# 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)

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|---|---|
| **Protocol Number:** | **CD12_COVID-19** |
| **Version:** | **6.0** |
| **Date:** | **28-Dec-2020** |


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## Confidentiality Statement

## PROTOCOL APPROVAL PAGE

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We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

### PROTOCOL APPROVAL FOR USE

## INVESTIGATOR'S SIGNATURE PAGE

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I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) and other global regulatory authority regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

## SPONSOR INFORMATION

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## CONTRACT RESEARCH ORGANIZATION INFORMATION

# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Name of Sponsor/Company:**<br>CytoDyn, Inc. | |
| **Name of Study Product:**<br>Leronlimab (PRO 140) | |
| **Protocol Number:**<br>CD12_COVID-19 | **Indication:**<br>Coronavirus Disease 2019 (COVID-19) |
| **Title of Study:**<br>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) | |
| **Study Center:** Up to 30 multinational centers. Centers must have the capability of implementing appropriate infection-control measures to prevent infection of study staff and others who share the clinical site space. | |
| **Planned Number of Subjects:**<br>Randomized Phase: 390 subjects<br>Non-Randomized, Open-label Phase: Enrollment will remain open until the decision is made by Sponsor and/or FDA to close the recruitment. | **Study Development Phase:**<br>Phase 2b/3 |
| **Indication for Use:** Leronlimab is indicated for treatment of adult patients with severe or critical symptoms of respiratory illness caused by Coronavirus disease 2019 (COVID-19). | |
| **Objective:**<br>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 COVID-19 disease. | |
| **Study Outcomes (Endpoints):**<br>**Primary Endpoint:**<br>• All-cause mortality at Day 28<br>**Secondary Endpoints:**<br>• All-cause mortality at Day 14<br>• Proportion of patients achieving a category of 6 or higher at Days 14 and 28 (on a 7 point ordinal scale).<br>• Change in clinical status of subject at Days 14 and 28 (on a 7 point ordinal scale)<br>*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,* | |

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*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)

**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

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- 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

**Safety Measures:**

- 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

**Trial Design:**

This is a Phase 2b/3, two-arm, randomized, double blind, placebo controlled, adaptive design multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with severe or critical 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.

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 will have three phases: Screening Period, Treatment Period, and Follow-Up Period.

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**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.

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| 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 |

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. 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, 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, 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, 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),

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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 the subject is discharged from the hospital prior to Visit 7 (Day 42), 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.

**Duration of Treatment:**

- **Screening Period** (Screening to Baseline): Up to 7 days (1 Week)
- **Treatment Period**: 14 Days (2 weeks)
- **Follow-Up Period**: 28 Days (4 weeks)

  **Total Study Duration**: 7 Weeks

**Inclusion Criteria:**

1. Male or female adult ≥ 18 years of age at time of screening.
2. Subjects hospitalized with severe or critical illness caused by coronavirus 2019 infection as defined below:

   **Severe Illness:**

   - Diagnosed with COVID-19 by standard RT-PCR assay or equivalent testing within 5 days of screening

     **AND**
   - Symptoms of severe systemic illness/infection with COVID-19:
     - At least 1 of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion, or symptoms of severe lower respiratory symptoms including dyspnea at rest or respiratory distress

     **AND**
   - Clinical signs indicative of severe systemic illness/infection with COVID-19, with at least 1 of the following:
     - RR ≥ 30, HR ≥ 125, SaO2 <93% on room air or requires > 2L oxygen by NC in order maintain SaO2 ≥93%, PaO2/FiO2 <300

     **AND**

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- No criteria for Critical Illness:
  - None of the following: Respiratory failure (defined by endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, or clinical diagnosis of respiratory failure in setting of resource limitations), Septic shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg), Multiple organ dysfunction/failure

**Critical Illness:**

- Diagnosed with COVID-19 by standard RT-PCR assay or equivalent testing within 5 days of screening

  **AND**
- Evidence of critical illness, defined by at least 1 of the following:
  - Respiratory failure defined based on resource utilization requiring at least 1 of the following: Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (in setting of resource limitation)

  **OR**
- Shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg or requiring vasopressors)

  **OR**
- Multiple organ dysfunction/failure

3. Subject, if intubated, positive end-expiratory pressure (PEEP) <15 cmH2O with PaO2/FiO2 >150 mmHg.

4. Electrocardiogram (ECG) with no clinically significant findings as assessed by the Investigator.

   *Note: Below are the examples of clinically significant and non-clinically significant ECG abnormalities:*

   – *ECG findings indicative of acute myocardial infarction or acute ischemic changes would be considered clinically significant abnormalities.*

   – *ECG finding such as atrial fibrillation, atrial flutter, paced rhythms in individuals who have undergone permanent pacemaker placement, evidence of prior infarction, unchanged stable conduction abnormalities e.g. right bundle branch block, or any other finding which does not significantly impact mortality would be considered non-clinically significant findings and subjects with these abnormal findings would be allowed to enroll in the study.*

5. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.

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6. Understands and agrees to comply with planned study procedures.
7. Women of childbearing potential and their partner must agree to use at least one highly effective method of contraception (e.g., hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], intrauterine devices, bilateral tubal occlusion, or sexual abstinence) for the duration of the study.

**Exclusion Criteria:**

1. Subjects with do-not-resuscitate (DNR) and/or do-not-intubate (DNI) orders or expected to be made DNR/DNI in setting of resource limitations or family wishes.
2. Not a candidate for dialysis or continuation of care (or full medical support) in setting of resource limitations.
3. Subject on continuous vasopressors (at the dose of norepinephrine >20µg/min and/or vasopressin >0.04 units/kg/min) for >48 hours at time of screening.
4. Subjects who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible.
5. Inability to provide informed consent or to comply with test requirements
6. Consideration by the investigator, for safety reasons, that the subject is an unsuitable candidate to receive study treatment
7. Pregnancy or breast feeding
8. Subject participating in another study with for an investigational treatment for COVID-19.

   *Note: Subject who were prescribed (1) hydroxychloroquine or chloroquine with or without azithromycin, (2) Remdesivir, (3) convalescent plasma therapy, or (4) immunomodulatory treatments (including but not limited to sarilumab, clazakizumab, tocilizumab, and anakinra) for the off-label treatment of COVID-19 prior to study enrollment may be included and may continue to receive these agents as part of standard-of-care.*

**Statistical Considerations:**

**Sample Size Determination and Rationale**

A total of three hundred ninty (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.

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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-tset 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.

**Analysis Populations**

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

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

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.

**Analysis Methods**

**Efficacy Analyses:**

Primary Endpoint: Mortality rate at Day 28

The proportion of subjects with mortality at Day 28 will be compared between the leronlimab and placebo treatment groups using Logistic regression model.

Secondary Endpoints: To maintain the trial-wise Type I error rate at 0.05, a closed test procedure will be used for the secondary endpoints. The order of the endpoints will be specified in the Statistical Analysis Plan (SAP).

Analysis of the secondary endpoints will be summarized according to the variable type and will be detailed in the SAP:

- Continuous data:

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- 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 will be used.
- Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and Kaplan-Meier methods will be used to depict the time to event data.

**Safety Assessments**

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

For continuous variables, data will be summarized by treatment using n, mean, SD, minimum and maximum values. For categorical variables, data will be summarized by treatment using frequency and percentage. No inferential statistics are planned.

**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 randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade
- By relationship

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

**Clinical Laboratory Data:** All laboratory values will be listed. Laboratory measurements will also be summarized as continuous variable and presented by treatment group and time point. For efficacy analysis, only lab data received from Central Lab will be used.

**Physical Examination:** All physical examination findings will be listed and/or summarized.

**Vital Signs:** All vital sign findings will be listed and summarized.

**ECG:** All ECG findings will be listed, coded, and summarized.

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| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Transaminase |
| ARDS | Acute Respiratory Distress Syndrome |
| ART | Antiretroviral Therapy |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CCR5 | C-C chemokine receptor type 5 |
| CD | Cluster of Differentiation |
| CFR | Code of Federal Regulations |
| Cmax | Maximal Concentration |
| CNS | Central Nervous System |
| 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 |
| DSMC | Data Safety Monitoring Committee |
| ECG | Electrocardiogram |
| ECMO | Extracorporeal Membrane Oxygenation |
| EOT | End of Treatment |
| FDA | U.S. Food and Drug Administration |
| FDP | Finished Drug Product |
| FUV | Follow-up Visit |
| 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 |
| HIV | Human Immunodeficiency Virus |
| IA | Interim Analysis |
| IC | Inhibitory Concentration |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |

| Abbreviation | Term |
|---|---|
| ICU | Intensive Care Unit |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ISR | Injection Site Reaction |
| ITT | Intent to Treat |
| IV | Intravenous |
| IWRS | Interactive Web Based Response System |
| LAR | Legally Authorized Representative |
| LTF | Lost to Follow-Up |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| MTD | Maximum Tolerated Dose |
| NEWS | National Early Warning Score 2 |
| OBT | Optimized Background Therapy |
| PD | Pharmacodynamic |
| PEEP | Positive End-Expiratory Pressure |
| PK | Pharmacokinetic |
| PI | Principal Investigator |
| RRT | Renal Replacement Therapy |
| SAE | Serious Adverse Event |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SC | Subcutaneous |
| SOFA | Sequential Organ Failure Assessment |
| SOP | Standard Operating Procedure |
| $SpO_2$ | Peripheral Capillary Oxygen Saturation |
| SV | Screening Visit |
| TEAE | Treatment Emergent Adverse Event |
| TNBC | Triple Negative Breast Cancer |
| Treg | T regulatory cell |
| TV | Treatment Visit |
| V | Visit |
| VL | Viral Load |

# 1 INTRODUCTION AND BACKGROUND

## 1.1. STATEMENT OF INTENT

The design, conduct and reporting of this study shall be conducted in compliance with the protocol, International Conference on Harmonization/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

## 1.2. BACKGROUND OF THE DISEASE

Coronavirus disease 2019 (COVID-19) is a respiratory illness that can spread from person to person. The infectious agent that causes COVID-19 is a novel Coronavirus, named 'SARS-CoV-2', was first identified during a recent outbreak in December 2019, in Wuhan, China. Patients with COVID-19 have had mild to severe respiratory illness with symptoms of fever, cough, and shortness of breath along with non-specific symptoms including myalgia and fatigue. Some patients were more likely to develop a severe respiratory illness similar to severe acute respiratory syndrome (SARS), or even die from the disease.

Current standard of care treatment includes oxygen therapy. There is no specific antiviral treatment recommended for COVID-19 by Centers for Disease Control and Prevention (CDC). People with COVID-19 should receive supportive care to help relieve symptoms. For severe cases, treatment should include care to support vital organ functions.

The aim of this study is to test efficacy and safety of leronlimab (PRO140) for treatment of adult patients with severe or critical symptoms of respiratory illness caused by 'SARS-CoV-2' coronavirus infection.

## 1.3. LERONLIMAB (PRO 140)

Leronlimab (PRO) 140 is a humanized IgG4,κ monoclonal antibody (mAb) to the C-C chemokine receptor type 5 (CCR5), under development as a therapy for human immunodeficiency virus (HIV) infection.

Leronlimab (PRO 140) has been shown to bind to the N terminus (Nt) and the extracellular loop 2 (ECL2) domain of the CCR5 cell surface receptor that HIV-1 uses to gain entry to a cell. Leronlimab (PRO 140) (binding to CCR5 blocks viral entry by interfering with the final phase of viral binding to the cell surface prior to fusion of the viral and cell membranes. Leronlimab (PRO 140) has been administered intravenously or subcutaneously to more than 750 healthy and HIV-1 infected individuals in Phase I/II/III studies. The drug has been well tolerated following intravenous administration of single doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as subcutaneous

(SC) injection. Overall, 324 subjects have been exposed to leronlimab (PRO 140) 350 mg SC weekly dose with the longest duration of exposure lasting 4 years. Similarly, more than 250 and 150 subjects have been exposed to leronlimab (PRO 140) 525 mg and 700 mg SC weekly dose, respectively.

## 1.4. SUMMARY OF PRIOR PRE-CLINICAL AND CLINICAL STUDIES

### 1.4.1. Pre-Clinical Studies with PRO 140

*In vitro* and *in vivo* preclinical studies have been conducted to determine the pharmacokinetic, immunogenicity, and toxicity profiles of leronlimab (PRO 140) following IV and SC administration. Several acute and chronic toxicity studies have been conducted to support the clinical development plan.

Acute toxicity of leronlimab (PRO 140) was evaluated in New Zealand rabbits, following IV administration of 5 or 15 mg/kg. Chronic toxicity was evaluated in cynomolgus monkeys following biweekly administration of IV doses up to 10 mg/kg for six months and biweekly administration of various SC doses up to 50 mg/kg for 24 weeks. The drug was generally well tolerated. Biweekly administration of IV doses up to 10 mg/kg for six months resulted in minimum to mild lymphoid hyperplasia in assorted lymph nodes and spleen, which was considered an expected immune response to a foreign protein. Biweekly administration of SC doses up to 50 mg/kg for 24 weeks resulted in minimum injection-site reactions (minimal, multifocal, mononuclear cell infiltrates in the subcutis), which were considered due to an inflammatory response to the injected antigen. Monkeys tolerated treatment with leronlimab (PRO 140) for 24 weeks without evidence of local or systemic toxicity. Leronlimab (PRO 140) caused no mortality, cageside observations, in-life injection-site observations, or gross pathologic findings. Chronic treatment with leronlimab (PRO 140) did not affect body weight, food consumption, hematology, clinical chemistry or coagulation parameters.

Both IV and SC administration resulted in elimination half-lives of approximately 200 hours, and overall exposure increased with increasing doses. Following SC administration of leronlimab (PRO 140) in monkeys, the maximal concentration ($C_{max}$) was achieved within 56 hours and bioavailability for leronlimab (PRO 140) after SC dosing was approximately 70%.

### 1.4.2. Clinical Studies with PRO 140

Current human experience with leronlimab (PRO 140) consists of nine completed and six ongoing clinical trials, mostly on healthy subjects or HIV-1 positive subjects. These studies are summarized in Table 1-1 and Table 1-2. In all clinical trials, the majority of adverse events (AEs) have been mild or moderate. No dose-limiting toxicities or patterns of drug-related toxicities were observed. Antiviral activity was potent, rapid, prolonged, dose-dependent, and highly significant.

#### 1.4.2.1. PRO 140 1101 Study

For the first-in-human trial, PRO 140 1101, the drug was administered IV at 0.1, 0.5, 2.0, or 5.0 mg/kg to healthy subjects and was generally well tolerated, non-immunogenic, and without clinically relevant toxicity. Treatment Emergent Adverse Events (TEAEs) did not increase with rising PRO 140 dose levels. Seventy-five percent (75%) of subjects reported TEAEs, most of which were deemed unrelated to study treatment by the investigator.

#### 1.4.2.2. PRO 140 1102 Study

For PRO 140 1102, the majority of AEs, other than injection-site reactions, were considered mild and possibly related to drug administration. The majority of injection-site reactions were considered mild, self-resolving, and definitely related to drug administration. PRO 140 derived from Chinese Hamster Ovary (CHO) cells and administered at 100 mg/mL was generally well tolerated in healthy, normal volunteers. Overall, PRO 140 administered SC using Autoject® 2 appeared better tolerated than manual injection.

#### 1.4.2.3. PRO 140 1103 Study

In PRO 140-1103, administration of PRO 140 at 350 mg using Autoject® 2 appeared well tolerated. Manual injections, on the other hand, were associated with a greater number of AEs. There did not appear, however, to be any substantial difference in subject perception of pain or discomfort related to site of drug administration. No anti-PRO 140 antibodies were detected in any subjects in this study. There was a tendency of higher exposure associated with SC administration of PRO 140 at 350 mg in the abdomen and the thigh. A higher number of AEs were associated with injections in the arm. Based on these observations, thigh and abdominal administration of PRO 140 were preferred over arm injection.

#### 1.4.2.4. PRO 140 1302 Study

The initial proof-of-concept study was a randomized, double-blind, placebo-controlled study in subjects with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks [Jacobson, 2008]. Subjects (n=39) were randomized to receive a single IV injection of placebo or PRO 140 at doses of 0.5, 2, or 5 mg/kg. Subjects were monitored for antiviral effects, safety, and PRO 140 pharmacokinetics (PK) for 58 days.

PRO 140 demonstrated potent, rapid, prolonged, and dose-dependent antiviral activity. Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose-limiting toxicity was observed [Jacobson, 2008]. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose

groups. There was no significant effect on QTc intervals or other electrocardiographic parameters, and there were no remarkably laboratory findings.

1.4.2.5. PRO 140 2301 Study

PRO 140 2301 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in 30 male and female adult subjects infected with HIV-1 [Jacobson, 2010]. Subjects were randomized to one of three groups (N=10/group), each receiving one of three treatments: (i) a single IV dose of 5 mg/kg by 30-minute IV infusion; (ii) a single IV dose of 10 mg/kg by 30-minute IV infusion; (iii) a single placebo dose by 30-minute IV infusion. The objective of the study was to assess and characterize the PK and PD of PRO 140 administered by IV infusion, assess efficacy at a new dosage level, and safety and tolerability of single doses of PRO 140.

All PRO 140-treated subjects had more than 10-fold reduction in viral loads [Jacobson, 2010]. Both the 5 mg/kg and 10 mg/kg doses have shown favorable tolerability and no dose-limiting toxicity has been observed. High levels of receptor occupancy (>85% reduction in the number of cells detected) were observed for 29 days after treatment with both 5 and 10 mg/kg doses.

1.4.2.6. PRO 140 2101 Study

A subcutaneous (SC) form of PRO 140 was tested in HIV-infected subjects. The trial was a randomized, double-blind, placebo-controlled study in subjects (n=44) with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks [Thompson, 2009]. Placebo (n=10) and three PRO 140 doses were examined: 162 mg weekly for three weeks (n=11), 324 mg weekly for three weeks (n=11), and 324 mg biweekly (every other week) for two doses (n=12). Subjects were followed for 44 days after the final dose.

Potent, dose-dependent and highly statistically significant antiviral activity was observed. The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection [Thompson, 2009].

Subcutaneous PRO 140 was generally well tolerated both locally and systemically. There was no obvious dose-related pattern of toxicity. The most common adverse events (diarrhea, headache, lymphadenopathy and hypertension) were mild to moderate and self-resolving. These events are common in HIV infection and were reported with similar frequencies in the placebo and PRO 140 treatment groups. Administration-site reactions were mild, transient, and observed in a fraction of subjects.

1.4.2.7. PRO 140_CD01 Study

PRO 140_CD01 study (open-label, 43 subjects, multi-center) evaluated the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 12 weeks) for the maintenance of viral suppression following substitution of antiretroviral therapy in HIV-1

infected patients (with exclusive CCR5-tropic virus). Participants in this study were experienced HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy. Consenting patients were shifted from combination antiretroviral regimen to PRO 140 monotherapy for 12 weeks.

Forty-three (43) subjects (M/F: 37/3) with median age of 54.5 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-two out of 40 (55%) enrolled subjects completed 12 weeks of PRO140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Of the 43 enrolled subjects, 3 subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 37 subjects were found to have exclusive CCR5-tropic virus. A letter of amendment was filed to increase the planned number of subjects from 40 to 43 subjects to compensate for the 3 Dual/Mixed subjects enrolled in the study.

All virologic failure subjects who had available lab data in both studies achieved viral suppression to < 400 HIV-1 RNA copies/mL, as well as viral suppression to 'Non Detectable' or < 50 HIV-1 RNA copies/mL after re-initiation of ART.

The by-subject analysis of PhenoSense® Entry Assay data for PRO140, maraviroc, and AMD3100 shows no significant changes in the post-treatment IC50 and IC90 values were noted when compared with baseline values in virologic failure and non-virologic failure groups of subjects. As the aggregate analysis shows for initial 40 subjects, the subjects who experienced virologic failure had higher IC90 value for PR0140 at baseline compared to subjects without virologic failure. The mean IC90 for subjects who experienced virologic failure was higher (10.84 µg/mL) than the IC90 for subjects without virologic failure (6.70 µg/mL) in the CD01 study (p=0.0115).

Anti-PRO140 antibodies were not identified in any post-treatment sample and data derived from the CD01 study further supports the favorable PRO140 PK profile data generated from both pre-clinical as well as prior Phase 1/2 clinical trials.

Safety data were analyzed for all 43 enrolled subjects. One (1) of 43 subjects experienced an SAE that was deemed not related to the study drug by the Principal Investigator. Twenty-eight (28) of 43 subjects (67%) experienced one or more adverse events (AEs) after receiving at least one dose of PRO140. The most commonly occurring AEs were infections and infestation conditions which were reported by 14 of 43 (32.5%) subjects. The majority of the reported AEs (62/87; 71.2%) were deemed either unlikely or not related to study treatment by the Investigator. Similarly, the majority of the reported AEs (70/87; 80.4%) were deemed mild in nature.

1.4.2.8. PRO 140 CD01 Extension Study

PRO 140_CD01-Extension study (open-label, 28 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly) for the continued maintenance of viral suppression following substitution of antiretroviral therapy in HIV patients (with exclusive CCR5-tropic virus). Participants in this study were HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy and completed the first 12 weeks of CD01 study without experiencing virologic failure. As with the CD01 study, virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy until PRO 140 receives marketing approval or IND is withdrawn by Sponsor.

A total of 17 subjects participated in the CD01-Extension study of which one subject was considered not eligible as subject experienced virologic failure prior to first extension treatment.

Sixteen (16) eligible subjects (M/F: 14/2) with median age of 54.9 years (26-68) and median CD4 T-cell count of 593 cells/mm3 (365-1059) were enrolled in an extension study. One patient discontinued at week 37 (with viral load of <40 copies/mL) due to relocation. Two subjects were withdrawn due to non-treatment related SAEs at week 140 and 149, respectively. One subject was withdrawn due to re-starting their ART at week 99. Two subjects withdrew consent at week 81 and 139, respectively. Five (5) subjects experienced virologic failure (VF) (two consecutive viral load of ≥400 copies/mL). The mean time to virologic failure was 329 days (106-691).

Five (5) subjects are currently receiving weekly 350 mg PRO140 SC monotherapy and have completed more than three years of treatment (176 - 198 weeks). Overall, 12 subjects completed at least one year of treatment and 9 subjects completed at least two years of treatment in this study

PRO140 was generally well tolerated, and no drug-related SAEs were observed.

This clinical study is currently ongoing.

1.4.2.9. PRO 140_CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 52 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 in combination with either existing ART (failing regimen) or Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 52 adult patients with a documented history of genotypic or phenotypic resistance to ART drugs within two or more drug classes who demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy and have limited treatment options. The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due to potential for toxicity), past adverse reactions such as

hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.

In Part 1 of double-blind treatment period, virally non-suppressed subjects will be randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days until HIV-1 genotypic drug resistance assay results are available to construct an OBT. The primary efficacy endpoint is proportion of participants with ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the 7 day functional monotherapy period.

In Part 2 of double-blind treatment period, subjects will continue treatment with PRO 140 in combination with OBT within the 24-week open-label period.

Fifty-two subjects with a mean age of 52.4 years, 73.1% male, 48.1% non-white and mean duration of HIV-1 infection of 20.4 years were randomized 1:1 to the PRO 140 SC or placebo arm. Subjects had been previously exposed to an average of 11 ART drugs and had documented resistance to >9 ART drugs. Mean baseline VL and CD4 cell count were 21,104 c/mL and 297.8 c/mm$^3$, respectively. The primary efficacy endpoint- the proportion of patients with ≥0.5 log10 reduction in HIV-1 VL from baseline at the end of the 1-week double-blind, randomized, placebo-controlled treatment period- was met (16/25 vs 6/26 [p-value <0.0032, ITT population]). Forty seven (47) of 52 patients have completed the 25-week study. Approximately 81% of patients completing 25-weeks of PRO 140 SC treatment demonstrated HIV-1 VL <50 c/mL and 92% had HIV-1 VL <400 c/mL. Continued access to PRO 140 SC was provided through a rollover study and 40 patients entered the extension protocol after completing the CD02 study. PRO 140 SC was generally well tolerated. No drug-related SAEs or treatment discontinuations were reported in the study.

This clinical study is completed.

#### 1.4.2.10. PRO 140_CD02 Extension Study

PRO 140_CD02 Extension study (open label, 40 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 weekly injection in combination with Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 40 treatment-experienced HIV-infected adult patients with CCR5-tropic virus who successfully completed PRO 140_CD02 study and continue to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

#### 1.4.2.11. PRO 140_CD03 HIV Study

PRO 140_CD03 HIV (open-label, 350 subjects, multi-center) is a three part study enrolling virally suppressed HIV-1 patients with CCR5-tropic HIV-1 receiving combination antiretroviral (cART) therapy. Patients received weekly doses of PRO 140 on single-agent maintenance therapy following one week of overlap of the existing cART regimen that is then discontinued. In part 1, 156

participants received 350 mg PRO 140 SC in a single-arm design. In part 2, 147 participants received 350 or 525 mg PRO 140 SC in a 1:1 ratio as randomized controlled, two-arm study. In an ongoing part 3, 51 participants have been randomized to receive 525 or 700 mg PRO 140 SC in a 1:1 ratio.

Despite reaching the enrollment target of 350 subjects for the PRO140_CD03 HIV study, the enrollment is ongoing as the goal of enrolling 20 subjects for the CNS sub-study have not achieved. As a result, sites that are currently participating in the CNS sub-study are permitted to continue enrollment in the CD03 HIV study.

Of the 354 patients enrolled, median age was 51 yrs (21-77) with the majority reported as male (79%) and 37% were non-white. A total of 27 subjects have been randomized to 700 mg dose. In addition, another 18 subjects have been exposed to 700 mg dose after rescuing from the lower doses (350 mg or 525mg). On average, participants were diagnosed with HIV-1 infection for 16.8 yrs and were on cART regimen for 14.8 yrs. The frequency and severity of injection site reactions were comparable between the three dose groups (350, 525 and 700mg) and the incidence or severity of injection site reactions was not increased in patients receiving higher doses. Overall, PRO 140 SC was generally well tolerated at all dose levels in this study.

This clinical study is currently ongoing.

1.4.2.12. PRO 140_CD03 HIV Extension Study

PRO 140_CD03 study (open-label, 350 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 SC as long-acting single-agent maintenance therapy in virologically suppressed subjects with CCR5-tropic HIV-1 infection. The study population includes up to 300 treatment-experienced HIV-infected adult patients who successfully completed PRO 140_CD03 HIV study and continue to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

1.4.2.13. PRO 140_CD06 Study

PRO 140_CD06 study (double-blind, 80 subjects, single-center) seeks to evaluate the evaluate comparability of PRO 140 formulation Batch Lot # 3-FIN-3143 versus formulation Batch Lot# 3-FIN-2618 as a one-time subcutaneous (SC) injection in healthy subjects under non-fasting conditions.

1.4.2.14. PRO 140_CD07 Study

CD07_TNBC study (open-label, two-part [Phase Ib: Up to 18 subjects; Phase II: 30 Subjects], multi-center) seeks to evaluate the efficacy, safety, tolerability and maximum tolerate dose (MTD)

of leronlimab (PRO 140) when combined with carboplatin in patients with CCR5+ metastatic triple-negative breast cancer (mTNBC).

The study population includes patients with CCR5-positive, locally advanced or metastatic triple-negative breast cancer (mTNBC) who are naïve to chemotherapy in metastatic setting but have been exposed to anthracyclines and taxane in neoadjuvant and adjuvant settings (first-line).

This clinical study is currently ongoing.

#### 1.4.2.15. CD08_mCRC Study

CD08_mCRC study (open-label, 30 subjects, multi-center) seeks to evaluate the effect on overall response rate (ORR) of Leronlimab (PRO 140) when combined with Regorafenib in patients with CCR5+, Microsatellite Stable (MSS), Metastatic Colorectal Cancer (mCRC).

The study population includes patients with CCR5+, Microsatellite Stable (MSS), metastatic Colorectal Cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild type, an anti-EGFR therapy.

#### 1.4.2.16. CD07_Compassionate Use

CD07_Compassionate Use study (open-label, two-part, multi-center) seeks to evaluate the efficacy, safety, and tolerability of leronlimab (PRO 140) when combined Treatment of Physician's Choice in the treatment of patients with CCR5+ Metastatic Triple Negative Breast Cancer (mTNBC). The study population includes patients with CCR5-positive, locally advanced or metastatic triple-negative breast cancer (mTNBC).

This clinical study is currently ongoing.

#### 1.4.2.17. CD09_Basket Study

CD09_Basket study (open-label, 30 subjects, multi-center) seeks to evaluate the anti-tumor activity of leronlimab (PRO 140) in patients with CCR5+, locally advanced or metastatic solid tumors who have disease progression on standard therapy, or receiving a standard anticancer treatment but no subsequent approved treatment would be available upon progression, or unable to receive standard therapy, or for whom standard therapy does not exist.

This clinical study is currently ongoing.

#### 1.4.2.18. CD10_COVID-19

CD10_COVID-19 (two-arm, randomized, double blind, placebo controlled) study seeks 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 were randomized to receive 2

weekly doses of 700 mg leronlimab (PRO 140), or placebo via subcutaneous injection at Day 0 and Day 7.

The study population was 60.7% female and 39.3% male, with an average age of 54.85 years. There were 56 subjects treated with leronlimab (PRO 140) and 28 with placebo.

CD10 study did not meet the pre-defined primary endpoint (change in symptom score at Day 14 analyzed as a continuous variable) or any of the pre-defined secondary efficacy endpoints (time to clinical resolution; change from baseline NEWS score at Days 3, 7, and 14 analyzed by ANCOVA method; change from baseline in pulse oxygen saturation Days 3, 7, 14; change from baseline health status by 7-point category ordinal scale at Days 3, 7, and 14; Incidence and Duration of hospitalization; incidence and duration of mechanical ventilation; incidence and duration of oxygen use; mortality at Day 14, or time to return to normal activity).

Post-hoc analyses described below, however did provide additional insights and information which helped design the further development of PRO 140 in COVID-19

- Day 3 total symptom score results:

  62.96% of the 56 subjects in PRO 140 group showed improvement in total symptom score, compared to 56% of the 28 subjects in the placebo group. In the sub-population of subjects with baseline total symptom score of ≥4, 90% of subjects treated with leronlimab (PRO 140) were reported with improvement in total symptom score, compared to 71% of subjects in the placebo group.

- National Early Warning Score 2 (NEWS2) (reported as proportion):

  24 of 56 (50%) of subjects treated with leronlimab (PRO 140) showed improvement from baseline in NEWS2 score at EOT visit, compared to 5 of 28 (20.83%) of subjects in the placebo group .

Safety was assessed primarily via reporting of adverse events (AEs) and serious adverse events (SAEs) throughout the study. In total, 34% (19 of 56 subjects) treated with leronlimab compared to 50% (14 of 28 patients) treated with placebo reported at least one AE. Additionally, 9% of subjects (5/56) reported SAEs in leronlimab group compared to 21% of subjects (6/28) in the placebo group.

The vast majority of the patients with mild to moderate COVID-19 recover with supportive care. The study sample size was not large enough to evaluate the effect of PRO 140 in this patient population. Post-hoc analyses indicate the potential for benefit of PRO 140 in patients with more severe (total symptom score of ≥4) COVID-19. Safety data shows that leronlimab (PRO 140) was well tolerated by subjects. The incidence, frequency, and severity of AEs and SAEs were not increased in the leronlimab (PRO 140) group compared to the placebo group.

**Table 1-1: List of Completed Clinical Studies with Leronlimab (PRO 140)**

| Protocol Number | Phase | No. of Subjects (Planned/ Analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| PRO 140 1101 | 1 | 20/20 | Single 0.1, 0.5, 2.0, or 5.0 mg/kg | Healthy | Generally well tolerated; non-immunogenic; dose-dependent coating of CCR5; significant coating of CCR5 over placebo at 0.5, 2, and 5 mg/kg |
| PRO 140 1102 | 1 | 20/20 | Either two or three doses totaling 200 or 350 mg respectively | Healthy | Generally well tolerated; drug derived from CHO cells well tolerated also; SC administration by Autoject® 2 better tolerated than manual injection |
| PRO 140 1103 | 1 | 15/14 | Two doses, each of 350 mg | Healthy | More AEs associated with arm injection; trend of lower exposure in arm injections; thigh and abdominal administration preferred |
| PRO 140 1302 | 1b | 40/39 | Single 0.5, 2.0, or 5.0 mg/kg | HIV-1 positive | Generally well tolerated; antiviral suppression maintained for approx. 10 days with higher doses; favorable tolerability and potent, dose-dependent antiviral activity provide proof-of-concept |
| PRO 140 2301 | 2a | 30/31 | Single 5.0 or 10.0 mg/kg | HIV-1 positive | Generally well tolerated with no dose-limiting toxicities; potent antiviral suppression maintained for approx. 20 days when administered IV at 5 or 10 mg/kg. No dose-limiting toxicities at 10 mg/kg. |
| PRO 140 2101 | 2a | 40/44 | Three doses of 162 or 324 mg each | HIV-1 positive | Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; antiviral activity was statistically significant; two-fold exposure at higher dose; single dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity. |
| PRO 140 CD01 | 2b | 43/43 | 350 mg SC weekly dose for 12 weeks of monotherapy (total treatment duration 14 weeks) | HIV-1 positive | Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; Open-label administration of PRO 140 demonstrated favorable tolerability, and potent, long-acting, antiviral activity. |

| Protocol Number | Phase | No. of Subjects (Planned/ Analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| PRO 140 CD02 | 2b/3 | 50/52 | 350 mg SC weekly dose of PRO 140 or placebo along with existing ART for 1 week then PRO 140 along with optimized background therapy for 24 weeks (total treatment duration 25 weeks) | HIV-1 positive, treatment-experienced | This study is completed pending database lock. |
| PRO 140 CD06 | PK | 80/79 | Single dose PK study with 350 mg SC dose | Healthy | This clinical study is completed. |
| CD10_COVID-19 | 2 | 75/86 | 700 mg SC weekly dose or placebo | Mild to moderate COVID_19 | This clinical study is completed and pending final clinical study report. |

**Table 1-2: List of Ongoing Clinical Studies with Leronlimab (PRO 140)**

| Protocol Number | Phase | No. of Subjects (Planned/ To be analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| PRO 140 CD_01-Extension | 2b | 17/16 | 350 mg SC weekly dose (as monotherapy) | HIV-1 positive, treatment experienced | This clinical study is currently ongoing. |
| PRO 140 CD02 Extension | 2b/3 | 50/40 | 350 mg SC weekly dose in combination with Optimized Background Therapy (OBT) | HIV-1 positive, treatment experienced | This clinical study is currently ongoing. |

| Protocol Number | Phase | No. of Subjects (Planned/ To be analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| PRO 140 CD03 | 2 | 350/TBD | 350 or 525 or 700 mg SC weekly dose for 46 weeks of monotherapy (total treatment duration 48 weeks) | HIV-1 positive, treatment-experienced | This clinical study is currently ongoing. |
| PRO 140 CD03 Extension | 2 | 350/TBD | 350 or 525 or 700 mg SC weekly dose (as monotherapy) | HIV-1 positive, treatment experienced | This clinical study is currently ongoing. |
| PRO 140 CD07 | 1a/2b | Phase Ib: Up to 18 subjects Phase II: 30 Subjects | 350 or 525 or 700 mg SC weekly dose (as monotherapy) | Triple negative breast cancer | This clinical study is currently ongoing. |
| CD08_mCRC | 2 | 30/TBD | 700 mg SC weekly dose in combination with Regorafenib | CCR5+, Microsatellite Stable (MSS), Metastatic Colorectal Cancer (mCRC). | This clinical study is pending start-up. |
| CD07_Compassionate Use | Comp. Use | 30/TBD | 350 mg SC weekly dose (as monotherapy or combination with Treatment of Physican's Choice) | Triple negative breast cancer | This clinical study is currently ongoing. |
| CD09_Basket | 2 | 30/TBD | 350 or 525 or 700 mg SC weekly dose (as monotherapy) | CCR5+, Locally Advanced or Metastatic Solid Tumors | This clinical study is currently ongoing. |

## 1.5. TREATMENT RATIONALE FOR THIS STUDY

### 1.5.1. Study Rationale

Chemokines regulate inflammation, leukocyte trafficking, and immune cell differentiation. The role of chemokines in tissue-specific homing of lymphocyte subsets and in trafficking of inflammatory cells has been well studied. Chemokines and chemokine receptors play a critical role in the recruitment, activation, and coordination of leukocytes in pathophysiology of lung inflammation.

The acute respiratory distress syndrome (ARDS) results from the accumulation of neutrophils within the pulmonary circulation and alveolar spaces via well-studied adhesion molecule-dependent and independent pathways [Doerschuk, 2000]. A published study demonstrated a crucial role for C-C chemokine receptor 5 (CCR5) in the accelerated recruitment of memory CD8(+) T cells to the lung airways during virus challenge [Kohlmeier, 2008]. This is consistent with our preliminary data showing very low CD8% and increased CD4/CD8 ratio both of which are improved at Day 3 after first dose of leronlimab (PRO 140) 700 mg in patients with severe COVID-19 infection treated under individual patient, emergency use INDs.

**Table 1-3: Immunologic Status - Post Leronlimab Therapy in COVID-19 Patients**

| | Patient: WS 56 yr/Male | | Patient: IW 74 yr/Female | |
|---|---|---|---|---|
| Test | Day 0 (18-Mar-20) | Day 3 (21-Mar-20) | Day 0 (18-Mar-20) | Day 3 (21-Mar-20) |
| CD4% | 52.1% | 30.3% | 28% | 30.2% |
| CD8% | 16.5% | 19.1% | 7% | 13.1% |
| CD4/CD8 | 3.15 | 1.6 | 4 | 2.3 |
| CCR5 RO – T cells | 0 | 69% | 0 | 54% |
| CCR5 RO – Macrophage | 0 | 83% | 0 | 63% |
| CCR5 RO – Treg | 0 | 61% | 0 | 94% |

RO=receptor occupancy

| | Patient: WSa 54 yr/Male | | Patient: KM 74 yr/Male | |
|---|---|---|---|---|
| Test | Day 0 (20-Mar-20) | Day 3 (23-Mar-20) | Day 0 (21-Mar-20) | Day 3 (24-Mar-20) |
| CD4% | 32.1% | 38.9% | 23.58% | 18.96% |
| CD8% | 5% | 9.6% | 5.45% | 7.15% |
| CD4/CD8 | 6.42 | 4 | 4.33% | 2.65% |
| CCR5 RO – T cells | 0 | 81% | 0 | 52% |
| CCR5 RO – Macrophage | 0 | 72% | 0 | 55% |
| CCR5 RO – Treg | 0 | 89% | 0 | 87% |

RO=receptor occupancy

Additionally, serum levels of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α showed substantial reduction at Day 3 after first dose of leronlimab (PRO 140) 700 mg in patients with severe COVID-19 infection treated under the individual patient, emergency use INDs.

**Table 1-4: Cytokine Levels - Post Leronlimab Therapy in COVID-19 Patients**

| Test | Patient: WS 56 yr/Male | Patient: IW 74 yr/Female |
|---|---|---|

| | Bead ID | Day 0 (18-Mar-20) | Day 3 (21-Mar-20) | Day 0 (18-Mar-20) | Day 3 (21-Mar-20) |
|---|---|---|---|---|---|
| IL-5 | A4 | <3 | <3 | <3.4 | <3.4 |
| IL-13 | A5 | <7 | <7 | <7.6 | <7.6 |
| IL-2 | A6 | <0.8 | <0.8 | <0.9 | <0.9 |
| IL-6 | A7 | 161 | 78 | 1000.1 | 344.2 |
| IL-10 | A10 | 13.3 | 2.6 | <1.9 | 7.7 |
| IL-9 | A8 | 6 | 5.6 | <2.2 | <2.2 |
| IFN-γ | B2 | <5.8 | <5.8 | <5.8 | 6.9 |
| TNF-α | B3 | 19.5 | 8.5 | 8.48 | <8.2 |
| IL-17A | B4 | 0.8 | <0.5 | <0.5 | <0.5 |
| IL-17F | B5 | 10.5 | 4.19 | <2.1 | <2.1 |
| IL-4 | B6 | <4.8 | <4.8 | <4.8 | <4.8 |
| IL-21 | B7 | 51.3 | 25.5 | <19.8 | <19.8 |
| IL-22 | B9 | 49.4 | 13.9 | <0.8 | 10.9 |

All values in pg/mL; All samples performed in duplicate

| | | Patient: WSa 54 yr/Male | | Patient: KM 74 yr/Male | |
|---|---|---|---|---|---|
| Test | Bead ID | Day 0 (20-Mar-20) | Day 3 (23-Mar-20) | Day 0 (21-Mar-20) | Day 3 (24-Mar-20) |
| IL-5 | A4 | 9.9 | <3.4 | <3.4 | 6.1 |
| IL-13 | A5 | 17.8 | 9.7 | <7.6 | <7.6 |
| IL-2 | A6 | 15.1 | 1.9 | <0.9 | <0.9 |
| IL-6 | A7 | 351.7 | 242.2 | 124.2 | 84.4 |
| IL-10 | A10 | 35.8 | 14.8 | <1.9 | 3.7 |
| IL-9 | A8 | 15.7 | 14.8 | <2.2 | 8.1 |
| IFN-γ | B2 | 10.6 | <5.8 | <5.8 | <5.8 |
| TNF-α | B3 | 22.6 | <8.2 | <8.2 | <8.2 |
| IL-17A | B4 | 3.5 | <0.5 | <0.5 | <0.5 |
| IL-17F | B5 | 8.1 | 30.6 | <2.1 | <2.1 |
| IL-4 | B6 | 7.3 | <4.8 | <4.8 | <4.8 |
| IL-21 | B7 | <19.8 | 66.3 | <19.8 | <19.8 |
| IL-22 | B9 | 17.9 | <0.8 | <0.8 | 4.2 |

All values in pg/mL; All samples performed in duplicate

The migration of macrophages and release of pro-inflammatory cytokines (cytokine storm) led to acute respiratory distress syndrome (ARDS) in lungs. Mice with genetic deficiency of CC-chemokine receptor (CCR) type 5, displayed reduced lung damage [Russkanmp-2020]. Moreover, treatment with a CCR5 antagonist, maraviroc, was protective against experimental acute lung injury/acute respiratory distress syndrome in the animal model [Russkanmp-2020].

The changes in the cytokine milieu influence CCR5 expression and may explain emergence of tropism-specific strains facilitating coronavirus transmission and disease progression similar to HIV transmission [Patterson 1999]. Chen et al. study on BALB/c mice showed that depletion of CD4+ T cells resulted in an enhanced immune-mediated interstitial pneumonitis and delayed clearance of SARS-CoV from the lungs, which was associated with reduced neutralizing antibody and cytokine production and reduced pulmonary recruitment of lymphocytes [Chen-2010].

Leronlimab (PRO 140) is a humanized IgG4, κ monoclonal antibody (mAb) specific for the type 5 C-C chemokine receptor (CCR5). Leronlimab (PRO 140) inhibits migration of Tregs into areas of inflammation which can inhibit the innate immune response against pathogens and most importantly, the migration of macrophages [Glass 2001] and release of pro-inflammatory cytokines in lungs. CCR5 engagement of macrophages changes them into effector cells rather than mediators of inflammation. In addition, the role of CCR5 antagonists in helping the innate immune response which is critical for infections the body has not been introduced to before (e.g. COVID-19), is discussed in Halama et al (2016).

The ARDS has known to be one of the main reasons for mortalities in patients with COVID-19. CytoDyn believes that leronlimab, CCR5 antagonist, is a potential therapeutics in inhibiting pro-inflammatory cytokines (cytokine storm) responses as observed in ARDS and thus could be useful in treatment of COVID-2019.

### 1.5.2. Rationale for Dose Selection and Treatment Duration

Leronlimab (PRO 140) is currently under development for the indication of HIV, Graft versus host disease (GVHD), metastatic triple negative breast cancer (mTNBC), and metastatic colorectal cancer (mCRC).

The safety profile of leronlimab (PRO 140) has been extensively evaluated in clinical trials. PRO 140 has been administered intravenously or subcutaneously to more than 750 healthy and HIV-1 infected individuals thus far, in Phase I/II/III studies. The drug has been well tolerated following intravenous administration of single doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as subcutaneous (SC) injection. Overall, 324 subjects have been exposed to PRO 140 350 mg SC weekly dose with the longest duration of exposure lasting 4 years. Similarly, more than 250 and 150 subjects have been exposed to PRO 140 525 mg and 700 mg SC weekly dose, respectively.

Available safety data from 131 subjects that received 700 mg dose in the ongoing PRO 140_CD03 study shows that less than 10% of subjects reported AEs considered definitely related to study treatment. All of these AEs were injection site reactions and considered to be mild or moderate in severity.

By severity, three subjects (2.3%, 3/131) reported AEs that were considered severe and two subjects (1.5%, 2/131) reported events that were deemed to be life-threatening. No events were considered related to the study treatment.

Serious adverse events (SAEs) were reported for six subjects (4.6%, 6/131). None of SAEs were considered related to the study treatment.

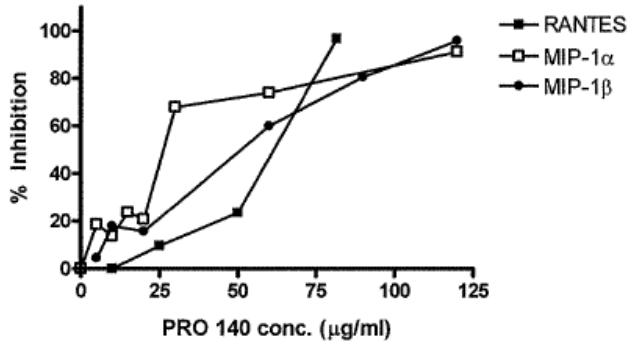
Additionally, there have been four patients with severe COVID-19 infection treated with 700 mg leronlimab (PRO 140) under individual patient, emergency use INDs. The current data from these patients are provided in the Investigational Brochure (IB).

Leronlimab (PRO 140) 700mg will be administered once weekly for two weeks only in this study as most patients with mild to moderate COVID-19 disease fully recovery within 2 weeks of developing initial symptoms.

While leronlimab showed weak activity relative to the positive control (2D7, an anti-CCR5 antibody) in Study 300-TD-018, the IC50 values were: 59.1 µg/mL for RANTES, 21.2 µg/mL for MIP-1α and 39.6 µg/mL for MIP-1β. The modeled Cmax* for the proposed 700 mg weekly dose is 267.2 µg/mL which is 4.5-12.6-fold higher than the IC50 values for these cytokines. In addition, at leronlimab concentrations greater than 75 µg/ml for RANTES and greater than 100 µg/ml for MIP-1α and MIP-1β, inhibition of 80% or more was seen for these cytokines (Appendix, Figure 2 of Study 300-TD-018). Therefore, leronlimab is anticipated to inhibit these cytokines following the 700 mg once weekly dose regimen.

**Figure 1-1: Dose-response curve for inhibition of CC-chemokine-induced calcium mobilization by PRO 140**

**Figure 2.** Dose-response curve for inhibition of CC-chemokine-induced calcium mobilization by PRO 140. Results are plotted as % inhibition of calcium influx= [1-(peak relative fluorescence in presence of MAb/peak relative fluorescence in absence of MAb)] x100%.




*The human Cmax was modeled for a dose of 700 mg once weekly in a 70 kg human subject. An interspecies population pharmacokinetic model was fit to available monkey and adult human data (concentration-time). Simulations were carried out to identify leronlimab serum concentration-time profiles (approximate to adults receiving 700 mg SC once weekly).

Leronlimab's role in the binding and signaling of chemokines MIP-1α(CCL3), MIP-1β(CCL4), and RANTES (CCL5) will be further evaluated in the Phase 2b/3 study. In addition, Cytokine and Chemokine Panel will include assessment of sCD40L, EGF, Eotaxin (CCL11), FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO alpha (CXCL1), IFN-alpha2, IFN-gamma, IL-1 alpha, IL-1

beta, IL-1RA, IL-2, IL-2R, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-12 (p40/p70) IL-13, IL-15, IL-17A, IL-17E/IL-25, IL-17F, IL-18, IL-22, IL-27, IP-10 (CXCL10), MCP-1 (CCL2), MCP-3, M-CSF, MDC (CCL22), MIG (CXCL9), MIP-1 alpha (CCL3), MIP-1 beta (CCL4), PDGF-AA, PDGF-AB/BB, RANTES (CCL5), TGF-alpha, TNF-alpha, TNF-beta, and VEGF-A.

### 1.6. RISKS / BENEFITS ASSESSMENT

**Allergic Reaction**

Leronlimab (PRO 140) belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions or flu-like reactions (such as fever, chills, and aches) or injection-site reactions. These events are usually of short duration if they occur at all. Severe allergic reactions, however, can be life-threatening. Although anaphylaxis has not been observed in prior trials of leronlimab (PRO 140), the protein infusion always carries theoretical risk for anaphylactic shock. Accordingly, whenever leronlimab (PRO 140) is administered to subjects, procedures should be available and in place to manage the occurrence of anaphylactic shock.

**Immune Response**

People who take leronlimab (PRO 140) or other monoclonal antibodies can also develop an immune response to leronlimab (PRO 140) that may affect their ability to receive monoclonal antibodies, or to benefit from diagnosis or therapy with a monoclonal antibody in the future.

**Pregnancy**

Risks to unborn babies exposed to leronlimab (PRO 140) are unknown at this time; thus pregnant females will be excluded from this study. Females of childbearing potential must have a negative pregnancy test prior to enrollment. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized).

**Venipuncture**

Blood sampling is required as part of the study protocol. Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

**Unknown Risks**

As with all research, there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

**Theoretical risk for increased severity of West Nile virus infection**

Individuals who lack a functional CCR5 gene are at increased risk for severe infection by West Nile virus [Thompson, 2009]. Because of this, treatment with CCR5 co-receptor antagonists poses a theoretical risk for increased severity of West Nile virus infection. However, this concern is mitigated by several factors. First, no increased risk was observed for individuals who possess one functional and one non-functional CCR5 gene, indicating that an intermediate amount of CCR5 is sufficient for defense against West Nile virus [Thompson, 2009]. Second, use of CCR5 co-receptor antagonists is unlikely to completely abrogate CCR5 function, and there has been no association reported to date between CCR5 co-receptor use and severe West Nile virus. Additionally, leronlimab (PRO 140) weakly antagonizes the natural activity of CCR5 and thus is less likely to adversely affect immune function. However, patients enrolled in this study may have immune suppression and therefore, DSMB and the investigators will be alerted to risks of West Nile infections. Furthermore, this has not been established to be a risk with maraviroc, the other FDA-approved anti-CCR5 drug already.

Collectively, the experience with both IV and SC, simulation modeling and the recent confirmation that a higher concentration of leronlimab (PRO 140) synthesized using a highly efficient CHO cell line can be conveniently and safely administered has resulted in the design of the current study.

# 2. STUDY OBJECTIVES

**Primary Objective:**

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

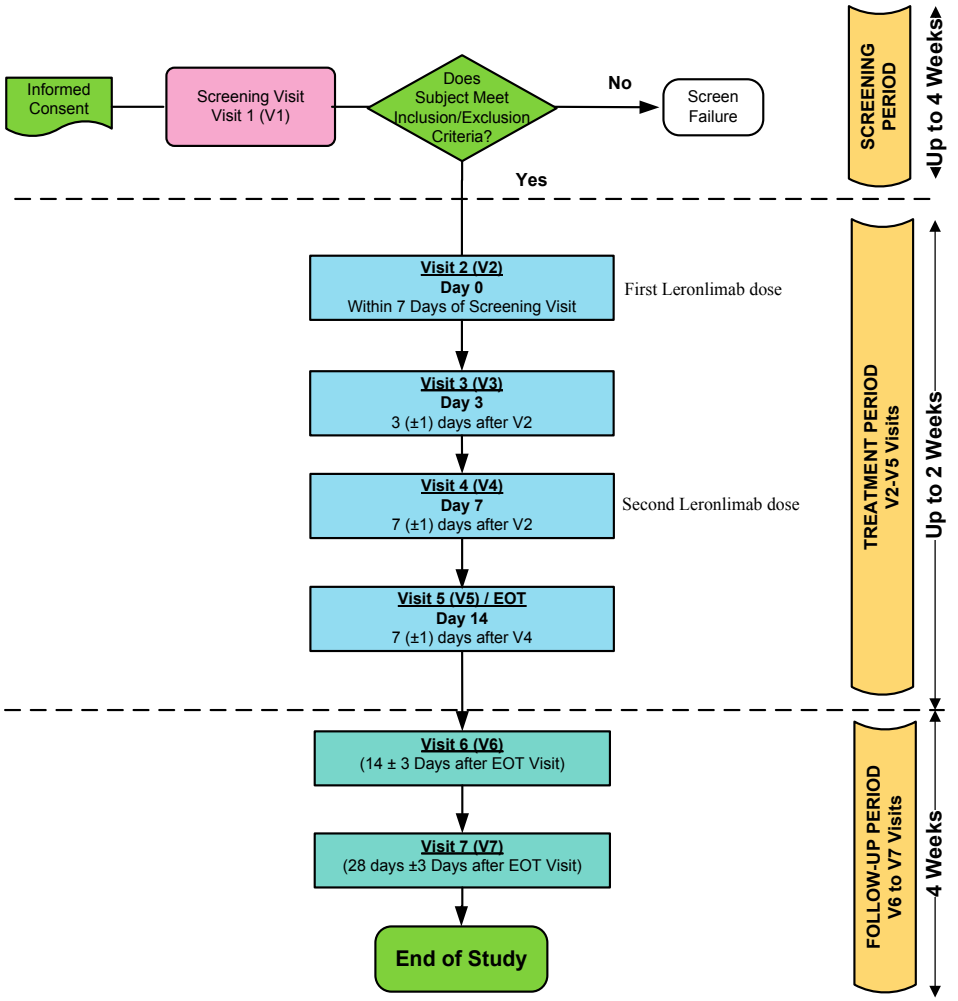
# 3. STUDY DESIGN

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.

A single arm, non-randomized, open-label phase is 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.

The study flow diagram is presented in Figure 3-1.

**Figure 3-1: Study Schematic**



## 3.1. STUDY CENTER

Up to 30 multinational centers. Centers must have the capability of implementing appropriate infection-control measures to prevent infection of study staff and others who share the clinical site space.

## 3.2. STUDY POPULATION

The target population for this study is adult subjects with severe or critical symptoms of respiratory illness caused by coronavirus disease 2019 (COVID-19).

## 3.3. ELIGIBILITY CRITERIA

### 3.3.1. Inclusion Criteria

Potential subjects are required to meet all of the following criteria for enrollment into the study:

1. Male or female adult ≥ 18 years of age at time of screening.
2. Subjects hospitalized with severe or critical illness caused by coronavirus 2019 infection as defined below:

   **Severe Illness:**

   - Diagnosed with COVID-19 by standard RT-PCR assay or equivalent testing within 5 days of screening

     **AND**
   - Symptoms of severe systemic illness/infection with COVID-19:
     - At least 1 of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion, or symptoms of severe lower respiratory symptoms including dyspnea at rest or respiratory distress

     **AND**
   - Clinical signs indicative of severe systemic illness/infection with COVID-19, with at least 1 of the following:
     - RR ≥ 30, HR ≥ 125, SaO2 <93% on room air or requires > 2L oxygen by NC in order maintain SaO2 ≥93%, PaO2/FiO2 <300

     **AND**
   - No criteria for Critical Illness:
     - None of the following: Respiratory failure (defined by endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, or clinical diagnosis of respiratory failure in setting of resource limitations), Septic shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg), Multiple organ dysfunction/failure

**Critical Illness:**

- Diagnosed with COVID-19 by standard RT-PCR assay or equivalent testing within 5 days of screening
  **AND**
- Evidence of critical illness, defined by at least 1 of the following:
  - Respiratory failure defined based on resource utilization requiring at least 1 of the following:
    Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (in setting of resource limitation)

  **OR**
- Shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg or requiring vasopressors)
  **OR**
- Multiple organ dysfunction/failure

3. Subject, if intubated, positive end-expiratory pressure (PEEP) <15 cmH2O with PaO2/FiO2 >150 mmHg.

4. Electrocardiogram (ECG) with no clinically significant findings as assessed by the Investigator.

   *Note: Below are the examples of clinically significant and non-clinically significant ECG abnormalities:*

   – *ECG findings indicative of acute myocardial infarction or acute ischemic changes would be considered clinically significant abnormalities.*

   – *ECG finding such as atrial fibrillation, atrial flutter, paced rhythms in individuals who have undergone permanent pacemaker placement, evidence of prior infarction, unchanged stable conduction abnormalities e.g. right bundle branch block, or any other finding which does not significantly impact mortality would be considered non-clinically significant findings and subjects with these abnormal findings would be allowed to enroll in the study.*

5. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.

6. Understands and agrees to comply with planned study procedures.

7. Women of childbearing potential and their partner must agree to use at least one highly effective method of contraception (e.g., hormonal contraceptives [implants, injectables,

combination oral contraceptives, transdermal patches, or contraceptive rings], intrauterine devices, bilateral tubal occlusion, or sexual abstinence) for the duration of the study.

### 3.3.2. Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from enrollment:

1. Subjects with do-not-resuscitate (DNR) and/or do-not-intubate (DNI) orders or expected to be made DNR/DNI in setting of resource limitations or family wishes.
2. Not a candidate for dialysis or continuation of care (or full medical support) in setting of resource limitations.
3. Subject on continuous vasopressors (at the dose of norepinephrine >20µg/min and/or vasopressin >0.04 units/kg/min) for >48 hours at time of screening.
4. Subjects who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible.
5. Inability to provide informed consent or to comply with test requirements
6. Consideration by the investigator, for safety reasons, that the subject is an unsuitable candidate to receive study treatment
7. Pregnancy or breast feeding
8. Subject participating in another study with for an investigational treatment for COVID-19.

   *Note: Subject who were prescribed (1) hydroxychloroquine or chloroquine with or without azithromycin, (2) Remdesivir, (3) convalescent plasma therapy, or (4) immunomodulatory treatments (including but not limited to sarilumab, clazakizumab, tocilizumab, and anakinra) for the off-label treatment of COVID-19 prior to study enrollment may be included and may continue to receive these agents as part of standard-of-care.*

# 4. STUDY SCHEDULE

The study will have three phases: Screening Period, Treatment Period, and Follow-Up Period. The study Schedule of Assessments in presented in Table 4-2.

**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.

**Table 4-1: 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 |

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 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 | | 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 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/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 | | 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 |
| Serum/Urine Pregnancy Test [12] | X | | | | | X | | |
| Urinalysis [13] | 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.

## 4.1. SCREENING PHASE

The subject (or Legally Acceptable Representative (LAR)) will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. All study centers will be instructed to maintain the study-specific screening and enrollment logs at their sites. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new unique identification number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

### 4.1.1. Screening Visit (V1)

After the ICF has been signed, screening procedures and information will be obtained to confirm subject eligibility, including:

- Demographic information (see Section 7.3);
- A detailed medical history (see Section 7.4);
- Physical examination (see Section 7.5);
- Vital signs (see Section 7.6),
- Clinical Status - Ordinal scale assessment (see Section 7.10);
- PaO2/FiO2, if intubated (See Section 7.11)
- Pulse oxygen saturation (SpO2) (see Section 7.12);
- Positive End-Expiratory Pressure (PEEP), if intubated (See Section 7.13)
- National Early Warning Score 2 (NEWS2) assessment (see Section 7.15);
- 12-lead electrocardiogram (see Section 7.17);
- Collection of blood specimens (see Section 7.8) for
    - Complete blood count;
    - Biochemistry;
    - Coagulation indices;
    - Serum/urine pregnancy test, for female subjects of childbearing potential; and
    - Urine sample for urinalysis parameters.

- Nasopharyngeal Swab Sample Collection (See Section 7.18)
- Chest radiograph or computer tomography (CT) scan (if clinically indicated) (See Section 7.19);
- Assessment for the requirement of mechanical ventilation, Non-Invasive Ventilation, Supplemental Oxygen, Vasopressors Use, Renal Replacement Therapy, ICU Admission, and hospital stay (see Section 7.20); and
- Prior medications assessment (see Section 7.7).

All screening information will be fully documented in the subject's medical records (i.e., source documents).

- For consented subjects who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the subject identification number, the date of ICF signature, demographic information (see Section 7.3), and the reason for screen failure. No additional information will be required for subjects who fail screening.
- For consented subjects who meet eligibility criteria, all required screening information will be transcribed onto the appropriate page of the CRF.

## 4.2. TREATMENT PHASE

Subjects who meet all eligibility criteria, as per data gathered from Screening Period are to be treated. All subjects who fail to meet eligibility criteria will be considered screen failure and will exit the study without further evaluation

### 4.2.1. Visit 2 (V2)

The following assessments will be performed at the first treatment visit prior to the first treatment administration. 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.

- Physical examination (see Section 7.5);
- Vital Signs (see Section 7.6),
- Clinical Status - Ordinal scale assessment (see Section 7.10);
- PaO2/FiO2, if intubated (See Section 7.11)
- Pulse oxygen saturation (SpO2) (see Section 7.12);
- Positive End-Expiratory Pressure (PEEP), if intubated (See Section 7.13)
- Sequential Organ Failure Assessment (SOFA) score, if intubated (See Section 7.14)

- National Early Warning Score 2 (NEWS2) Assessment (see Section 7.15);
- Collection of blood specimens (see Section 7.8) for
  - CD3+, CD4+ and CD8+ T cell count;
  - CCR5 receptor occupancy for Treg and macrophage;
  - Serum cytokine and chemokine levels; and
  - CCR5 Gene Polymorphisms.
- Nasopharyngeal Swab Sample Collection (See Section 7.18)
- Assessment for the requirement of mechanical ventilation, Non-Invasive Ventilation, Supplemental Oxygen, Vasopressors Use, Renal Replacement Therapy, ICU Admission, and hospital stay (see Section 7.20);
- Assessment for any new infections; and
- Prior medications assessment (see Section 7.7).

Subjects will be randomized 2:1 via WebView CTMS system to Leronlimab (PRO 140) or Placebo (see Section 7.21).

- Leronlimab (PRO 140) 700 mg or
- Placebo

Note: In the single arm, non-randomized, open-label phase, all eligible subjects will be assigned to receive Leronlimab (PRO 140).

Leronlimab (PRO 140) or placebo will be administered subcutaneously to all subjects at a weekly dose of 700 mg. After receiving the first leronlimab (PRO 140) dose, the following assessments will be performed:

- Vital signs (see Section 7.6),
- Concomitant medications assessment (see Section 7.7),
- Review of adverse events (see Section 9)

#### 4.2.2. Visits 3 and 4, (V3 and V4)

The following assessments will be performed during the remaining visits during the treatment period:

- Physical examination (see Section 7.5);
- Vital Signs (see Section 7.6),

- Clinical Status - Ordinal scale assessment (see Section 7.10);
- PaO2/FiO2, if intubated (See Section 7.11)
- Pulse oxygen saturation (SpO2) (see Section 7.12);
- Positive End-Expiratory Pressure (PEEP), if intubated (See Section 7.13)
- Sequential Organ Failure Assessment (SOFA) score, if intubated (See Section 7.14)
- National Early Warning Score 2 (NEWS2) assessment (see Section 7.15)
- Assessment of Clinical Recovery (See Section 7.16)
- Collection of blood specimens (see Section 7.8) for
    - Complete blood count;
    - Biochemistry;
    - Coagulation indices;
    - Urine sample for urinalysis parameters;
    - CD3+, CD4+ and CD8+ T cell count;
    - CCR5 receptor occupancy for Treg and macrophage;
    - Serum cytokine and chemokine levels; and
    - CCR5 Gene Polymorphisms
- Nasopharyngeal Swab Sample Collection (See Section 7.18)
- Leronlimab (PRO 140) or Placebo Administration – V4 only (see Section 6.1.3);
- Assessment for the requirement of mechanical ventilation, Non-Invasive Ventilation, Supplemental Oxygen, Vasopressors Use, Renal Replacement Therapy, ICU Admission, and hospital stay (see Section 7.20);
- Assessment for any new infections;
- Prior medications assessment (see Section 7.7); and
- Review of adverse events (see Section 9).

#### 4.2.3. End of Treatment – EOT (V5)

The last visit during the treatment phase will be considered at the End of Treatment (EOT) visit. The assessments performed at this visit will include:

- Physical examination (see Section 7.5);

- Vital Signs (see Section 7.6),
- Clinical Status - Ordinal scale assessment (see Section 7.10);
- PaO2/FiO2, if intubated (See Section 7.11)
- Pulse oxygen saturation (SpO2) (see Section 7.12);
- Positive End-Expiratory Pressure (PEEP), if intubated (See Section 7.13)
- Sequential Organ Failure Assessment (SOFA) score, if intubated (See Section 7.14)
- National Early Warning Score 2 (NEWS2) assessment (see Section 7.15);
- Assessment of Clinical Recovery (See Section 7.16)
- 12-lead electrocardiogram (see Section 7.17);
- Collection of blood specimens (see Section 7.8) for
    - Complete blood count;
    - Biochemistry;
    - Coagulation indices;
    - Serum/urine pregnancy test, for female subjects of childbearing potential;
    - Urine sample for urinalysis parameters;
    - CD3+, CD4+ and CD8+ T cell count;
    - CCR5 receptor occupancy for Treg and macrophage;
    - Serum cytokine and chemokine levels; and
    - CCR5 Gene Polymorphisms.
- Nasopharyngeal Swab Sample Collection (See Section 7.18)
- Chest radiograph or computer tomography (CT) scan (if clinically indicated) (See Section 7.19);
- Assessment for the requirement of mechanical ventilation, Non-Invasive Ventilation, Supplemental Oxygen, Vasopressors Use, Renal Replacement Therapy, ICU Admission, and hospital stay (see Section 7.20);
- Assessment for any new infections;
- Review of mortality status;
- Prior medications assessment (see Section 7.7); and

- Review of adverse events (see Section 9).

### 4.3. FOLLOW-UP PHASE

The first visit of the follow-up phase is scheduled 14(±3) days after EOT Visit. Two follow-up visits are included in the follow-up phase.

#### 4.3.1. Visits 6 and 7 (V6 and V7)

The assessments performed at these visits will include:

- Physical examination (see Section 7.5);
- Vital Signs (see Section 7.6),
- Clinical Status - Ordinal scale assessment at Visit 6 only (see Section 7.10);
- Collection of blood specimens at Visit 7 only (see Section 7.8) for
    - Complete blood count;
    - Biochemistry;
    - Coagulation indices; and
    - Urine sample for urinalysis parameters.
- Nasopharyngeal Swab Sample Collection (See Section 7.18)
- Review of mortality status;
- Prior medications assessment (see Section 7.7); and
- Review of adverse events (see Section 9).

*Note: The follow-up visits (V6 and V7) can be conducted as telephone or video contact visits. 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.*

The following assessments are not applicable for the single arm, non-randomized, open-label phase of the study:

- National Early Warning Score 2 (NEWS2) Assessment
- Blood sample collection for
    - CCR5 receptor occupancy for Treg and macrophage
    - Serum cytokine and chemokine levels
    - CCR5 Gene Polymorphisms
- Nasopharyngeal Swab Sample Collection

### 4.4. UNSCHEDULED VISITS

In the event that the subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the eCRF.

# 5. SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

## 5.1. SUBJECT COMPLETION

A subject is considered to have completed the study once all follow-up visit assessments have been completed.

## 5.2. EARLY STOPPING RULES

Upon occurrence of any of the following events, data will be reviewed by the Medical Monitor and the Lead Principal Investigator.

1. Death in any subject in which the cause of death is judged to be probably or definitely related to the study drug by the treating investigator;
2. The occurrence in any subject of a life-threatening SAE whose causal relationship to study drug is judged to be probable or definite by the treating investigator;
3. Two (2) occurrences of Grade 4 toxicities that are assessed to be probably or definitely related to the study drug by the treating investigator;
4. Two (2) occurrences of a Grade 2 or higher allergic/hypersensitivity reaction directly related to the study drug that lead to permanent discontinuation of study drug.

In case the above listed event(s) occurred, patient accrual will be suspended pending further review and the FDA and other global regulatory authority will be notified. The study will be stopped if any of these stopping criteria are met unless, after reviewing the safety events of interest, the medical monitor and Sponsor, agree to allow the study to proceed. The FDA and other global regulatory authority will be consulted for any protocol amendment before restarting the trial if a stopping rule is met.

## 5.3. REMOVAL OF SUBJECTS FROM STUDY TREATMENT AND/OR STUDY AS A WHOLE

Subjects can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. In the case that a subject is removed from the study due to safety reasons, the FDA and other global regulatory authority will be notified. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Subject voluntarily withdraws from treatment (follow-up permitted)
- Subject withdraws consent (no follow-up permitted)
- Subject is unable to comply with protocol requirements

- Subject experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the subject's best interest
- Subject becomes pregnant
- Subject becomes lost to follow-up (LTF)
- Subject will be withdrawn from the study if 2 consecutive injections of study drug are missed
- Subject manifesting Grade 4 or Grade 3 toxicity attributable to the Leronlimab (PRO 140)

If a subject fails to return for the scheduled study visit or is discontinued from the study, an attempt will be made to determine the reason(s). If the subject is unreachable by telephone, a registered letter will be sent to the subject requesting that he/she contact the clinic.

All patients with an ongoing SAE or AE attributable (definitely, probably, or possibly related) to the study treatment at the Post-Study (Follow-up) Visit (scheduled or premature) must be followed until the event is resolved (with or without sequelae) or deemed stable.

### 5.4. DATA COLLECTED FROM WITHDRAWN SUBJECTS

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the CRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

In the event that a subject is withdrawn from the study at any time due to an adverse event or SAE, the procedures stated in Section 9 (Safety) must be followed.

### 5.5. SCREEN FAILURES

A subject who signed a consent form, but did not meet the inclusion/exclusion criteria is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

In the event that a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened again (i.e., up to two screenings) and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

# 6. STUDY TREATMENT

Leronlimab (PRO 140) or placebo will be administered subcutaneously (SC) at a weekly as follows:

**Table 6-1: Treatment Administration Summary**

| Study Drug | Dose | Route | Schedule |
|---|---|---|---|
| Leronlimab (PRO 140) | 700 mg | SC | Weekly (2 doses) |
| Placebo | 0 mg | SC | Weekly (2 doses) |

## 6.1. LERONLIMAB (PRO 140)

Leronlimab (PRO 140) is a humanized IgG4,κ monoclonal antibody (mAb) to the chemokine receptor CCR5. Leronlimab (PRO 140) is provided at a concentration of 175 mg/mL and is intended for SC route of administration.

Leronlimab (PRO 140) kit will contain two vials. Each vial of the Leronlimab (PRO 140) product contains ~2.4 mL antibody at 175mg/mL in a buffer containing 5 mM L-histidine, 15.0 mM glycine, 95 mM sodium chloride, 0.3% (w/v) sorbitol, 0.005% (w/v) polysorbate 20 (Tween 20®), and sterile water for injection, at pH of 5.5. For subjects assigned to Leronlimab (PRO 140) arm, one kit will be assigned per treatment visit.

**Note:** *2 mL will be drawn from 2.4 mL solution filled vial. Remaining 0.4 mL medication will be discarded appropriately from each vial.*

Isotonic 0.9% Sodium Chloride Injection, USP will be used as Placebo.

A dose of 700 mg of Leronlimab (PRO 140) (175 mg/mL) or placebo will be delivered as two injections of 2 mL each and administered subcutaneously on opposite sides of the abdomen.

**Table 6-2: Investigational Product - Leronlimab (PRO 140)**

| IP Dosage | 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 mL/inj.) per week on opposite sides of abdomen for two weeks | SC injection |
| Placebo | Parenteral solution | 0 mg/mL | 2 injections of placebo (2 X 2 mL/inj.) per week on opposite sides of abdomen for two weeks | SC injection |

***Note**: Patients with low body fat percentages may find subcutaneous injections uncomfortable. In such cases, leronlimab (PRO 140) 700 mg can be injected as four 175mg/ml injections and/or subcutaneous injections can be placed at different areas other than abdomen as per discretion of the Investigator.*

### 6.1.1. Leronlimab (PRO 140) - Packaging and Labeling

Study drug will be prepared by Ajinomoto Althea, Inc. and will be packaged, labeled, and shipped by Sherpa Clinical Packaging, LLC.

The contents of each vial are described in Section 6.1. Leronlimab (PRO 140) kits will be labeled with information such as: study protocol #; fill volume; concentration; storage condition; a "use as per study protocol" statement; a cautionary statement; sponsor's name and address; and the kit number.

Below are representative samples of the Investigational Product, finished drug product (FDP) individual vial (Figure 6-1), syringe label (Figure 6-2), and kit labels (Figure 6-3) designated for use in this clinical protocol. Each kit contains two labeled vials and two syringe labels.

**Figure 6-1: Investigational Product - Vial Label**

| | |
|---|---|
| Protocol: CD12_COVID-19 Kit No. xxx<br>Subject No. _____<br>Single use 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection<br>Store at 2ºC to 8ºC (36ºF to 46ºF)<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA | Protocol: CD12_COVID-19 Kit No. xxx<br>Subject No. _____<br>Single use 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection<br>Store at 2ºC to 8ºC (36ºF to 46ºF)<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA |

**Figure 6-2: Investigational Product - Syringe Label**

Protocol: CD12_COVID-19

This syringe contains 2 mL PRO 140 (175 mg/mL) or placebo solution for subcutaneous injection

USE AS PER STUDY PROTOCOL

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

CytoDyn Inc., Vancouver, WA, USA

**Figure 6-3: Investigational Product - Kit Label**

Protocol: CD12_COVID-19 Kit No. xxx

| |
|---|
| Site No. _____ Subject No. _____ |
| This kit contains 2 single-use vials |
| Each 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection |
| Store at 2°C to 8°C (36°F to 46°F) |
| USE AS PER STUDY PROTOCOL |
| Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use |
| CytoDyn Inc., Vancouver, WA, USA |

The pharmacy manual provides the criteria regarding vial acceptance or rejection, as well as instructions for the preparation of the IP syringes to be used to administer drug.

### 6.1.2. Leronlimab (PRO 140) - Storage and Handling

Study drug will be shipped at 2°C to 8°C (refrigerated [36°F to 46°F]) to the investigator's site. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored at 2°C to 8°C (refrigerated [36°F to 46°F]). The contents of the vial should appear as a clear to opalescent, colorless to yellow solution; fine translucent particles may be present. This is normal.

The investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each subject must be available for inspection at any time. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

### 6.1.3. Leronlimab (PRO 140) - Administration

Guidelines for dose preparation can be found in the pharmacy manual.

Leronlimab (PRO 140) or placebo will be provided to the administering personnel in single-use syringes prepared from vials of study drug stored at 2-8°C at the site pharmacy prior to use. Syringes will be prepared by an unblinded pharmacist or designated site staff. Each of two syringes is filled to deliver 2 mL of study drug.

Equivalent volumes of PRO 140 will be administered subcutaneously on opposite sides of the abdomen.

A 20-guage needle should be used to remove PRO 140 from vial and a 25-guage needle is used for administration to subjects.

**Note:** After the leronlimab solution is drawn into the syringe, it can be stored at room temperature (20°C to 25°C, 68°F to 77°F) for up to 2 hours, or refrigerated (2°C to 8°C, 36°F to 46°F) for up to 4 hours.

IP should be administered slowly over 15 seconds per mL.

Following each SC delivery of drug, careful examination will be made to assess the appearance of any study drug Injection Site Reactions (ISRs) as per CTCAE v5.0.

Leronlimab (PRO 140) will be administered as SC injection by a qualified medical professional at the study 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.

**Note:** It is preferred that the same injection site be used throughout the study. At the same time, it is not recommended to inject the study drug into areas where skin shows signs of a previous injection site reaction. It is advised to change the injection site if any previous injection site reaction remains unresolved.

### 6.1.4. Leronlimab (PRO 140) - Post Injection Monitoring

Subject will be observed at approximately 30 minutes post-injection or longer if necessary for injection site reaction as per CTCAE v5.0.

### 6.1.5. Leronlimab (PRO 140) – Toxicity Management

**Refer to Table 6-3 and Table 6-4**

Table 6-4below. Recovery to acceptable levels must occur to allow leronlimab (PRO 140) continuation.

**Table 6-3: Leronlimab (PRO 140) - Management for Injection Site Reactions**

| CTCAE Grade | Treatment Management |
|---|---|
| Grade 1 | No dose adjustment is required. |
| Grade 2 | First Occurrence: No dose adjustment is required.<br>Second Occurrence of the same event: Closely follow-up for resolution of the AE to Grade ≤ 1 |
| Grade 3 | Withhold treatment until symptoms resolve to:<br>• Grade 1 or less |
| Grade 4 | Study treatment will be permanently discontinued |

**Table 6-4: Leronlimab (PRO 140) - Management for all Other Potential Toxicities (Attributable to Leronlimab)**

| CTCAE Grade (attributable to leronlimab) | Treatment Management |
|---|---|
| Grade 1 | No dose adjustment is required. |
| Grade 2 | Withhold treatment until symptoms resolve to:<br>• Grade 1 or less or baseline; |
| Grade 3 | Study treatment will be permanently discontinued |
| Grade 4 | Study treatment will be permanently discontinued |

### 6.1.6. Leronlimab (PRO 140) - Disposition

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels or any partially used or unused drug supply until instructed by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers and drug labels to the drug distributor as directed by the Sponsor. A copy of the completed drug disposition form will be sent to CytoDyn, Inc. or to its designee.

### 6.1.7. Leronlimab (PRO 140) - Accountability

Study drug must be used in accordance with this protocol and only under the direction of the responsible investigator. The investigational site must maintain complete and accurate records showing receipt and disposition of all study drug, including master records listing the date of receipt, the number and nature of medication units received, and a dispensing record which includes each quantity dispensed, identification of the staff member/subject to whom dispensed, the date of dispensing, the intended study participant, and the identification of the preparer. All used and unused study kits will be retained by the investigational site until drug accountability can be confirmed by study CRA during the monitoring visits. Instructions will be provided by Sponsor regarding final disposition of all study drugs in compliance with applicable regulations.

# 7. DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

## 7.1. INFORMED CONSENT

A written informed consent will be obtained for this study by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the trial. All questions addressed by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

## 7.2. ASSESSMENT OF ELIGIBILITY

The Investigator must assess subject's continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Phase. The eligibility criteria are described in Section 3.3.1 (Inclusion Criteria) and Section 3.3.2 (Exclusion Criteria). In the event that the subject is not suitable or eligible for the study, the subject will be considered "screen failure".

### 7.2.1. Re-screening

If a subject fails initially to meet the eligibility criteria, and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled in the study only if they meet all Inclusion and no Exclusion criteria when re-screened.

## 7.3. DEMOGRAPHIC INFORMATION

In this study the demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, or Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, or Unknown)
- Use of tobacco products

### 7.4. MEDICAL HISTORY

A medical history will be recorded during the Screening Phase and will include:

- All ongoing medical conditions
- All previously resolved medical conditions that are relevant in the judgment of the Investigator
- Any prior medical conditions that have resolved within the last year

Events that emerge prior to the first treatment will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to the subject's receiving investigational product treatment.

Medical histories will be recorded using the body system categories outlined below:

- HEENT
- Cardiovascular
- Endocrinal
- Respiratory
- Gastrointestinal
- Substance Abuse
- Neurologic
- Genitourinary
- Lymphatic
- Musculoskeletal and Extremities
- Hematological
- Immunological
- Dermatologic
- Psychiatric-Psychological
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing).

Note: For COVID-19 diagnosis, the number of days between the onset of symptoms and the initiation of treatment for each subject will be documented.

### 7.5. PHYSICAL EXAMINATION

The physical examination will include routine examinations for the following:

- Constitutional/General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Neurologic
- Cardiovascular
- Musculoskeletal and Extremities
- Dermatologic
- Respiratory
- Gastrointestinal
- Genitourinary
- Lymphatic
- Psychiatric

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

### 7.6. VITAL SIGNS, HEIGHT AND WEIGHT

The following will be collected:

  - Systolic Blood Pressure
  - Diastolic Blood Pressure
  - Heart Rate
  - Temperature
  - Respiratory Rate
- Height
- Weight
- Body Mass Index

### 7.7. CONCOMITANT MEDICATIONS

All medications and therapies administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the Case Report Form (CRF). **Additionally, all other investigational and off-label therapies for COVID-19 will be recorded.** Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

### 7.7.1. Excluded Medications

The following medications are prohibited while on study drug:

- Other CCR5 antagonists
- Other investigational products

### 7.7.2. Allowable Medications and Therapies

The following medications and therapies are allowed:

- Patients with underlying chronic viral illnesses will be allowed to receive antiviral therapy.

  *Note: Subjects infected with chronic hepatitis B virus or hepatitis C virus will be eligible for the study if they have no signs of hepatic decompensation.*

  *Note: Subjects infected with HIV-1 will be eligible for the study with undetectable viral load and are on a stable ART regimen. Investigators are required to review the subjects' medical records to confirm HIV-1 RNA suppression within the previous 3 months.*

- Organ transplant patients will be allowed to continue baseline immunosuppressive therapy during the course of study.

- Empirical antibiotic treatment for secondary bacterial infections is allowed during the course of study.
- Intravenous immunoglobulin (IVIG)
- Treatment for COVID-19 in accordance with standards of care and/or institutional policy
- Hydroxychloroquine or chloroquine with or without azithromycin for the off-label treatment of COVID-19 prescribed prior to study enrollment is permitted for continued use during the trial.
- Remdesivir and convalescent plasma therapy prescribed prior to study enrollment is permitted for continued use during the trial.
- Off-label immunomodulatory treatments for COVID-19 including but not limited to sarilumab, clazakizumab, tocilizumab, and anakinra prescribed prior to study enrollment is permitted for continued use during the trial.

### 7.8. CLINICAL LABORATORY ASSESSMENTS

Blood samples will be collected for analysis of the following parameters described in Table 7-1.

- Biochemistry and Complete Blood Count (CBC): At Screening (V1), V3, V4, V5 (EOT), and V7.
- Serum/urine pregnancy test (for female subjects of childbearing potential): At Screening (V1) and V5 (EOT)

All laboratory reports will be reviewed by the Investigator. Abnormal results that are considered by the Investigator to be clinically significant will be recorded as adverse events. If in the Investigator judgment, in order to make the determination of clinical significance the testing may be needed to be repeated. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

**Table 7-1: Lab Parameters**

| CBC Parameters | Biochemistry Parameters | Urinalysis |
|---|---|---|
| Hemoglobin (g/dL)<br>Hematocrit (%)<br>RBC/Erythrocytes (10^12/L)<br>WBC/Leukocytes (10^6/L)<br>Absolute Neutrophil Count (10^6/L)<br>Platelets (10^9/L)<br>Differential WBC:<br>– Neutrophils (%)<br>– Lymphocytes (%)<br>– Monocytes (%)<br>– Eosinophils (%)<br>– Basophils (%) | **Liver Function Tests**<br>Total bilirubin (mg/dL)<br>Alkaline Phosphatase (ALP) (U/L)<br>Aspartate Aminotransferase (AST) (or SGOT) (U/L)<br>Alanine Aminotransferase (ALT) (or SGPT) (U/L)<br>Total Protein (g/dL)<br>Albumin (g/dL)<br>Lactate Dehydrogenase (U/L)<br>**Renal Function Tests**<br>Serum creatinine<br>Creatinine clearance,<br>eGFR<br>**Electrolytes**<br>Sodium (mEq/L)<br>Potassium (mEq/L)<br>Chloride (mEq/L)<br>Calcium (mg/dL)<br>Bicarbonate (mEq/L)<br>**Other:**<br>Glucose, Random (mg/dL)<br>Cholesterol, Total (mg/dL)<br>Creatine kinase,<br>C-reactive protein<br>Serum ferritin<br>d-dimer<br>**Coagulation Parameters**<br>Prothrombin time (PT)<br>International Normalized Ratio (INR) | pH<br>Specimen Appearance<br>Color<br>Specific Gravity<br>Ketones<br>Bilirubin<br>Occult Blood<br>Glucose<br>Protein<br>Nitrite<br>Urobilinogen (mg/dL)<br>Leukocyte Esterase<br>Leukocytes(/HPF) |
| **Miscellaneous** | | **Cytokine and Chemokine Panel** |
| Serum pregnancy test<br>Urine pregnancy test<br>(for female subjects of childbearing potential)<br>CD3+, CD4+ and CD8+ T cell count<br>CCR5 receptor occupancy for Treg and macrophage<br>CCR5 Gene Polymorphisms | | sCD40L, EGF, Eotaxin (CCL11), FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO alpha (CXCL1), IFN-alpha2, IFN-gamma, IL-1 alpha, IL-1 beta, IL-1RA, IL-2, IL-2R, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-12 (p40/p70) IL-13, IL-15, IL-17A, IL-17E/IL-25, IL-17F, IL-18, IL-22, IL-27, IP-10 (CXCL10), MCP-1 (CCL2), MCP-3, M-CSF, MDC (CCL22), MIG (CXCL9), MIP-1 alpha (CCL3), MIP-1 beta (CCL4), PDGF-AA, PDGF-AB/BB, RANTES (CCL5), TGF-alpha, TNF-alpha, TNF-beta, VEGF-A. |

### 7.9. Study Treatment Application

Refer to Section 6.1.3 for details.

### 7.10. Clinical Status –Ordinal Scale Assessment

Subject clinical status will be assessed using a 7-category ordinal scale. The scale 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.

### 7.11. PaO2/FiO2 Measurement

PaO2/FiO2 will be measured at Screening and at V2 (pre-dose), V3, V4, and V5 (EOT).

### 7.12. Pulse Oxygen Saturation (SpO2)

Pulse Oxygen Saturation (SPO2) will be measured at Screening and at V2 (pre-dose), V3, V4, and V5 (EOT).

### 7.13. Positive End-Expiratory Pressure (PEEP), if intubated

If the subject is intubated, positive end-expiratory pressure (PEEP) will be measured at Screening and at V2 (pre-dose), V3, V4, and V5 (EOT).

### 7.14. Sequential Organ Failure Assessment (SOFA) score

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 (See Appendix 17.3)

### 7.15. National Early Warning Score 2 Assessment

The 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). See Appendix 17.1.

### 7.16. Assessment of Clinical Recovery

The assessment of clinical recovery is based on hospital discharge or normalization of fever, respiratory rate, alleviation of cough and resolution of hypoxia.

### 7.17. 12-Lead Electrocardiogram

A resting supine 12-lead ECG will be conducted at the Screening Visit (V1) and Visit 5 (End of Treatment). A 12-lead ECG will be repeated during the study only if clinically indicated and at the discretion of the treating physician. The results will be evaluated by the Investigator. The following parameters will be recorded: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant or clinically significant. If abnormalities are observed, each will be recorded.

### 7.18. NASOPHARYNGEAL SWAB SAMPLE COLLECTION

Nasopharyngeal swabs will be used for quantitative virologic testing. Sample collection is recommended but no required. The subject will be followed and samples will be collected for the entire duration of the study.

Samples are to be stored at -70°C.

### 7.19. CHEST RADIOGRAPH OR COMPUTED TOMOGRAPHY SCAN

If clinically indicated by the treating physician, a chest radiograph or CT scan will be performed at Screening Visit (V1) and V5 (EOT)

### 7.20. REQUIREMENT OF MECHANICAL VENTILATION, NON-INVASIVE VENTILATION, SUPPLEMENTAL OXYGEN, VASOPRESSORS USE, RENAL REPLACEMENT THERAPY, ICU ADMISSION, AND HOSPITAL STAY

The incidence and duration, in days, of mechanical ventilation, non-invasive ventilation, supplemental oxygen, vasopressors use, renal replacement therapy, ICU admission and hospital stay will be assessed at Screening (V1) and V3, V4, and V5 (EOT).

### 7.21. RANDOMIZATION

Subjects who are eligible to participate in the trial will be randomized to one of the treatment groups via IWRS (Interactive Web Based Randomization System) at Visit 2 prior to IP administration. The randomization will be central with a 2:1 ratio of Active Treatment to Control Treatment to ensure even distribution of Active and Control subjects.

# 8. STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

## 8.1. TREATMENT GROUPS

There will be two treatment groups in the study:

- 700 mg Leronlimab (PRO 140)
- Placebo

## 8.2. DESCRIPTION OF STUDY OUTCOMES (ENDPOINTS)

### 8.2.1. 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.*

### 8.2.2. Secondary Endpoints

The secondary efficacy endpoints for the study are:

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

### 8.2.3. 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 Day14.
- 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

### 8.2.4. 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

## 8.3. 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 ninty (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-tset 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.

### 8.4. 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.

### 8.5. STRATIFICATION

Randomization will be stratified into one of the three categories based on clinical status of the study 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.

Additionally, randomization will be stratified by region (North America, Europe etc.) if multinational sites are involved in the study.

### 8.6. 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.

## 8.7. TIME TO UNBLINDING

### 8.7.1. 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.

### 8.7.2. 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.

### 8.7.3. 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.

## 8.8. INTERIM ANALYSIS

An Interim Analysis (IA) will be conducted when approximately 50% (~195 subjects) of the study participants have been in the study for at least 4 weeks after randomization or are withdrawn from the study, whichever occurs first.

The main objectives of the IA are safety and sample size re-assessment.

The IA will have prospectively assigned rules and a method to protect the type I error rate and the integrity of the trial, due to the unblinded look. The IA will be conducted under the auspices of an independent Data Safety Monitoring Committee (DSMC) according to a written Charter. The procedures for this IA will be based on a standard operating procedure (SOP) that has a well-established a 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 details of the interim analysis will be included in the Statistical Analysis Plan.

## 8.9. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables.

### 8.9.1. Analysis Populations

8.9.1.1. Intent-to-Treat Population

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

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

8.9.1.3. 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.

### 8.9.2. Covariates

For efficacy analyses important prognostic factors that need adjustment will be specified in the Statistical Analysis Plan (SAP) for the study

### 8.9.3. 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 imputation will be carried out in SAS version 9.4 or later using PROC MI. Each imputation model will include the stratification factor as a covariate in the model. The details of multiple imputation will be included in the statistical analysis plan.

## 8.10. ANALYSIS METHODS

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the data from this trial.

### 8.10.1. Subject Disposition

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

### 8.10.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics including medical history, will be summarized by treatment group using appropriate descriptive statistics.

8.10.3. Concomitant Medications/Therapies

Concomitant medications/therapies will be summarized separately for the Safety population. All prior and concomitant medications recorded in the case report form will be coded to matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries by treatment group will be prepared using the coded term. All concomitant medications/therapies recorded in the case report form will be listed.

### 8.10.4. Efficacy Analyses

**Primary Analysis**

The ITT population will be the primary population for the analysis of the efficacy endpoints of the study.

**Primary Endpoint**

The primary endpoint for this study is the proportion of subjects with Mortality at Day 28 between leronlimab and placebo. The difference in the Day 28 mortality between the leronlimab and placebo treatment groups will be compared using Logistic regression model.

**Secondary Endpoints**

To maintain the trial-wise Type I error rate at 0.05, a closed test procedure will be used for the secondary endpoints. The order of the secondary endpoints will prospectively specified in the SAP.

Analysis of the secondary and 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 will be used.
- Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and to depict the time to event data.

8.10.5. Supportive Analysis

To assess the consistency of the Primary Analysis results, supportive analysis will be conducted using the Intent to Treat (ITT) and Per Protocol (PP) populations. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used.

8.10.6. Subgroup Analysis

Subgroup analyses will be conducted for the predefined stratification factors (Section 8.5) for the study. Additional exploratory subgroup analysis will be conducted using the baseline clinical characteristics and laboratory parameters such as, CD4/CD8 ratio and IL-6. The details will be prospectively specified in the SAP.

**Safety Summaries**

8.10.6.1. 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.

8.10.6.2. Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized by treatment group and presented by time point.

8.10.6.3. ECG

All ECG values will be listed. ECG measurements will also be summarized by treatment group and presented by time point.

8.10.6.4. Vital Signs

All vital sign findings will be listed and/or summarized by treatment group.

8.10.6.5. Physical Examination

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

# 9. ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

## 9.1. ADVERSE EVENT (AE)

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

## 9.2. REPORTING OF ADVERSE EVENTS

Report initiation for all AEs and SAEs will begin at the time of the first treatment visit and continue until the end of final study visit. All events will be followed to resolution or until the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.3), the impact the event had on study treatment (see Section 9.2.1), the Common Terminology Criteria for Adverse Events (CTCAE) grade (intensity) of the event (see Section 9.2.2), the causality of the event (see Section 9.2.3), whether treatment was given as a result of the event (see Section 9.2.4), and the outcome of the event (see Section 9.2.5)

### 9.2.1. Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown. The "not applicable" assessment will be used only when the subject is no longer in the Treatment Phase of the protocol.

### 9.2.2. CTCAE Grade (Intensity) Assessment

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event (See Appendix 17.2). The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

**Table 9-1: CTCAE v5.0 General Guidelines**

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

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

### 9.2.3. Causality Assessment

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
4. **Remotely related**: In general this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

#### 9.2.4. Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

#### 9.2.5. Outcome Assessment

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

### 9.3. SERIOUS ADVERSE EVENTS

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Requires subject's hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

## 9.4. REPORTING OF SERIOUS ADVERSE EVENTS (SAE)

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Medical Monitor within 24 hours.

| | |
|---|---|
| **Medical Monitor** | Attn: Safety DepartmentAmarex Clinical Research, LLC<br>20201 Century Boulevard, 4th Floor<br>Germantown, MD 20874<br>Email: saereporting@amarexcro.com<br>Phone: +1 (240) 235-6852<br>Fax: +1 (240) 454-6602 |

The Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, ECG reports, discharge summary, hospital notes, etc, if applicable. Additional follow-up information as it becomes available must be reported to the Medical Monitor.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

## 9.5. SAE FOLLOW-UP

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

Study participants should be instructed to notify the investigator and discontinue investigational product immediately if they become pregnant at any time during the study or if they become pregnant within 30 days of last investigational product dose. A participant whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. The Investigator is required to report any notification of pregnancy to CytoDyn, Inc/designated CRO promptly. The participants should receive appropriate monitoring and care

until the conclusion of the pregnancy. Any complication experienced through the end of the pregnancy should be considered as an adverse event (AE), and should be recorded, and if it meets the seriousness criteria, it must be reported to CytoDyn, Inc/designated CRO promptly. Pregnancy outcomes will be reported in the clinical study report.

### 9.6. EXPECTED/ANTICIPATED EVENTS

Refer to Investigator Brochure for the expected/anticipated events.

# 10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA and other global regulatory authorities, the monitors, auditors and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

# 11. QUALITY CONTROL AND QUALITY ASSURANCE

## 11.1. MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

## 11.2. ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each subject who has signed an informed consent form, a CRF must be completed. For subjects who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the subject's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor's or designated CRO's monitor, who will make a decision as to their acceptability.

## 11.3. MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

## 11.4. REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

### 11.4.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

### 11.4.2. Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

# 12. DATA SAFETY MONITORING COMMITTEE (DSMC)

A Data Safety and Monitoring Committee (DSMC), independent of the study operations will be established to consider safety data generated during the study and to make recommendations about IA data for sample size re-estimation once 50% of enrolled patients have been in the study for at least 4 weeks after randomization or are withdrawn from the study, whichever occurs first. The details of the DSMC responsibilities will be included in the DSMC charter. The DSMC charter will be developed and operated in adherence to the current FDA guidance on DSMC (Establishment and Operation of Clinical Trial Data Safety Monitoring Committees [March 2006]). The DSMC meetings will take place at least once after the IA, and at other time-points as determined by the DSMC charter. In addition to the pre-specified time-points, the DSMC may also decide to schedule a meeting whenever they decide a review of emergent safety data is warranted. The charter will detail the roles and responsibilities of the DSMC members once they have been appointed. The study data will be provided to the Committee members in the form of a data report. Meetings to discuss the data will be held in person or by teleconference, based on the DSMC Chair's decision. The meetings will be in two stages: an "open stage" which will involve discussion on general aspects of the trial, and a "closed stage" between the DSMC members only. The remit of the DSMC will be primarily to assess the safety aspects of the trial.

# 13. ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

## 13.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at each site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

## 13.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

### 13.3. SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

# 14. DATA HANDLING AND RECORD KEEPING

## 14.1. RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

## 14.2. CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

### 14.3. ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA and other global regulatory authorities has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

# 15. PUBLICATION PLAN

All information supplied by CytoDyn, Inc. in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of CytoDyn, Inc., shall not be disclosed to others without the written consent of CytoDyn, Inc., and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of CytoDyn, Inc.. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

**Publication and Disclosure**: The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

# 16. REFERENCES

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# 17. APPENDIX

## 17.1. APPENDIX 1: NATIONAL EARLY WARNING SCORE 2 (NEWS2)

The National Early Warning Score 2 (NEWS2) determines the degree of illness of a patient and prompts critical care intervention.

| Variable | | Points |
|---|---|---|
| Respiratory rate, breaths per minute | ≤8 | 3 |
| | 9-11 | 1 |
| | 12-20 | 0 |
| | 21-24 | 2 |
| | ≥25 | 3 |
| $SpO_2$ (on room air or supplemental) | ≤91% | 3 |
| | 92-93% | 2 |
| | 94-95% | 1 |
| | ≥96% | 0 |
| $SpO_2$ (if patient has hypercapnic respiratory failure) | ≤83% | 3 |
| | 84-85% | 2 |
| | 86-87% | 1 |
| | 88-92%, ≥93% on room air | 0 |
| | 93-94% on supplemental oxygen | 1 |
| | 95-96% on supplemental oxygen | 2 |
| | ≥97% on supplemental oxygen | 3 |
| Room air or supplemental oxygen | Supplemental oxygen | 2 |
| | Room air | 0 |
| Temperature | ≤35.0°C (95°F) | 3 |
| | 35.1-36.0°C (95.1-96.8°F) | 1 |
| | 36.1-38.0°C (96.9-100.4°F) | 0 |
| | 38.1-39.0°C (100.5-102.2°F) | 1 |
| | ≥39.1°C (102.3°F) | 2 |
| Systolic BP, mmHg | ≤90 | 3 |

| | | |
|---|---|---|
| | 91-100 | 2 |
| | 101-110 | 1 |
| | 111-219 | 0 |
| | ≥220 | 3 |
| Pulse, beats per minute | ≤40 | 3 |
| | 41-50 | 1 |
| | 51-90 | 0 |
| | 91-110 | 1 |
| | 111-130 | 2 |
| | ≥131 | 3 |
| Consciousness | Alert | 0 |
| | New-onset confusion (or disorientation/agitation), responds to voice, responds to pain, or unresponsive | 3 |

## 17.2. APPENDIX 2: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.03

For complete detailed information please refer to the link below:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

## 17.3. APPENDIX 3: SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

Predicts ICU mortality based on lab results and clinical data

| Variable | Points |
|---|---|
| **$PaO_2/FiO_2$, mmHg** | |
| ≥400 | 0 |
| 300-399 | +1 |
| 200-299 | +2 |
| 100-199 and mechanically ventilated | +3 |
| <100 and mechanically ventilated | +4 |
| **Platelets, $\times 10^3/\mu L$** | |
| ≥150 | 0 |
| 100-150 | +1 |
| 50-99 | +2 |
| 20-49 | +3 |
| <20 | +4 |
| **Glasgow Coma Scale** | |
| 15 | 0 |
| 13–14 | +1 |
| 10–12 | +2 |
| 6–9 | +3 |
| <6 | +4 |
| **Bilirubin, mg/dL (µmol/L)** | |
| <1.2 (<20) | 0 |
| 1.2–1.9 (20-32) | +1 |
| 2.0–5.9 (33-101) | +2 |
| 6.0–11.9 (102-204) | +3 |
| ≥12.0 (>204) | +4 |
| **Mean arterial pressure OR administration of vasoactive agents required (listed doses are in units of mcg/kg/min)** | |

| | |
|---|---|
| No hypotension | 0 |
| MAP <70 mmHg | +1 |
| DOPamine ≤5 or DOBUTamine (any dose) | +2 |
| DOPamine >5, EPINEPHrine ≤0.1, or norEPINEPHrine ≤0.1 | +3 |
| DOPamine >15, EPINEPHrine >0.1, or norEPINEPHrine >0.1 | +4 |
| **Creatinine, mg/dL (µmol/L) (or urine output)** | |
| <1.2 (<110) | 0 |
| 1.2–1.9 (110-170) | +1 |
| 2.0–3.4 (171-299) | +2 |
| 3.5–4.9 (300-440) or UOP <500 mL/day) | +3 |
| ≥5.0 (>440) or UOP <200 mL/day | +4 |