A Phase 2, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19)

Protocol Number:	**CD10_COVID-19**
Version:	**5.0**
Date:	**30-Mar-2020**

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Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**CD10_COVID-19**
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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.

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**CD10_COVID-19**
Version:	**5.0**
Date:	**30-Mar-2020**

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) 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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PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140)	
Protocol Number: CD10_COVID-19	**Indication:** Coronavirus Disease 2019 (COVID-19)
Title of Study: A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19)	
Study Center: Up to 10 centers in the United States. 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: 75 subjects	**Study Development Phase:** Phase 2
Indication for Use: Leronlimab is indicated for treatment of adult patients with mild-to-moderate symptoms of respiratory illness caused by Coronavirus disease 2019 (COVID-19).	
Objective: The purpose of this study is to assess the safety and efficacy of leronlimab (PRO 140) administered as weekly subcutaneous injection in subjects with COVID-19.	
Study Outcomes (Endpoints): **Primary Outcome (Endpoint) Measure:** • Clinical Improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea and cough) *Note: The total score per patient ranges from 0 to 12 points. Each symptom is graded from 0 to 3. [0=none, 1=mild, 2=moderate, and 3=severe].* **Secondary Outcome (Endpoints) Measures:** 1. Time to clinical resolution (TTCR) *Time to clinical resolution (TTCR), defined as the time from initiation of study treatment until resolution of clinical symptoms (fever, myalgia, dyspnea and cough).* 2. Change from baseline in National Early Warning Score 2 (NEWS2) at Days 3, 7, and 14. *This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).* 3. Change from baseline in pulse oxygen saturation (SpO2) at Days 3, 7, and 14	

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

   A 7-category ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.
5. Incidence and duration (days) of hospitalization
6. Incidence and duration (days) of mechanical ventilation supply
7. Incidence and duration (days) of oxygen use
8. Mortality rate at Day 14
9. Time to return to normal activity

Exploratory Outcome (Endpoints) Measures:

1. Change in size of lesion area by chest radiograph or CT
2. Change from baseline in serum cytokine and chemokine levels at Days 3, 7, and 14
3. Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages at Days 3, 7, and 14
4. Change from baseline in CD3+, CD4+ and CD8+ T cell count at Days 3, 7, and 14

Safety Measures:

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

Trial Design:

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

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injection.

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

Screening Period (up to 1 week):

Screening assessments will commence at Visit 1 (V1) after obtaining signed informed consent, and will include review of medical and medication history, eligibility evaluation, physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, electrocardiogram (ECG), nasopharyngeal swab sample collection, chest radiograph or CT (if clinically indicated), ordinal scale assessment, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, and serum/urine pregnancy (if applicable). These assessments must be conducted within 7 days of the First Treatment Visit (V2).

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

Treatment Period (2 weeks ± allowed windows):

The schedule of visits during Treatment Period is as follows:

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

Subjects who meet the eligibility criteria will have completed the following evaluations and assessments at V2 prior to treatment: review of any changes in medical and medication history, physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, baseline assessment for the requirement of: Mechanical Ventilation, Oxygen, and Hospital Stay, and blood sample collection for CD3+, CD4+ and CD8+ T cell count, CCR5 receptor occupancy for Treg and macrophages, serum cytokine and chemokine levels, and CCR5 gene polymorphisms. If Visit 2 (V2) takes place on the same day as the Screening Visit (V1), scheduled assessments performed under screening (V1) do not need to be repeated at V2.

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

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At V2, subjects will be randomized to receive leronlimab (PRO 140) or placebo which will be administered subcutaneously weekly at Visit 2 (Day 0) and Visit 4 (Day 7) by a qualified medical professional at clinic or subject's home.

The following assessments will be performed at V3, V4, and V5/EOT: physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, assessment for the requirement of: Mechanical Ventilation, Oxygen, and Hospital Stay, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, CD3+, CD4+ and CD8+ T cell count, CCR5 receptor occupancy for Treg and macrophage, serum cytokine and chemokine levels, and CCR5 gene polymorphisms.

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

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

Follow-up visits will be performed at 2 weeks (V6) and 4 weeks (V7) after the End of Treatment (EOT) visit. The following assessments will be performed at V6 and V7 visit: review of adverse events and concomitant medications, physical examination, vital signs, nasopharyngeal swab sample collection, mortality status, and blood collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V7 only).

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

During visits conducted at the subject's home, the visiting nurse (or trained site staff) will administer study drug (if applicable), monitor subjects for safety, perform blood draw, and all other assessments related to study outcomes measures.

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 enrollment.

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2. Subjects with mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection as defined below:

   Mild (uncomplicated) Illness:

   - Diagnosed with COVID-19 by a standardized RT-PCR assay AND
   - Mild symptoms, such as fever, rhinorrhea, mild cough, sore throat, malaise, headache, muscle pain, or malaise, but with no shortness of breath AND
   - No signs of a more serious lower airway disease AND
   - RR<20, HR <90, oxygen saturation (pulse oximetry) > 93% on room air

   Moderate Illness:

   - Diagnosed with COVID-19 by a standardized RT-PCR assay AND
   - In addition to symptoms above, more significant lower respiratory symptoms, including shortness of breath (at rest or with exertion) OR
   - Signs of moderate pneumonia, including RR ≥ 20 but <30, HR ≥ 90 but less than 125, oxygen saturation (pulse oximetry) > 93% on room air AND
   - If available, lung infiltrates based on X-ray or CT scan < 50% present

3. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator.
4. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
5. Understands and agrees to comply with planned study procedures.
6. Women of childbearing potential must agree to use at least one medically accepted method of contraception (e.g., barrier contraceptives [condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or intrauterine devices) for the duration of the study.

Exclusion Criteria:

1. Subjects showing signs of acute respiratory distress syndrome (ARDS) or respiratory failure necessitating mechanical ventilation at the time of screening;
2. History of severe chronic respiratory disease and requirement for long-term oxygen therapy;
3. Subjects showing signs of clinical jaundice at the time of screening;

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4. History of moderate and severe liver disease (Child-Pugh score >12);
5. Subjects requiring Renal Replacement Therapy (RRT) at the time of screening;
6. History of severe chronic kidney disease or requiring dialysis;
7. Any uncontrolled active systemic infection requiring admission to an intensive care unit (ICU);

   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.

   Note: Empirical antibiotic treatment for secondary bacterial infections is allowed during the course of study.
8. Patients with malignant tumor, or other serious systemic diseases;
9. Patients who are participating in other clinical trials;
10. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible; and
11. Inability to provide informed consent or to comply with test requirements

Statistical Considerations:

Sample Size Determination and Rationale

A total of 75 subjects will be randomized 2:1 in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this proof-of-concept study.

Analysis Populations

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

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

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.

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Analysis Methods Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.	

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LIST OF ABBREVIATIONS

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
DSMB	Data Safety Monitoring Board
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

Abbreviation	Term
ICF	Informed Consent Form
ICH	International Conference on Harmonization
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
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
PK	Pharmacokinetic
PI	Principal Investigator
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
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 mild-to-moderate 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.

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

Protocol Number	Phase	No. of Subjects (Planned/ Analyzed)	Doses	Subject Population	Comments
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.
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.

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.
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)	Triple negative breast cancer	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

		Patient: WS 56 yr/Male		Patient: IW 74 yr/Female	
Test	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.

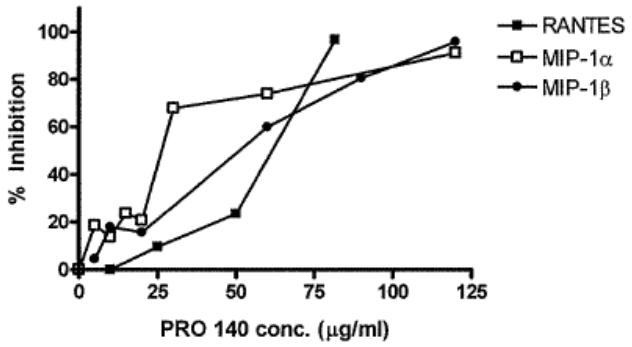
Additionally, there have been four patients with severe COVID-19 infection treated with 700 mg leronlimab (PRO 140) under individual patient, emergency use INDs. The current data from these patients are provided in the Investigational Brochure (IB).

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 2 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 from chemotherapy 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

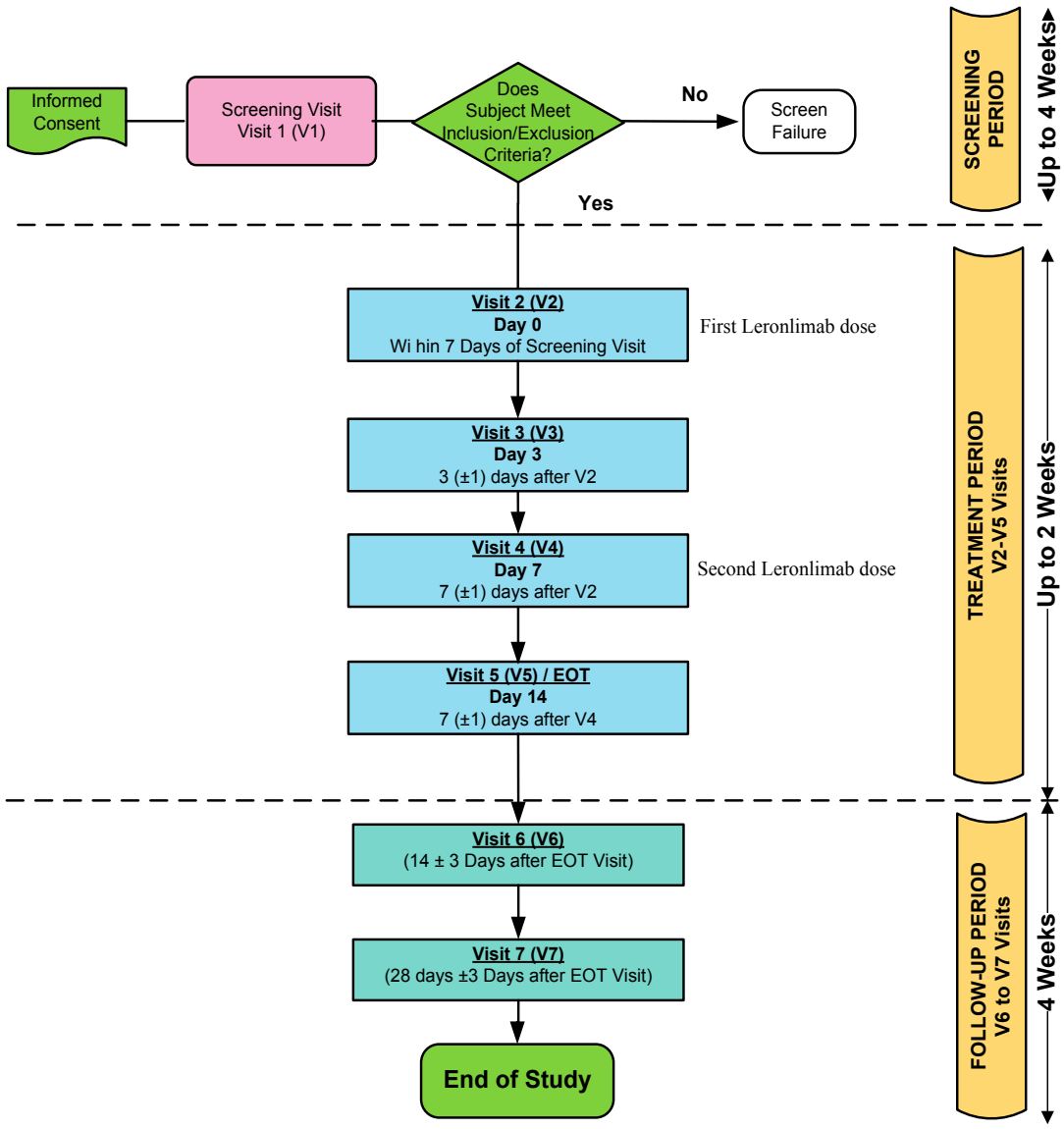
Primary Objective:

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

3. STUDY DESIGN

This study is a Phase 2, two arm, randomized, double blind, placebo controlled study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with mild-to-moderate 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 30 subjects. The study flow diagram is presented in Figure 3-1.

Figure 3-1: Study Schematic



3.1. STUDY CENTER

Up to 10 study centers in the United States (US). 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 mild-to-moderate 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 adults ≥ 18 years of age at time of enrollment;
2. Subjects with mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection;

   Mild (uncomplicated) Illness:

   - Diagnosed with COVID-19 by a standardized RT-PCR assay AND
   - Mild symptoms, such as fever, rhinorrhea, mild cough, sore throat, malaise, headache, muscle pain, or malaise, but with no shortness of breath AND
   - No signs of a more serious lower airway disease AND
   - RR<20, HR <90, oxygen saturation (pulse oximetry) > 93% on room air

   Moderate Illness:

   - Diagnosed with COVID-19 by a standardized RT-PCR assay AND
   - In addition to symptoms above, more significant lower respiratory symptoms, including shortness of breath (at rest or with exertion) OR
   - Signs of moderate pneumonia, including RR ≥ 20 but <30, HR ≥ 90 but less than 125, oxygen saturation (pulse oximetry) > 93% on room air AND
   - If available, lung infiltrates based on X-ray or CT scan < 50% present
3. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator;
4. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures;

5. Understands and agrees to comply with planned study procedures; and
6. Women of childbearing potential must agree to use at least medically accepted method of contraception (e.g., barrier contraceptives [condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or intrauterine devices) 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 showing signs of acute respiratory distress syndrome (ARDS) or respiratory failure necessitating mechanical ventilation at the time of screening;
2. History of severe chronic respiratory disease and requirement for long-term oxygen therapy;
3. Subjects showing signs of clinical jaundice at the time of screening;
4. History of moderate and severe liver disease (Child-Pugh score >12);
5. Subjects requiring Renal Replacement Therapy (RRT) at the time of screening;
6. History of severe chronic kidney disease or requiring dialysis;
7. Any uncontrolled active systemic infection requiring admission to an intensive care unit (ICU)

   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.

   Note: Empirical antibiotic treatment for secondary bacterial infections is allowed during the course of study.
8. Patients with malignant tumor, or other serious systemic diseases;
9. Patients who are participating in other clinical trials;
10. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible; and
11. Inability to provide informed consent or to comply with test requirements.

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, physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, electrocardiogram (ECG), nasopharyngeal swab sample collection, chest radiograph or CT (if clinically indicated), ordinal scale assessment, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, and serum/urine pregnancy (if applicable). These assessments must be conducted within 7 days of the First Treatment Visit (V2).

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

Treatment Period (2 weeks ± allowed windows):

The schedule of visits during Treatment Period is as follows:

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

Subjects who meet the eligibility criteria will have completed the following evaluations and assessments at V2 prior to treatment: review of any changes in medical and medication history, physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, National Early Warning Score 2 (NEWS2) assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, baseline assessment for the requirement of: mechanical ventilation, oxygen, and hospital stay, and blood sample collection for CD3+, CD4+ and CD8+ T cell count, CCR5 receptor occupancy for Treg and macrophages, serum cytokine and chemokine levels, and CCR5 gene polymorphisms. If Visit 2 (V2) takes place on the same day as the Screening Visit (V1), scheduled assessments performed under screening (V1) do not need to be repeated at V2.

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 or at subject's home.

The following assessments will be performed at V3, V4, and V5/EOT: physical examination, vital signs, Clinical Symptom Score assessment, pulse oxygen saturation, NEWS2 assessment, nasopharyngeal swab sample collection, health status assessment on an ordinal scale, assessment for the requirement of: mechanical ventilation, oxygen, and hospital stay, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, CD3+, CD4+ and CD8+ T cell count, CCR5 receptor occupancy for Treg and macrophage, serum cytokine and chemokine levels, and CCR5 gene polymorphisms.

Additionally, a chest radiograph or CT (if clinically indicated), mortality assessment, and ECG will be performed at V7/EOT visit. Adverse events and medications will be monitored throughout the study.

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

Follow-up visits will be performed at 2 weeks (V6) and 4 weeks (V7) after the End of Treatment (EOT) visit. The following assessments will be performed at V6 and V7 visit: review of adverse events and concomitant medications, physical examination, vital signs, mortality status, and blood collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V7 only).

Note: During visits conducted at the study clinic, subjects and site personnel will use appropriate protective gear (e.g., masks, gloves) to prevent the spread of the infection. If possible, scheduled 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 [16] (Pre-Rx)	V2 [16] (Post-Rx)	V3	V4	V5 (EOT)	V6	V7
Day		Day 0		Day 3	Day 7	Day 14	Day 28	Day 42
Window Period		Within 7 days of the Screening Visit		3(±1) days after V2	7(±1) days after V2	7(±1) days after V4	14(±3) days after EOT Visit	28(±3) days after EOT Visit
Informed Consent [1]	X							
Eligibility Evaluation [2]	X							
Subject Demographics	X							
Medical History [3]	X							
Physical Examination	X	X		X[4]	X[4]	X	X[4]	X [4]
Vital Signs [5]	X	X	X	X	X	X	X	X
Clinical Symptom Score Assessment [6]	X	X		X	X	X		
Pulse oxygen saturation (SpO2)	X	X		X	X	X		
National Early Warning Score 2 (NEWS2) Assessment[7]	X	X		X	X	X		
ECG	X					X		
Laboratory tests:								
Complete Blood Count [8]	X			X	X	X		X
Biochemistry [9]	X			X	X	X		X
Coagulation Indices [10]	X			X	X	X		X
Serum/Urine Pregnancy Test [11]	X					X		
Urinalysis [12]	X			X	X	X		X
CD3+, CD4+ and CD8+ T cell count		X		X	X	X		
CCR5 receptor occupancy for Treg and macrophage		X		X	X	X		

Procedure/Assessments	Screening Visit	Treatment Phase					Follow-Up	
Visit	V1	V2 [16] (Pre-Rx)	V2 [16] (Post-Rx)	V3	V4	V5 (EOT)	V6	V7
Day		Day 0		Day 3	Day 7	Day 14	Day 28	Day 42
Window Period		Within 7 days of the Screening Visit		3(±1) days after V2	7(±1) days after V2	7(±1) days after V4	14(±3) days after EOT Visit	28(±3) days after EOT Visit
Serum cytokine and chemokine levels		X		X	X	X		
CCR5 Gene Polymorphisms [13]		X		X	X	X		
Nasopharyngeal Swab Sample Collection [14]	X	X		X	X	X	X	X
Chest radiograph or CT (if clinically indicated) [15]	X					X		
Ordinal Scale Assessment	X	X		X	X	X		
Randomization [17]		X						
PRO 140 (700 mg) or Placebo Administration		X			X			
Assessment for the requirement of: Mechanical Ventilation, Oxygen, and Hospital Stay	X	X		X	X	X		
Mortality Status						X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X

[1] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.
[2] Initial evaluation of patient eligibility will be performed by Investigator.
[3] Medical history and current therapies (medications and non-medications).
[4] Symptom-directed physical examination
[5] Post treatment vital signs will be recorded at V2, V4, V5 (EOT) and will include blood pressure, heart rate, respiration rate, and temperature.
[6] Clinical Improvement will be assessed based on symptom score for fever, myalgia, dyspnea and cough. Each symptom is graded from 0 to 3. [0=none, 1=mild, 2=moderate, and 3=severe].The total score per patient ranges from 0 to 12 points. Clinical Improvement will be assessed daily while subject is hospitalized and will continue to be assessed on the scheduled treatment visits and at EOT after the subject is discharged from the hospital.
[7] National Early Warning Score 2 (NEWS2) Assessment is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness)
[8] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.
[9] Biochemistry

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

Renal function indicators: creatinine clearance, eGFR

Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random), cholesterol (total), Creatine kinase, C-reactive protein

[10] Prothrombin time (PT) and International Normalized Ratio (INR)
[11] ONLY performed on women of childbearing potential.
[12] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.
[13] Blood samples collected for receptor occupancy testing will also be used for CCR5 gene polymorphism for PRO 140 susceptibility.
[14] Swabs will be used for quantitative virologic testing. Samples are to be stored at -70°C.
[15] Chest radiograph or CT will be performed if clinically indicated by the treating physician.
[16] If Visit 2 (V2) takes place on the same day as the Screening Visit (V1), scheduled assessments performed under screening (V1) do not need to be repeated at V2.
[17] Randomization via WebView CTMS system

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 symptom score assessment (see Section 7.10);
- Pulse oxygen saturation (SpO2) (see Section 7.11);
- National Early Warning Score 2 (NEWS2) assessment (see Section 7.12);
- 12-lead electrocardiogram (see Section 7.13);
- 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 7.14)
- Chest radiograph or computer tomography (CT) scan (if clinically indicated) (See Section 7.15);

- Ordinal scale assessment (see Section 7.16);
- Assessment for the requirement of mechanical ventilation, oxygen, and hospital stay (see Section 7.17); 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 symptom score assessment (see Section 7.10);
- Pulse oxygen saturation (SpO2) (see Section 7.11);
- National Early Warning Score 2 (NEWS2) Assessment (see Section 7.12);
- 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 7.14)
- Ordinal scale assessment (see Section 7.16);
- Assessment for the requirement of mechanical ventilation, oxygen, and hospital stay (see Section 7.17); 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 7.18).

- Leronlimab (PRO 140) 700 mg or
- Placebo

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 symptom score assessment (see Section 7.10);
- Pulse oxygen saturation (SpO2) (see Section 7.11);
- National Early Warning Score 2 (NEWS2) Assessment (see Section 7.12);
- 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 7.14)
- Ordinal scale assessment (see Section 7.16);
- Leronlimab (PRO 140) or Placebo Administration – V4 only (see Section 6.1.3);
- Assessment for the requirement of mechanical ventilation, oxygen, and hospital stay (see Section 7.17);
- 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 symptom score assessment (see Section 7.10);
- Pulse oxygen saturation (SpO2) (see Section 7.11);
- National Early Warning Score 2 (NEWS2) Assessment (see Section 7.12);
- 12-lead electrocardiogram (see Section 7.13);
- 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 7.14)
- Chest radiograph or computer tomography (CT) scan (if clinically indicated);
- Ordinal scale assessment (see Section 7.16);
- Assessment for the requirement of mechanical ventilation, oxygen, and hospital stay (see Section 7.17);
- 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),
- Collection of blood specimens at Visit 9 only (see Section 7.8) for
  - Complete blood count;
  - Biochemistry;
  - Coagulation indices; and
  - Urine sample for urinalysis parameters.
- Nasopharyngeal Swab Sample Collection (See Section 7.14)
- Review of mortality status;
- Prior medications assessment (see Section 7.7); and
- Review of adverse events (see Section 9).

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 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.

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 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.

One study injection kit will be assigned per subject per treatment visit. Kits will be labeled with a unique identification number. Each kit used during the Treatment Period will contain four vials of leronlimab (PRO 140) or placebo for SC injection.

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.

Each vial of the Leronlimab (PRO 140) product contains ~1.4 mL antibody at 175mg/mL in a buffer containing [redacted]

Each vial of the Placebo product contains [redacted]

Note: *1 mL will be drawn from 1.4 mL solution filled vial. Remaining 0.4 mL medication will be discarded appropriately from each vial. The contents from 2 vials (2 mL) will be drawn into a syringe and administered as subcutaneous injection.*

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: CD10_COVID-19 Kit No. xxx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) or placebo 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	Protocol: CD10_COVID-19 Kit No. xxx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) or placebo 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

Figure 6-2: Investigational Product - Syringe Label

Protocol: CD10_COVID-19 Contents of Kit No. xxx 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: CD10_COVID-19 Kit No. xxx

Site No. _____ Subject No. _____

This kit contains 4 single-use vials

Each 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) or placebo 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. 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.

IP should be administered slowly over 15 seconds per mL. Leronlimab (PRO 140) should not be kept in syringe for longer than 60 minutes.

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 or 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 below. 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 Modifications
Grade 1	No dose adjustment is required.
Grade 2	First Occurrence: No dose adjustment is required. 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: • 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 Modifications
Grade 1	No dose adjustment is required.
Grade 2	Withhold treatment until symptoms resolve to: • 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:

- The use of immunosuppressive medications are prohibited with the following exceptions:
    - Intranasal, inhaled, topical steroids, or local steroid injections
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

  Note: Organ transplant patients will be allowed to continue baseline immunosuppressive therapy during the course of study.
- Other CCR5 antagonists
- Other investigational products

7.7.2. Allowable Medications and Therapies

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

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)

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

<table>
<tr><th>CBC Parameters</th><th>Biochemistry Parameters</th><th>Urinalysis</th></tr>
<tr><td>Hemoglobin (g/dL)
Hematocrit (%)
RBC/Erythrocytes (10^12/L)
WBC/Leukocytes (10^6/L)
Absolute Neutrophil Count (10^6/L)
Platelets (10^9/L)
Differential WBC:
– Neutrophils (%)
– Lymphocytes (%)
– Monocytes (%)
– Eosinophils (%)
– Basophils (%)</td><td rowspan="2"><u>Liver Function Tests</u>
Total bilirubin (mg/dL)
Alkaline Phosphatase (ALP) (U/L)
Aspartate Aminotransferase (AST) (or SGOT) (U/L)
Alanine Aminotransferase (ALT) (or SGPT) (U/L)
Total Protein (g/dL)
Albumin (g/dL)
Lactate Dehydrogenase (U/L)
<u>Renal Function Tests</u>
Creatinine clearance,
eGFR
<u>Electrolytes</u>
Sodium (mEq/L)
Potassium (mEq/L)
Chloride (mEq/L)
Calcium (mg/dL)
Bicarbonate (mEq/L)
<u>Other:</u>
Glucose, Random (mg/dL)
Cholesterol, Total (mg/dL)
Creatine kinase,
C-reactive protein
<u>Coagulation Parameters</u></td><td>pH
Specimen Appearance
Color
Specific Gravity
Ketones
Bilirubin
Occult Blood
Glucose
Protein
Nitrite
Urobilinogen (mg/dL)
Leukocyte Esterase
Leukocytes(/HPF)</td></tr>
<tr><th>Miscellaneous</th><th>Cytokine and Chemokine Panel</th></tr>
<tr><td>Serum pregnancy test
Urine pregnancy test
(for female subjects of childbearing potential)
CD3+, CD4+ and CD8+ T cell count
CCR5 receptor occupancy for Treg and macrophage
CCR5 Gene Polymorphisms</td><td>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-</td></tr>
</table>

	Prothrombin time (PT) International Normalized Ratio (INR)	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 SYMPTOM SCORE ASSESSMENT

Clinical Improvement will be assessed based on symptom score for fever, myalgia, dyspnea and cough. Each symptom is graded from 0 to 3. [0=none, 1=mild, 2=moderate, and 3=severe].

The total score per patient ranges from 0 to 12 points. Clinical Improvement will be assessed daily while subject is hospitalized and will continue to be assessed on the scheduled treatment visits and at EOT after the subject is discharged from the hospital.

7.11. PULSE OXYGEN SATURATION (SPO2)

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

7.12. 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 16.1.

7.13. 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.

7.14. NASOPHARYNGEAL SWAB SAMPLE COLLECTION

Nasopharyngeal swabs will be used for quantitative virologic testing. 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.

7.15. 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)

7.16. 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.

7.17. REQUIREMENT OF MECHANICAL VENTILATION, OXYGEN, AND HOSPITAL STAY

The incidence and duration, in days, of mechanical ventilation, oxygen, and hospital stay will be assessed at Screening (V1) and V3, V4, and V5 (EOT).

7.18. 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 and will use mixed block size of 3 and 6 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 Outcome (Endpoints) Measures

The primary outcome (endpoint) measure is:

- Clinical Improvement as assessed by change in total symptom score (for fever, myalgia, dyspnea and cough)
  Note: The total score per patient ranges from 0 to 12 points. Each symptom is graded from 0 to 3. [0=none, 1=mild, 2=moderate, and 3=severe].

8.2.2. Secondary Outcome (Endpoints) Measures

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

1. Time to clinical resolution (TTCR)

   Time to clinical resolution (TTCR), defined as the time from initiation of study treatment until resolution of clinical symptoms (fever, myalgia, dyspnea and cough).

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

   This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).

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

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

   A 7-category ordinal scale of patient health status ranges from: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3)

Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.

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

8.2.3. Exploratory Outcome (Endpoints) Measures

1. Change in size of lesion area by chest radiograph or CT
2. Change from baseline in serum cytokine and chemokine levels at Days 3, 7, and 14
3. Change from baseline in CCR5 receptor occupancy levels for Tregs and macrophages at Days 3, 7, and 14
4. Change from baseline in CD3+, CD4+ and CD8+ T cell count at Days 3, 7, and 14

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

A total of 75 subjects will be enrolled in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this proof-of-concept study.

8.4. RANDOMIZATION

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. BLINDING

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

The Amarex Information Technology department will be unblinded to treatment. As noted above, the Amarex 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).

8.6. STRATIFICATION

Randomization will be stratified by baseline total symptom score (i.e., using categories ≤4, >4)), and also by age (i.e., using categories <60, ≥60).

8.7. INTERIM ANALYSIS

No Interim Analysis (IA) will be performed for efficacy

8.8. 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.

8.8.1. Analysis Populations

8.8.1.1. Intent-to-Treat Population

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

8.8.1.2. PP Population

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

8.8.1.3. 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.

8.8.2. Covariates

There is no planned inferential statistics and there will be no covariates for this study. Stratification factors will be included in the analysis model.

8.8.3. 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.

8.9. ANALYSIS METHODS

A 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.

8.9.1. Subject Disposition

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

8.9.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics including medical history, prior and concomitant medications/therapies will be summarized using appropriate descriptive statistics.

8.9.3. Study Outcome Assessment

Efficacy Summaries

The evaluable population will be the primary analysis population for the analysis of the efficacy outcome measures of the study. All the primary and secondary outcome measures will be analyzed according to the variable type:

- Continuous data summaries will include:
  - Number of observations, mean, standard deviation, median, and minimum and maximum values.
  - Analysis of Covariance (ANCOVA) adjusted for the stratification factors for inferential statistics.
- Categorical data summaries will include:
  - Frequency counts and percentages.
  - Logit model will be used for inferential statistics using the stratification factors.

Safety Summaries

8.9.3.1. Adverse Events

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

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

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

8.9.3.2. Clinical Laboratory Data

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

8.9.3.3. ECG

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

8.9.3.4. Vital Signs

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

8.9.3.5. 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 16.2). 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

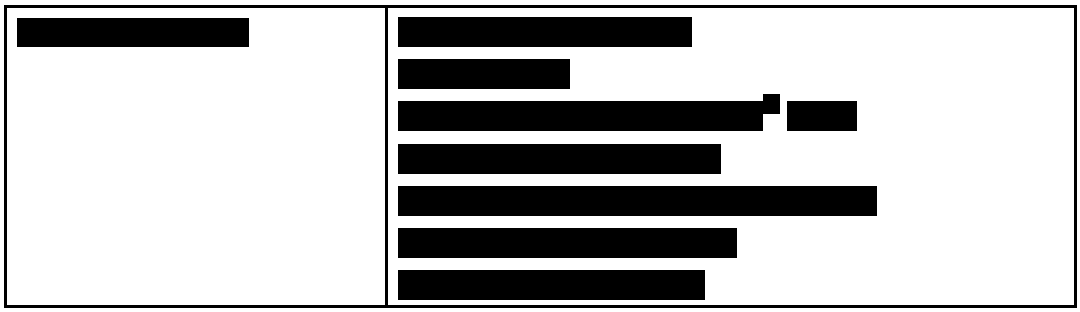
A SAE is defined as any AE that:

- 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.



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.

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.

9.5. 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.

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, 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. 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.

12.1. 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.

12.2. 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.

12.3. 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.

13. DATA HANDLING AND RECORD KEEPING

13.1. 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.

13.2. 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.

13.3. 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 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.

14. 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.

15. REFERENCES

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16. APPENDIX

16.1. 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

16.2. 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