length of hospital stay (days)

3.3 Exploratory Outcome Measures (Endpoints)

- All-cause mortality at Day 42
- Change in clinical status of subject at Days 3 and 7 (on a 7 point ordinal scale)

  A 7-category ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Days 3 and 7.
- Proportion of subjects extubated within 14 days of start of study treatment.

  Note: This applies only for subjects who were intubated at the time of randomization
- Proportion of subjects admitted into an intensive care unit (ICU) after randomization

  Note: This applies only for subjects who were hospitalized but not in an intensive care unit (ICU) at the time of randomization
- Proportion of subjects requiring initiation of mechanical ventilation after randomization

  Note: This applies only for subjects who does not require mechanical ventilation at the time of randomization
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14.
- Length of ICU stay (days)
- Duration (days) of mechanical ventilation (if applicable)
- Time to clinical recovery

  Time from initiation of the study to discharge or to normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), respiratory rate (< 24 bpm while breathing room air), alleviation of cough (defined as mild or absent in a patient reported scale of 0=absent, 1=mild, 2=moderate, and 3=severe) and resolution of hypoxia (defined as SpO2 ≥ 93% in room air or P/F ≥ 300 mmHg). All these improvements must be sustained for at least 24 hours.
- Change from baseline in pulse oxygen saturation (SpO2) at Days 3, 7, and 14
- Change from baseline in National Early Warning Score 2 (NEWS2) at Days 3, 7, and 14.

  This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).
- Incidence of transaminitis, defined as an increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to > 5 times the upper limit of normal.

- Incidence of subjects requiring Renal Replacement Therapy (RRT) after randomization
- Incidence of new bacterial, invasive fungal, or opportunistic infection
- Change in size of lesion area by chest radiograph or CT
- Change from baseline in serum cytokine and chemokine levels at Days 3, 7, and 14
- Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages at Days 3, 7, and 14
- Change from baseline in CD3+, CD4+ and CD8+ T cell count at Days 3, 7, and 14

3.4 Safety Measures

Safety will be assessed using:

- Incidence of treatment-related adverse events (TEAEs)
- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Incidence of serious adverse events (SAEs)
- Incidence of TEAEs and SAEs leading to discontinuation of study medication.
- Changes in blood chemistry, hematology and coagulation parameter results
- Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure
- Changes in physical examination results
- Changes in electrocardiogram (ECG) results

4. SAMPLE SIZE DETERMINATION AND RATIONALE

This is a randomized study with two treatment groups. The subjects will be randomized to the treatment groups (leronlimab or placebo) in a 2:1 ratio.

A total of three hundred ninety (390) subjects will be randomized in a 2:1 ratio to leronlimab or placebo groups with the goal of having 369 subjects (246 subjects in the leronlimab and 123 in the placebo group) complete the study.

The sample size is obtained based on the assumption that there will be a clinically meaningful difference in the rate of Day 28 mortality (i.e., 15% which is 45% Day 28 mortality rate for the placebo group versus 30% Day 28 mortality rate in the leronlimab group). This sample size is based on using a 2-sided Z-test with 80% power and an overall significance level of 0.05. The expected

dropout rate is 5%. To accommodate subject attritions due to the potential discontinuations, it is recommended randomizing an estimated 390 subjects (260 in the leronlimab group and 130 placebo group). Sample size is estimated using PASS sample size software, tests for two proportions.

A single arm, non-randomized, open-label phase is added to the protocol after completion of enrollment in the Randomized Phase of the study in order to provide access to leronlimab for the eligible patients. Approximately, 100 subjects are expected to be enrolled in the non-randomized phase. Enrollment will remain open until the decision is made by Sponsor and/or FDA to close the recruitment. No statistical power calculation is used for the sample size calculation for the non-randomized portion of the trial.

5. INTERIM ANALYSIS (IA)

The Interim Analyses (IA) planned in the below sections will be conducted under the auspices of an independent Data Safety Monitoring Committee (DSMC) according to a written Charter. The procedures to be followed will be based on a standard operating procedure (SOP) that has a well-established firewall to protect the integrity of the trial. The IA will be performed by an independent un-blinded statistician, who is not otherwise associated with the conduct of this trial.

5.1 Interim Safety Assessment

*5.1.1 **Timing***

The safety assessment analysis will be conducted after approximately 25% (~100 subjects) and 75% (~300 subjects) of the required population have completed 2 weeks of randomized treatment or are withdrawn from the study, whichever occurs first.

*5.1.2 **Objective of this IA***

The objective of this safety assessment analysis to ensure subject safety by DSMC review of the unblinded data

*5.1.3 **Analysis Population***

All subjects who have been randomized and treated at the time of data snapshot for this analysis. All available data from these subjects will be included in the analysis.

*5.1.4 **Procedures***

a. Cut-off dates for eCRFs, data cleaning, and analysis will be established based on an estimated target date of the 25% (~100 subjects) or 75% (~300 subjects) treated subject completing 2 weeks of randomized treatment.

b. All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.

c. The data snapshot will be taken. This database will not contain the treatment assignments (i.e., will be blinded).

d. The data snapshot will be saved in a drive to which only the independent statistician responsible for the safety analysis has access.

e. The randomization code to un-blind the data will be delivered to the independent statistician by the IWRS master for the study.

f. The independent statistician will merge the randomization code with the data and will generate planned data and information for the DSMC, as described below.

5.1.5 Data and Information Provided to DSMC

The DSMC will receive the following data: disposition, demographics, AEs, SAEs, and death. No inferential statistics will be conducted for this safety analysis.

5.1.6 Stopping Rule

There is no intention of stopping the study as a result of this safety analysis. However, DSMC may recommend stopping the trial for safety reasons at any time.

5.1.7 Information Provided to Sponsor by DSMC

Following each meeting, formal minutes, including any recommendations for continuation or modification of the trial, will be prepared according to the procedure outlined in the DSMC Charter. These minutes will not contain any information or comments that might possibly unblind the trial.

5.1.8 Type I Error Rate Adjustment

No type I error adjustment will be made due to this safety analysis.

As there are no planned inferential statistics, the type I error rate for the final analysis will not be inflated because of this interim analysis.

5.2 Efficacy Interim Analysis

An efficacy Interim Analysis (IA) will be conducted when approximately 50% (~195 subjects) have been randomized and completed 4 weeks of randomized treatment or are withdrawn from the study, whichever occurs first.

5.2.1 Objectives of this IA

The main objective of the IA is sample size re-assessment.

5.2.2 Analysis Population

The IA population will be approximately 50% (~195 subjects) who have been randomized and completed 4 weeks of randomized treatment or are withdrawn from the study, whichever occurs first.

5.2.3 Procedures for the IA

The procedures for this IA will be based on a standard operating procedure (SOP) that has a well-established firewall to protect the integrity of the trial. The IA will be performed by an independent un-blinded statistician, who is not otherwise associated with the conduct of this trial. The procedures include the following:

a. Cut-off dates for collection of eCRFs, data cleaning, database lock and analysis will be established based on an estimated target date of 50% of subjects have completed 4 weeks of randomized treatment or are withdrawn from the study.

b. All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.

c. The database will be locked for the IA. This database will not contain the treatment assignments (i.e., will be blinded).

d. The locked database will be saved in a drive to which only the independent statistician responsible for the IA has access.

e. The randomization code to un-blind the data will be delivered to the independent statistician by the IWRS master for the study.

f. The independent statistician will merge the randomization code with the validated data and will generate planned data and information for the DSMC.

5.2.4 Metrics to be Calculated for the IA

Using IA unblinded data, the independent statistician will prepare disposition, summaries along with a conditional power (CP) using the primary endpoint data. The CP will be calculated for using the difference in mortality between the leronlimab and the placebo group.

The sample size re-assessment will be based on CP. The CP will be calculated based on:

1. The Day 28 mortality rate in the leronlimab group (P_A) and the observed number of subjects in the group
2. The Day 28 mortality rate in the placebo treatment group (P_p) and the observed number of

subjects in the group

3. The difference in mortality rate between P_A group and Pp group ($P_A - P_p$)
4. The CP of the study at the time of the IA (The method for this calculation is provided in Section 5.5.

5.2.5 Conditional Power

The CP will be calculated according to the below formula (Chen, 2004) using the response rate between P_A group and Pp group:

$$CP(f_I, Z) = \Phi\{ - Z_\alpha / \sqrt{(1-f_1)} + Z / \sqrt{f_1 (1-f_1)} \}$$

Where :

- $CP(f_I, Z)$ is the CP at the IA
- $\Phi\{.\}$ is the cumulative distribution function of a Standard Normal distribution ($\mu=0$, $\sigma^2 = 1$)
- f_1 *is the fraction of patients enrolled and used in the IA before decision of increasing the sample size, which is 50% for this protocol* ($f_1 = (n_A + n_p) / N_A+N_p$, *where* n_A *and* n_p *are the number of subjects used for the IA in the* leronlimab *and the placebo groups, respectively, and* N_A+N_p *is the original sample size* (N_0) *for the two groups)*
- Z_α is the upper (1-α) percentile for standard normal distribution
- Z is the test statistics at the IA:

$$Z = \frac{\hat{\delta}}{se(\hat{\delta})}$$

Where:

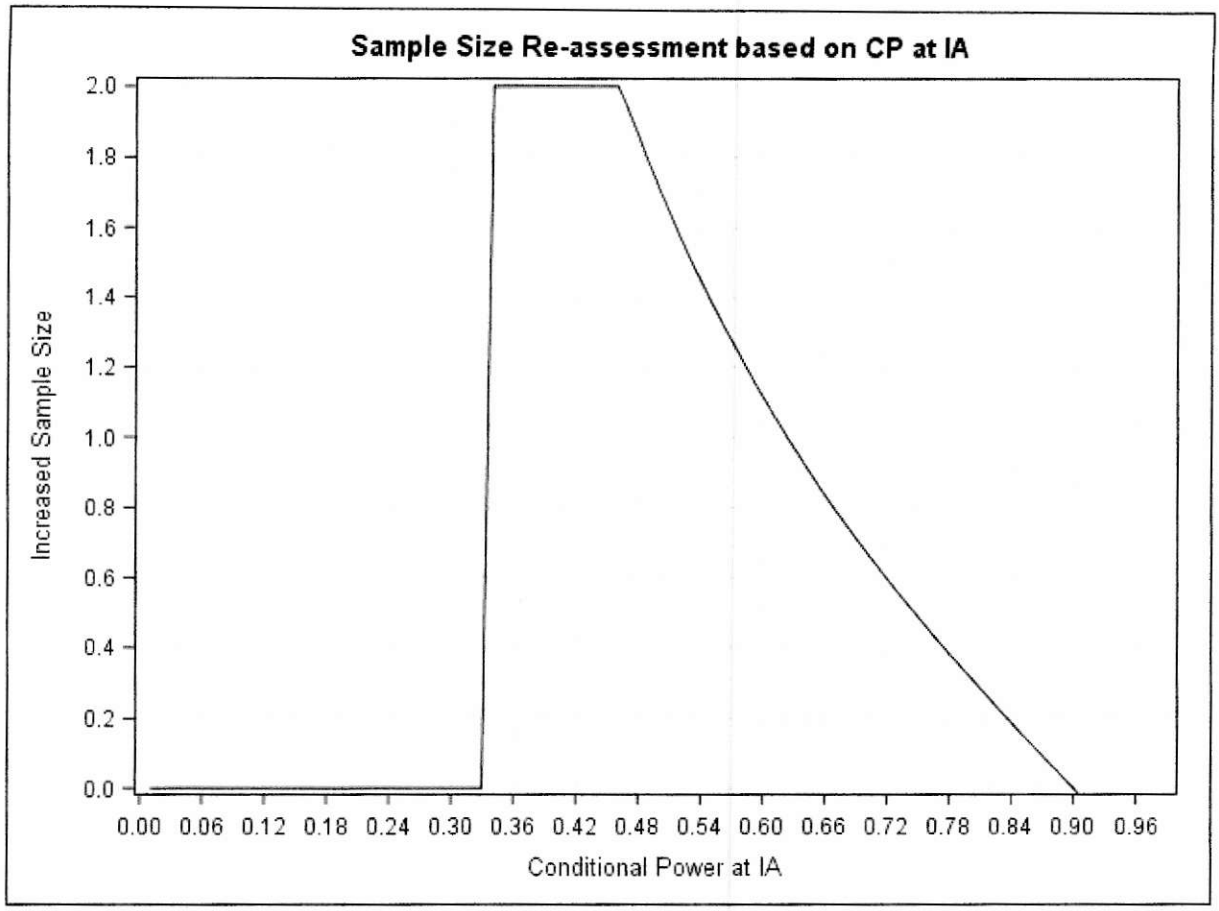
- $\hat{\delta}$ = the maximum likelihood estimate of the proportion difference calculating from logistic model at IA

The resulting CP will be used to determine whether the sample size needs to be increased or remain unchanged.

5.2.6 Rules and Method for Increasing Sample Size

Rule: The sample size for the study is planned to be adjusted only if the CP at the IA is less than 90% and greater than 35% (i.e., out of the promising zone).The adjustment would be an increase in the sample size in order to bring the CP to at least 90% up to a maximum increase of 1170 subjects (780 for leronlimab group and 390 for the placebo group), using the observed differences at the time of

the IA. The sample size is to be maintained as the original sample size, if the CP is larger than or equal to 90% or less than 34%. The promising zone is depicted in the below figure.



Method: This sample size recalculation will be made by adjusting the f_2 in the CP equation below:

$$CP(f_2, Z) = \Phi\{ - Z_\alpha / \sqrt{(1-f_2)} + Z / \sqrt{f_2 (1-f_2)} \}$$

Where:

- CP(f_2, Z) is the CP at the IA to be increased to 80% by adjusting f_2
- f_2 is the fraction of subjects enrolled and used in the IA before decision of increasing the sample size relative to the new sample in the adjusted trial. It is defined as:

  $$f_2 = (n_b + n_p) / (N_0 + n_{added})$$

- $\Phi\{.\}$, Z_α, Z, n_b, n_p *and* N_0 are the same as those defined above

The number of subjects to be added to the trial is then calculated from the f_2 that yields the CP of 90% as follows:

$$n_{added} = (n_b + n_p - N_0 * f_2) / f_2$$

5.2.7 Type I Error Rate Adjustment Due to the IA

There will be no statistical penalty on the Type I error rate due to the IA as the sample size will be increased only if the conditional power calculated at the IA falls into the promising zone.

5.2.8 Data Provided to DSMC

The DSMC will receive a statistical report. The report will include disposition, demographics, mortality data and safety summaries. Besides the mortality data, the report will also include descriptive summary of key outcome indicators such as, change in clinical status based on a 7 point ordinal scale and total duration of hospitalization, ICU, and mechanical ventilation use.

5.2.9 Stopping Rule

The trial will not be stopped for efficacy reasons.

5.2.10 Information Provided to Sponsor by DSMC

The DSMC will only make recommendations to sponsor on the sample size adjustment in a blinded fashion.

6. PRIMARY HYPOTHESIS TO BE TESTED

The primary hypothesis to be tested for this study is:

H_0: $P_{leronlimab} = P_{Placebo}$ (i.e. there is no difference in the Day 28 mortality rate between the two treatment groups)

H_1: $P_{leronlimab} \neq P_{Placebo}$ (i.e. there is difference in the Day 28 mortality rate between the two treatment groups)

7. ANALYSIS POPULATIONS

7.1 Modified Intent-to-Treat Population

The **Modified Intent-to-Treat (mITT) population** is defined as the set of subjects who randomized and have received at least one dose of leronlimab (PRO 140) or placebo. This population will be used as the primary analysis population for analysis of the primary and secondary efficacy endpoints.

7.2 Intent-to-Treat Population

The **Intent-to-Treat (ITT) population** is defined as all randomized subjects. This population will be used as the sensitivity analysis for analysis of the primary and secondary efficacy endpoints.

7.3 PP Population

The **Per Protocol (PP) population** is defined as the set of subjects who meet the ITT Population requirements and are not associated with any major protocol violations per ICH definition including:

- Informed consent not properly attained
- Did not meet inclusion/ exclusion criteria but entered into study

  Note: Subjects who have confirmed COVID-19 diagnosis but results not available within 5 days of screening will not be considered major protocol deviation/violation.
- Developed withdrawal criteria during the study, but not withdrawn
- Study drug dosing deviation

  Note: Subjects who do not receive two doses of study treatment (except in case of mortality within 7 days of treatment initiation) will be considered major protocol deviation/violation and will be excluded from the PP population.
- Received excluded concomitant medication

This population will be identified programmatically before the database lock. This population will be used as the supportive analysis population for analysis of the primary and secondary efficacy endpoints.

7.4 Safety Population

The **Safety Population** will include all subjects who have received one dose of Study Treatment. This population will be used for the analysis of safety parameters or measurements. This population will include the subjects from the single arm, non-randomized, open-label phase that received leronlimab.

8. DATA CONVENTION AND RELATED DEFINITIONS

8.1 Baseline Definition

For all parameters, baseline will be defined as the last available value prior to randomization.

8.2 Duplicate Data

For unplanned duplicate data within a protocol-specified visit, the last measured value will be used for the analysis. If it is not possible to identify the "last measured value" the average of the duplicate values will be used.

No data will be excluded. All collected data will be listed.

8.3 Handling of Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized to minimize missing data. However, in the event when there is missing data the following imputation methods will be used.

For efficacy evaluations, multiple imputation methods will be used to handle missing data. This imputation method is a robust method to impute missing measurements. The method for imputing variables is available in SAS PROC MI for both monotone and arbitrary missing data patterns and will be implemented with the PREDICT MEAN MATCHING option. Each imputation model will include the stratification factor as a covariate in the model. The multiple imputation is used for subjects that have some baseline and post-baseline data, i.e., if a subject is missing all pre and post baseline data, no data will be imputed.

8.3.1 Multiple Imputation for Continuous variables

If the missing data point is **continuous** in nature with **monotone** pattern, predictive mean matching (PMM) method will be used in the model.

If the missing data point is **continuous** in nature with **arbitrary** pattern, a fully conditional specification (FCS) using the predictive mean matching (PMM) method with joint distribution for all variables will be used.

8.3.2 Multiple Imputation for Categorical variables

If the data point is **categorical** in nature with **monotone** pattern, logistic method will be used in the model.

If the data point is **categorical** in nature with **arbitrary** pattern, a fully conditional specification (FCS) using logistic regression approach with joint distribution for all variables will be used.

8.4 Multiple Comparisons and Type I Error Rate Multiplicity adjustments

For the primary endpoint only one hypothesis will be tested, the final p-value will be adjusted as specified in Section 5.7 to protect the trial wise Type I error due to the interim analysis.

For the secondary endpoints, the hierarchical test procedure, with fixed sequence approach will be used to protect the trial-wise error rate. Please see Section 9.2.2 for the order of the secondary endpoints.

8.5 Subgroups

Subgroup analyses will be conducted to evaluate whether the treatment effects are consistent across different subgroups as following. All subgroup analyses will be considered exploratory, except for some that were prespecified in the protocol for specific reasons.

1. Based on baseline Ordinal Scale

- Baseline ordinal scale of Score 2 - Critical patients;
- Baseline ordinal scale of Score 3 – Severe patients;
- Baseline ordinal scale of Score 4 – Severe patients;
- Baseline ordinal scale of Score 3 and 4 - Severe patients;

2. Based on age group

- Age < 40
- 40 <= Age <= 65
- Age > 65

3. Based on Dexamethasone use
4. Laboratory parameters such as, CD4/CD8 ratio and IL-6

In addition, the study allowed co-administration of any off-label COVID-19 treatments. Hence, subgroup analyses will be performed to evaluate whether the treatment effects are consistent without and with the different co-administered off-label treatments including but not limited to hydroxychloroquine or chloroquine with or without azithromycin, remdesivir, dexamethasone (or other corticosteroids), monoclonal antibodies (such as bamlanivimab, casirivimab, imdevimab, siltuximab), immunomodulatory agents (such as baricitinib, sarilumab, clazakizumab, tocilizumab, anakinra), convalescent plasma therapy.

8.6 Sensitivity Analysis

Sensitivity analysis is planned for the primary and secondary efficacy endpoints, based on mITT population. Sensitivity analyses will be conducted to assess the impact of potential deviations about the mechanism of missing data assumption in the primary and secondary analysis and the robustness of the primary and secondary analysis.

8.7 Standard Calculations and Conventions

8.7.1 Age

Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

Age (years) = integer of[(date of informed consent – date of birth)/ 365.25]

8.7.2 Body Mass Index (BMI)

BMI will be calculated using height (in cm) and weight (in kg) according to the formula noted below.

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

8.7.3 Change from Baseline

For any of the effectiveness measurements change from baseline will be calculated using the formula noted below.

Change from baseline = Post Baseline Measurement – Baseline Measurement

8.7.4 Censoring rule for subjects with outcome of Death

For analyses of length of stay (i.e., ICU or hospitalization) or duration of mechanical ventilation all deaths within 42 days will be considered censored at Day 42. Conceptually, a death corresponds to an infinite length of stay or MV support but censoring at any time greater than or equal to Day 42 gives the same answer as censoring at Day 42; both correspond to giving deaths the worst rank.

9. STATISTICAL METHODS

All data collected during this study will be presented in subject data listings. All statistical analyses will be performed using SAS® for Windows, version 9.4 or later.

9.1 Summarizing and Tabulating the Collected Data

All data collected will be summarized according to the variable type:

- Continuous data summaries will include number of observations, mean, standard deviation, median, and minimum and maximum values.
- Categorical data summaries will include frequency counts and percentages.

9.1.1 Subject Disposition and Withdrawals

The disposition of all subjects who sign an ICF will be provided. The number of subjects screened, screen failure, randomized, received at least one treatment, completed, and discontinued during the study, as well as the reasons for all post treatment discontinuations will be summarized. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

9.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major before un-blinding.
Protocol deviations for all randomized subjects will be listed as by-subject listing and major deviations will be summarized descriptively according to the following categories:

- Did not meet Inclusion/Exclusion criteria but entered into study
- Developed withdrawal criteria during the study but not withdrawn
- Received excluded concomitant medication
- Study treatment dosing deviation

9.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Race, Gender etc.) will be summarized using appropriate descriptive statistics.
Medical history of the subjects will also be summarized and also provided as a by-subject listing.

9.1.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the Safety population. All prior and concomitant medications recorded in the eCRFs will be coded to generic term and all matching Anatomic Therapeutic Classification (ATC) codes using WHO Drug Summaries will be prepared using the coded terms. All prior and concomitant medications recorded in the eCRFs will also be listed.

9.1.5 Treatment Exposure

All data from administration of study drug will be listed and summarized.

9.2 Analysis of Efficacy Data

The primary analysis will be conducted on the mITT population. The PP population will be used as a supportive analysis if there is at least 5% difference between the numbers of subjects in the two populations. All statistical tests for efficacy will be two-sided tests, with α=0.05

9.2.1 Primary Efficacy Endpoint

The primary endpoint for the study is all-cause mortality at Day 28. All-cause mortality at Day 28 will be summarized. The estimated difference in mortality rates along with 95% confidence interval and p-value will be calculated using Logistic Regression adjusting for stratification factors (Ge et al. 2011).

9.2.2 Secondary Efficacy Endpoints

9.2.2.1 Proportion of patients achieving a category of 6 or higher at Days 14 and 28 (on a 7 point ordinal scale).

Proportion of patients achieving a category of 6 or higher at Days 14 and 28 (on a 7 point ordinal scale) will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.2.2 Change in clinical status of subject at Days 14 and 28 (on a 7 point ordinal scale)

The change in clinical status of subject at Days 14 and 28 will be summarized descriptively and will be compared using rank-ANCOVA. In addition, the clinical status of subject at Days 14 and 28 will be compared using proportional odds model. .

9.2.2.3 All-cause mortality at Day 14

All-cause mortality at Day 14 will be summarized descriptively by treatment group. Similar analysis methods used for the primary endpoint will be applied to analyze the data from this endpoint

9.2.2.4 Length of hospital stay (days)

Length of hospital stays will be considered as continuous outcome and summarized descriptively.

The median length of hospital stay will be compared between the treatment groups using a non-parametric method or a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data. For this analysis, the censoring rule in Section 8.6.4 will be used.

9.2.3 Exploratory Outcome Measures (Endpoints)

9.2.3.1 All-Cause Mortality at Day 42

All-cause mortality at Day 42 will be summarized descriptively by treatment group. Similar analysis methods used for the primary endpoint will be applied to analyze the data from this endpoint

9.2.3.2 Change in clinical status of subject at Days 3 and 7 (on a 7 point ordinal scale)

Change in clinical status of subject at Days 3 and 7 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.3 Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Days 3 and 7

Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Days 3 and 7 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.4 Proportion of subjects extubated within 14 days of start of study treatment

Proportion of subjects extubated within 14 days of start of study treatment will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.3.5 Proportion of subjects admitted into an intensive care unit (ICU) after randomization

Proportion of subjects admitted into an intensive care unit (ICU) after randomization will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.3.6 Proportion of subjects requiring initiation of mechanical ventilation after randomization

Proportion of subjects requiring initiation of mechanical ventilation after randomization will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.3.7 Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14

Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.8 Length of ICU stay (days)

Length of ICU stay will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.9 Duration (days) of mechanical ventilation (if applicable)

Duration of mechanical ventilation will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.10 Time to clinical recovery

Time to clinical recovery will be compared between the treatment groups using Cox proportional hazards model with the stratification factors in the model. Kaplan-Meier analysis will also be used to depict the median time (days) to clinical recovery for the treatment groups. The likelihood score test in the Cox proportional hazards model (which is the equivalent of the Log Rank test) will be used to compare the time to return to normal activity between the treatment groups.

9.2.3.11 Change from baseline in pulse oxygen saturation (SpO2) at Days 3, 7, and 14

Change from baseline in pulse oxygen saturation (SpO2) at Days 3, 7, and 14 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e.,

an ANCOVA analysis on rank-transformed data will be used.

9.2.3.12 Change from baseline in National Early Warning Score 2 (NEWS2) at Days 3, 7, and 14

Change from baseline in National Early Warning Score 2 (NEWS2) at Days 3, 7, and 14 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.13 Incidence of transaminitis

Incidence of transaminitis will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.3.14 Incidence of subjects requiring Renal Replacement Therapy (RRT) after randomization

Incidence of subjects requiring Renal Replacement Therapy (RRT) after randomization will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.3.15 Incidence of new bacterial, invasive fungal, or opportunistic infection

Incidence of new bacterial, invasive fungal, or opportunistic infection will be summarized and compared using Logit model, adjusting for stratification factors.

9.2.3.16 Change in size of lesion area by chest radiograph or CT

Change in size of lesion area by chest radiograph or CT will be summarized descriptively and compared using Logit model, adjusting for stratification factors.

9.2.3.17 Change from baseline in serum cytokine and chemokine levels at Days 3, 7, and 14

Change from baseline in serum cytokine and chemokine levels at Days 3, 7, and 14 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.
If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.18 Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages at Days 3, 7, and 14

Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages at Days 3, 7, and 14 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.

If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.2.3.19 Change from baseline in CD3+, CD4+ and CD8+ T cell count at Days 3, 7, and 14

Change from baseline in CD3+, CD4+ and CD8+ T cell count at Days 3, 7, and 14 will be summarized descriptively and compared using ANCOVA adjusting for stratification factors.

If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

9.3 Analysis of Safety Data

The Safety population will be used for the analysis of safety assessments.

9.3.1 Adverse Events

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by System Organ Class and preferred term by treatment group. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment);
- By intensity (mild, moderate, severe, life threatening or death);
- By causality (definitely, probably, possibly, remotely or unrelated);
- By impact on study treatment (dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown).

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

9.3.2 Clinical Laboratory Evaluations

All available results of the clinical laboratory evaluations will be listed and summarized. Laboratory evaluations include serum biochemical, hematologic, coagulation, urinalysis, and serum/urine

pregnancy (if applicable).

9.3.2.1 Laboratory Values over Time

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented. Data will be summarized as appropriate to the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9.3.2.2 Individual Subject Changes (Shift Tables)

Individual subject changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of subjects, for shift (change) from baseline.

9.3.2.3 Clinically Significant Abnormalities

A by-subject listing of treatment-emergent clinically significant laboratory values, by treatment group, will be prepared.

9.3.3 Vital Signs

Tabulations of raw data and change from baseline values will be presented by time point for each vital sign parameter including temperature, pulse, respiratory rate, systolic and diastolic blood pressure.

Tabulations will include the number of observations, mean, standard deviation, median, and minimum and maximum values. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9.3.4 Electrocardiogram (ECGs)

The ECG parameters include ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec).

9.3.4.1 ECG Values over Time

Descriptive statistics of raw data and change from baseline values for each ECG measurement will be presented by treatment group. For change from baseline summaries, subjects with an undefined

change from baseline, because of missing baseline data, will be excluded.

9.3.4.2 Individual Subject Changes (Shift Tables)

Individual subject changes will be identified through shift tables. Shift tables will be presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group, for shift (change) from baseline, using the normal ranges.

9.3.5 Physical Examination

All physical examination findings will be listed and/or summarized by treatment group.

9.4 Analysis of Open-Label Arm Data

The data from the single arm, non-randomized, open-label phase will be captured in the same EDC system. The data from this phase of the study will mainly be used for safety analysis as part of the safety population using the metrics laid out in Section 9.3 of this SAP. In addition, the data from this phase will also be used as a supportive efficacy analysis by pooling the data from this phase with the Leronlimab group of the randomized phase. The endpoints to be assessed include:

- All-cause mortality
- Proportion of patients achieving a category of 6 or higher at Days 14 and 28 (on a 7-point ordinal scale).

10. APPENDIX – PLANNED TLG

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

ELIGIBILTY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)

DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)

TREATMENT ADMINISTRATION LISTINGS (LISTINGS 16.2.5.X)

EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT DATA (LISTINGS 16.2.7.X)

SAFETY DATA (LISTINGS 16.2.8.X)

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS

POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS

CONCOMITANT MEDICATION USAGE

EFFICACY SUMMARIES

SAFETY SUMMARIES

- ADVERSE EVENT SUMMARIES
- SERIOUS ADVERSE EVENTS
- LABORATORY
- VITAL SIGNS
- PE
- ECG
- OTHER SAFETY

11. VERSION HISTORY

Changes incorporated into Version 2.0 of this document.

Editorial changes were made per Version 5.0 of the protocol.

Changes incorporated into Version 3.0 of this document.

Safety assessment at an interim per the LOA dated 06 Jul 2020.

Changes incorporated into Version 4.0 of this document.

- Efficacy Interim Analysis to be conducted after 50% (~195 subjects) have been randomized and completed **4 weeks** of randomized treatment instead of 2 weeks of treatment per the request from the DSMC, since the primary endpoint is Mortality at Day 28.
- Descriptive summary of key outcome indicators such as, change in clinical status based on a 7 point ordinal scale, and total duration of hospitalization, ICU, and mechanical ventilation use added as part of the interim report to be shared with the DSMC.

Changes incorporated into Version 5.0 of this document.

- A single arm, non-randomized, open-label phase added to the protocol after completion of enrollment in the Randomized Phase of the study. Up to 100 subjects will be enrolled in the non-randomized phase.
- Proportion of patients achieving a category of 6 or higher at Days 14 and 28 (on a 7 point ordinal scale) was added to Secondary Endpoint
- Length of hospital stay (days) was moved from Exploratory Endpoint to Secondary Endpoint
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 14 was moved from Secondary Endpoint to Exploratory Endpoint
- All- cause mortality at Day 42 was added to Exploratory Endpoint
- Section 9.4 Analysis of Safety Data was added

Changes incorporated into Version 5.0 Amendment of this document (Version 6.0).

- ITT population is updated to mITT population in Section 8.6 and 9.2

- Section 7.3 PP Population more clarification added to the description of the major protocol violations.
- Section 8.5 Subgroups were updated to be in line with what is stated in the protocol and more details provided.
- Section 9.2.2.2 analysis method for change in clinical status of subject at Days 14 and 28 (on a 7 point ordinal scale) was updated to be in line with the FDA guidance (i.e. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention).

Changes incorporated into Version 7.0 of this document.

- Section 8.5 Subgroups were updated to remove subgroups based on predefined stratification factors and subgroups based on IRT (post clinical review) per the memorandum of electronic correspondence received from FDA on February 12, 2021.

12. REFERENCES

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