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STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CD10_COVID-19

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Protocol Number: **CD10_COVID-19**

Protocol Title: A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19)

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SAP Version:	Final Version 1.0
SAP Date:	26 Apr 2020

I have read and approve the Statistical Analysis Plan specified above and agree with its content:

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Transaminase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CCR5	C-C chemokine receptor type 5
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
CV	Curriculum Vitae
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FDP	Finished Drug Product
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LTF	Lost to Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-Treat

Abbreviation	Term
NEWS	National Early Warning Score 2
PI	Principal Investigator
SAE	Serious Adverse Event
SC	Subcutaneous
SOP	Standard Operating Procedure
SpO_2	Peripheral Capillary Oxygen Saturation
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
Treg	T regulatory cell
V	Visit

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol CD10_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 5.0 / 30 Mar 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

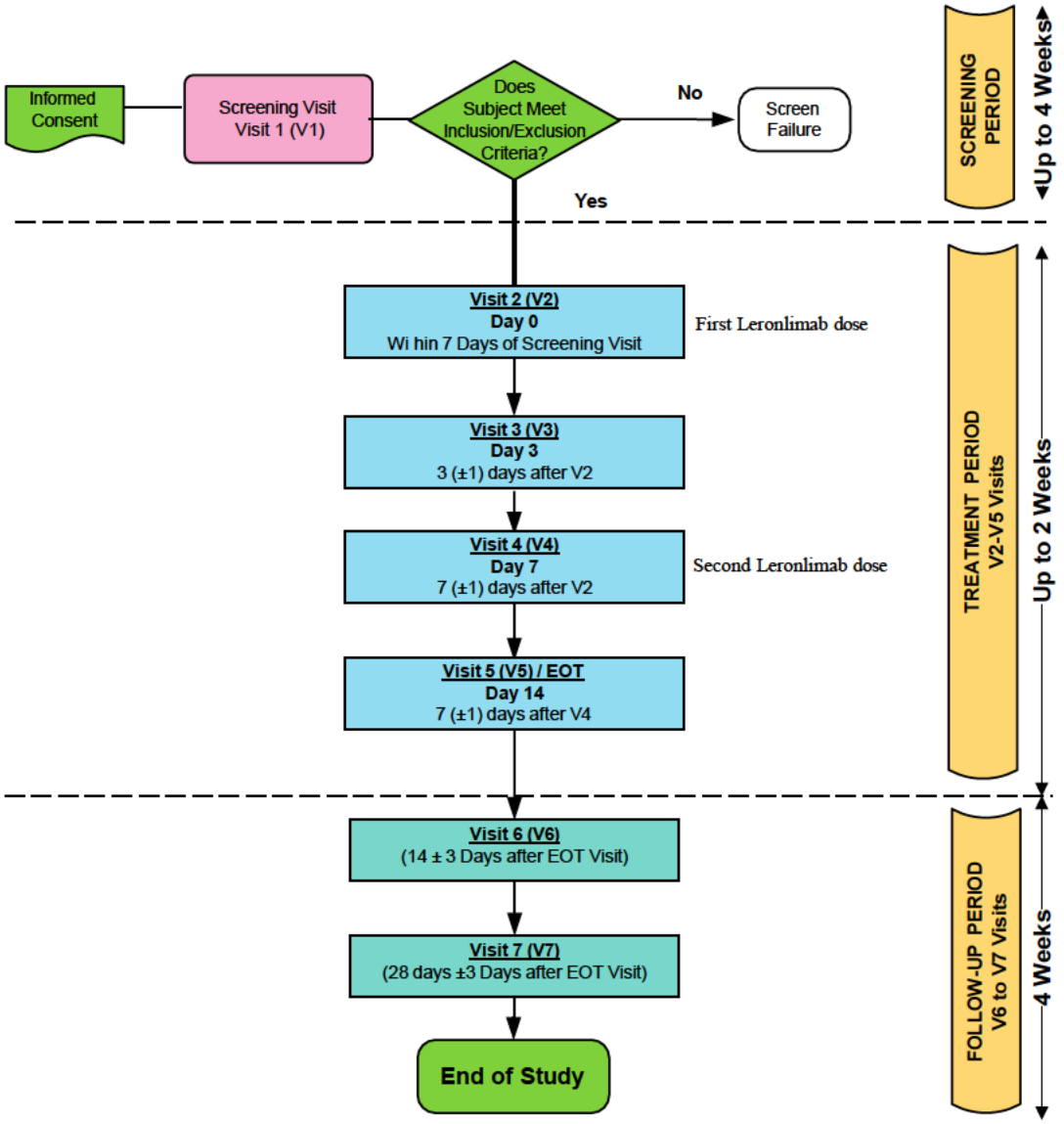
2.1 Study Objectives

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

2.2 Design Overview

This is a Phase 2, two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection. Patients will be randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection. The study flow diagram is presented in Figure 2-1.

Figure 2-1: Study Schematic



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, physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, electrocardiogram (ECG), nasopharyngeal swab sample collection, chest radiograph or CT (if clinically indicated), ordinal scale assessment, 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 Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, baseline assessment for the requirement of: Mechanical Ventilation, Oxygen, and Hospital Stay, and 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. 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 or subject's home.

The following assessments will be performed at V3, V4, and V5/EOT: physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, assessment for the requirement of: Mechanical Ventilation, Oxygen, and Hospital Stay, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, 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, 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. The following assessments will be performed at V6 and V7 visit: review of adverse events and concomitant medications, physical examination, vital signs, nasopharyngeal swab sample collection, mortality status, and blood collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V7 only).

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 possible, scheduled 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.

Table 2-1: Schedule of Assessments

Procedure/Assessments	Screening Visit	Treatment Phase					Follow-Up	
Visit	V1	V2 [16] (Pre-Rx)	V2 [16] (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		3(±1) days after V2	7(±1) days after V2	7(±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 Symptom Score Assessment [6]	X	X		X	X	X		
Pulse oxygen saturation (SpO2)	X	X		X	X	X		
National Early Warning Score 2 (NEWS2) Assessment[7]	X	X		X	X	X		
ECG	X					X		
Laboratory tests:								
Complete Blood Count [8]	X			X	X	X		X
Biochemistry [9]	X			X	X	X		X
Coagulation Indices [10]	X			X	X	X		X
Serum/Urine Pregnancy Test [11]	X					X		
Urinalysis [12]	X			X	X	X		X
CD3+, CD4+ and CD8+ T cell count		X		X	X	X		
CCR5 receptor occupancy for Treg and macrophage		X		X	X	X		
Serum cytokine and chemokine levels		X		X	X	X		
CCR5 Gene Polymorphisms [13]		X		X	X	X		
Nasopharyngeal Swab Sample Collection [14]	X	X		X	X	X	X	X
Chest radiograph or CT (if clinically indicated) [15]	X					X		

Procedure/Assessments	Screening Visit	Treatment Phase					Follow-Up	
Visit	V1	V2 [16] (Pre-Rx)	V2 [16] (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		3(±1) days after V2	7(±1) days after V2	7(±1) days after V4	14(±3) days after EOT Visit	28(±3) days after EOT Visit
Ordinal Scale Assessment	X	X		X	X	X		
Randomization [17]		X						
PRO 140 (700 mg) or Placebo Administration		X			X			
Assessment for the requirement of: Mechanical Ventilation, Oxygen, and Hospital Stay	X	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] Clinical Improvement will be assessed based on symptom score for fever, myalgia, dyspnea and cough. Each symptom is graded from 0 to 3. [0=none, 1=mild, 2=moderate, and 3=severe].The total score per patient ranges from 0 to 12 points. Clinical Improvement will be assessed daily while subject is hospitalized and will continue to be assessed on the scheduled treatment visits and at EOT after the subject is discharged from the hospital.
[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] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.
[9] Biochemistry Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin Lactate dehydrogenase (LDH) Renal function indicators: creatinine clearance, eGFR Electrolytes: sodium, potassium, chloride, calcium and bicarbonate Other: glucose (random), cholesterol (total), Creatine kinase, C-reactive protein
[10] Prothrombin time (PT) and International Normalized Ratio (INR)
[11] ONLY performed on women of childbearing potential.
[12] 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.
[13] Blood samples collected for receptor occupancy testing will also be used for CCR5 gene polymorphism for PRO 140 susceptibility.
[14] Swabs will be used for quantitative virologic testing. Samples are to be stored at -70 C.
[15] Chest radiograph or CT will be performed if clinically indicated by the treating physician.
[16] 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.
[17] Randomization via WebView CTMS system

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
PRO 140 (700 mg)	Parenteral solution	175 mg/mL	2 injections of 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 four categories based on clinical status of the study at baseline:

- Baseline total symptom score <=4 and age < 60
- Baseline total symptom score <=4 and age >= 60
- Baseline total symptom score > 4 and age < 60
- Baseline total symptom score > 4 and age >= 60

2.6 BLINDING

All subjects, Investigators and their staff, and all Sponsor/CRO personnel involved in the management of the study will be blinded to treatment assignments.

[redacted]

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 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), 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.

2.7.2 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 Outcome (Endpoints) Measures

The primary outcome (endpoint) measure is:

- Clinical Improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea and cough)

  Note: The total score per patient ranges from 0 to 12 points. Each symptom is graded from 0 to 3. [0=none, 1=mild, 2=moderate, and 3=severe].

3.2 Secondary Outcome (Endpoints) Measures

The secondary efficacy outcome (endpoints) for the study are:

1. Time to clinical resolution (TTCR)

   Time to clinical resolution (TTCR), defined as the time from initiation of study treatment until resolution of clinical symptoms (fever, myalgia, dyspnea and cough).
2. 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).
3. Change from baseline in pulse oxygen saturation (SpO2) at Days 3, 7, and 14
4. Change from baseline in the patient's health status on a 7-category ordinal scale at Days 3, 7, and 14

   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.

5. Incidence and duration (days) of hospitalization
6. Incidence and duration (days) of mechanical ventilation supply
7. Incidence and duration (days) of oxygen use
8. Mortality rate at Day 14
9. Time to return to normal activity

3.3 Exploratory Outcome (Endpoints) Measures

1. Change in size of lesion area by chest radiograph or CT
2. Change from baseline in serum cytokine and chemokine levels at Days 3, 7, and 14
3. Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages at Days 3, 7, and 14
4. 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 75 subjects will be enrolled in this study. The sample size is based on clinical judgment.

No statistical power calculation is used to establish the sample size for this proof-of-concept study.

5. INTERIM ANALYSIS

No Interim Analysis (IA) will be performed for efficacy

6. PRIMARY HYPOTHESIS TO BE TESTED

This clinical trial is designed to primarily test the hypothesis that leronlimab provides a Clinical Improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea and cough). Hence, the statistical inference will be done on $\mu_{leronlimab}$ (i.e., mean change from baseline in total symptom score for the subjects in the leronlimab group) vs. $\mu_{Control}$ (i.e., mean change from baseline in total symptom score for the subjects in the Placebo group); that is the following hypothesis will be examined:

H_0: $\mu_{leronlimab} = \mu_{Control}$

H_1: $\mu_{leronlimab} \neq \mu_{Control}$

7. ANALYSIS POPULATIONS

7.1 Intent-to-Treat Population

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

7.2 PP Population

The **Per Protocol (PP) population** is defined as the set of subjects who meet the Evaluable Population requirements and were not associated with any major protocol violations. This population will be identified before the database lock.

7.3 Safety Population

The **Safety Population** will include all subjects who have received one dose of leronlimab (PRO 140) or placebo. This population will be used for the analysis of safety parameters or measurements.

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, hence there is no adjustment for Type I error rate.

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

As several factors are considered to be related to treatment, subgroup analyses will be performed to evaluate whether the treatment effects are consistent across different subgroups. These factors include:

- Baseline total symptom score <=4
- Baseline total symptom score>4
- Age < 60
- Age >= 60

In addition, subgroup analyses will be performed to evaluate whether the treatment effects are consistent without and with use of any off-label COVID-19 treatments including hydroxychloroquine, chloroquine or azithromycin at baseline.

8.6 Standard Calculations

8.6.1 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]

8.6.2 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]

8.6.3 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

8.6.4 Time to Any Event

The number of days from the randomization date to any event will be calculated as follows.

Time to Event (days) = (Date of Event – Date of randomization) + 1

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 $\alpha=0.05$

9.2.1 Primary Efficacy Outcome (Endpoint) Measure

The primary endpoint for the study is clinical Improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea and cough).
The estimated difference in change in total symptom score along with 95% confidence interval and p-value will be calculated using ANCOVA adjusting for stratification factors in the model.

9.2.2 Secondary Efficacy Outcome (Endpoint) Measure

9.2.2.1 Time to clinical resolution (TTCR)

Time to clinical resolution 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 resolution 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 clinical resolution between the treatment groups.

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

The change in National Early Warning Score 2 of subject at Days 3, 7 and 14 will be summarized descriptively and compared using ANCOVA.
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.

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

The change from baseline in oxygen saturation (SpO2) at Days 3, 7, and 14 will be summarized descriptively and compared using ANCOVA .
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.

9.2.2.4 Change from baseline in the patient's health status on a 7-category ordinal scale at Days 3, 7, and 14.

The change from baseline in *patient's health status on a 7-category ordinal scale at Days 3, 7, and 14* will be summarized descriptively and compared using ANCOVA.
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.

9.2.2.5 Incidence and duration (days) of hospitalization

Incidence and duration (days) of hospitalization will be summarized descriptively by treatment

group. The duration of hospitalization will be compared between the treatment groups using the a non-parametric method or a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data.

9.2.2.6 Incidence and duration (days) of mechanical ventilation supply

Incidence and duration (days) of mechanical ventilation supply will be summarized descriptively by treatment group. The duration (days) of mechanical ventilation supply will be compared between the treatment groups using the a non-parametric method or a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data.

9.2.2.7 Incidence and duration (days) of oxygen use

Incidence and duration (days) of oxygen use will be summarized descriptively by treatment group. The duration (days) of oxygen use will be compared between the treatment groups using the a non-parametric method or a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data.

9.2.2.8 Mortality rate at Day 14

Mortality rate at Day 14 will be summarized. The estimated difference in mortality rates will be calculated using Logistic Regression adjusting for stratification factors.

9.2.2.9 Time to return to normal activity

Time to return to normal activity 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 return to normal activity 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 Exploratory Outcome Measures (Endpoints)

Analysis of the exploratory endpoints will be summarized according to the variable type:

- Continuous data summaries will include:
    - If the Normality assumption is met, Analysis of Covariance (ANCOVA) would be used.
    - 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.
- Categorical data summaries will be based on Logit model.
- Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and to depict the time to event data.

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.

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

This is the first version of the SAP.

12. REFERENCES

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April, 2016.
2. The Royal Statistical Society: Code of Conduct (2014).
3. E8 General Considerations for Clinical Trials, ICH Guidance, Federal Register, 1997.
4. E9 Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1998
5. Guideline for the Format and Content of the Clinical and Statistical Section of an Application, 1988.
6. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.