A Phase 2, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab in Patients Experiencing Prolonged Coronavirus Disease 2019 (COVID-19) Symptoms [Long-Haulers]

Protocol Number:	**CD15_COVID-19**
Version:	**5.0**
Date:	**26-May-2021**

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Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**CD15_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.

PROTOCOL APPROVAL FOR USE

[redacted]

Jun 2, 2021
Date

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INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**CD15_COVID-19**
Version:	**5.0**
Date:	**26-May-2021**

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

_____ _____

Principal Investigator's Signature Date

_____

Print Name

_____

Site Number

SPONSOR INFORMATION

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CONTRACT RESEARCH ORGANIZATION INFORMATION

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140)	
Protocol Number: CD15_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 in Patients Experiencing Prolonged Coronavirus Disease 2019 (COVID-19) Symptoms [Long-Haulers]	
Study Center: Up to 5 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: 50 subjects	**Study Development Phase:** Phase 2
Indication for Use: Leronlimab is indicated for treatment of adult patients with prolonged symptoms of 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 experiencing prolonged symptoms (> 12 weeks) of COVID-19.	
Study Outcomes (Endpoints): **Primary Outcome (Endpoint) Measure:** • Changes from baseline in daily COVID-19-related symptom severity score through Day 56. *Note: A set of common COVID-19-related symptoms (see patient diary template) will be evaluated daily by the patient regardless of which symptoms a subject had at baseline, as new symptoms may appear following the baseline assessment.* **Secondary Outcome (Endpoints) Measures:** • Duration of COVID-19 associated symptoms from start of study treatment (Day 0) based on self-assessment using daily symptom diary. *Duration is defined as number of days when any symptoms scored as* – *moderate or severe at baseline are still scored as moderate or severe (i.e., not mild or absent) through Day 56, or* – *mild or absent at study entry are scored as mild or worse (i.e., not absent)through Day 56.* • Number of symptom-free days of COVID-19 associated symptoms that were present at the start of study treatment (Day 0) based on self-assessment using daily symptom diary.	

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Symptom-free days are defined as number of days when any symptoms scored as mild, moderate or severe at baseline are scored as absent (or none) through Day 56.

- Progression (or worsening) of COVID-19-associated symptoms through Day 56 compared to baseline.

  Progression or symptom worsening is defined as number of days when any symptoms scored as

  - *moderate at baseline are scored as severe through Day 56.*
  - *mild at baseline are scored as moderate or severe through Day 56.*
  - *absent at baseline are scored as mild, moderate or worse through Day 56.*
- Change from baseline in PROMIS® Fatigue Score at Days 28 and 56.
- Change from baseline in PROMIS® Cognitive Function Score at Days 28 and 56.
- Change from baseline in PROMIS® Sleep Disturbance Score at Days 28 and 56.
- Incidence of hospitalization during the treatment phase
- Duration (days) of hospitalization during the treatment phase

Exploratory Outcome (Endpoints) Measures:

- Change from baseline in pulse oxygen saturation (SpO2) at Day 7, 14, 21, 28, 35, 42, 49, and 56.
- Change from baseline in serum cytokine and chemokine levels on Days 28 and 56.
- Change from baseline in CD4+ and CD8+ T cell count on Days 28 and 56.
- Change from baseline in Transgrowth factor beta 1 (TGF beta1) on Days 28 and 56.
- Change from baseline in CRP on Days 28 and 56.
- Change from baseline in CCR5 receptor occupancy on Days 28 and 56.
- To explore biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of leronlimab.
- Evaluation of Global Health Assessment at Day 56

Safety Measures:

- Incidence of treatment-related adverse events (TEAEs).
- Incidence and severity of treatment-emergent adverse events (TEAEs).
- Incidence of serious adverse events (SAEs).
- Incidence of TEAEs and SAEs leading to discontinuation of study medication.
- Changes in blood chemistry, hematology and coagulation parameter results.

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- Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure.
- Changes in physical examination results.
- Change 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 prolonged symptoms caused by COVID-19. Patients will be randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection.

The study 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, vital signs, pulse oxygen saturation, physical examination, electrocardiogram (ECG), clinical symptom score assessment, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, and 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 (56 Days± 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) days after V2
- Visit 4 (V4) [second treatment]: 7 (±1) days after V2
- Visit 5 (V5): 3 (±1) days after V4
- Visit 6 (V6) [third treatment]: 7 (±1) days after V4
- Visit 7 (V7): 3 (±1) days after V6
- Visit 8 (V8) [fourth treatment]: 7 (±1) days after V6
- Visit 9 (V9): 3 (±1) days after V8
- Visit 10 (V10) [fifth treatment]: 7 (±1) days after V8
- Visit 11 (V11): 3 (±1) days after V10

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- Visit 12 (V12) [sixth treatment]: 7(±1) days after V10
- Visit 13 (V13): 3 (±1) days after V12
- Visit 14 (V14) [seventh treatment]: 7(±1) days after V12
- Visit 15 (V15): 3 (±1) days after V14
- Visit 16 (V16) [eighth treatment]: 7(±1) days after V14
- Visit 17 (V17) / End of Treatment (EOT) Visit: 7 (±1) days after V16.

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, vital signs, pulse oxygen saturation, physical examination, PROMIS® Fatigue Scale, PROMIS® Cognitive Function, PROMIS® Sleep Disturbance, and blood sample collection for CD4+ and CD8+ T cell count and serum cytokine and chemokine levels and urine pregnancy (if applicable). Subjects will also be given a diary to record all symptoms daily throughout the entire treatment period starting at baseline.

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

At V2, subjects will be randomized to receive leronlimab (PRO 140) or placebo which will be administered subcutaneously weekly at V2, V4, V6, V8, V10, V12, V14, and V16.

The following assessments will be performed at V4, V6, V8, V10, V12, V14, V16, and V17(EOT): vital signs, pulse oxygen saturation, physical examination, electrocardiogram (ECG) (V17 only), PROMIS® Fatigue Scale, PROMIS® Cognitive Function, PROMIS® Sleep Disturbance, Global Health Assessment (V17 only), blood sample collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V10 and V17), CD4+ and CD8+ T cell count and serum cytokine and chemokine levels (V10 and V17), assessment for the requirement of hospitalization and patient compliance to daily diary completion will be checked by the site staff.

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Additionally, telephone or video contact visits will be performed 3 days (±1 day) after each treatment administration visit. The requirement of hospitalization and patient compliance to daily diary completion will be checked during V3, V5, V7, V9, V11, V13, and V15 via telephone.

Adverse events and concomitant medications will be monitored throughout the study.

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

Follow-up visit (V18) will be performed at 4 weeks after the End of Treatment (EOT) visit. The following assessments will be performed at V18: vital signs, physical examination, pulse oxygen saturation, blood sample collection for immunophenotypic biomarker analysis, assessment for the requirement of hospitalization, review of adverse events and concomitant medications.

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.

Duration of Treatment:

- **Screening Period** (Screening to Baseline): Up to 7 days (1 Week)
- **Treatment Period**: 56 Days
- **Follow-Up Period**: 28 Days (4 weeks)

  Total Study Duration: 91 Days

Inclusion Criteria:

1. Male or female adult ≥ 18 years of age at time of enrollment.
2. Prior confirmed COVID-19 diagnosis by standard RT-PCR assay or equivalent testing
3. Clinical Symptom Score of ≥6 AND at least two symptoms of moderate or higher severity as listed below at the time of Screening and currently experiencing two or more of the following symptoms consistent with COVID-19 infection for a prolonged period of time (>12 weeks).

   Clinical symptoms include the following:

   - Respiratory symptoms such as cough, sore throat, stuffy or runny nose, shortness of breath (difficulty breathing), tightness of chest..
   - Neurological symptoms such as difficulty in concentration (brain fog), sleep disturbance/insomnia, headache, dizziness, anxiety, tingling or numbness, loss of sense of smell or taste.
   - Cardiovascular and Gastrointestinal symptoms such as feeling of fast heartbeat, nausea, vomiting, diarrhea.

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- Musculoskeletal symptoms such as muscle aches/cramps, muscle weakness, joint pain/swelling.
- General immune response symptoms such as fatigue (low energy or tiredness), chills or shivering, feeling hot or feverish, or exertional malaise (feeling of discomfort, illness, or lack of well-being after physical activity or mental stress).

Note: Clinical Symptom Score is obtained from the patient diary (refer to Appendix 1 for scoring instructions).

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

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

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

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

5. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
6. Men and women of childbearing potential and their partner must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, bilateral tubal occlusion, or vasectomy) or must practice complete sexual abstinence for the duration of the study (excluding women who are not of childbearing potential and men who have been sterilized).
7. Females of child-bearing potential must have a negative urine pregnancy test at Screening Visit and prior to receiving the first dose of study drug; and Male participants must agree to use contraception and refrain from donating sperm for at least 90 days after the last dose of study intervention.
8. Subject is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions

Exclusion Criteria:

1. Exhibiting signs of moderate or severe pulmonary disease (such as COPD, asthma, or pulmonary fibrosis)

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2. Ongoing requirement of oxygen therapy
3. Pulse oxygen saturation (SpO2) of <94% on room air at the time of screening
4. History of splenectomy
5. Liver cirrhosis or patient showing signs of clinical jaundice at the time of screening
6. Chronic kidney disease stage 4 or requiring dialysis at the time of screening
7. NYHA Class III or IV congestive heart failure (CHF)
8. Exhibiting signs of uncontrolled hypo-or hyper- thyroidism at the time of Screening
9. Uncontrolled rheumatologic disorders at the time of screening
10. History of organ transplantation or are candidates for organ transplantation at the time of screening
11. History of Chronic Fatigue Syndrome prior to COVID-19 infection
12. History of fibromyalgia prior to COVID-19 infection
13. History of major psychiatric disorder including bipolar disorders, schizophrenia, schizoaffective disorder, major depression. Patients with major depression can be enrolled if patient has had no episode within the past year or is considered in remission or controlled by treatment.
14. Any malignancy within the past 5 years, excluding successfully treated basal cell carcinoma or squamous cell carcinoma without evidence of metastases.
15. Any other clinically significant serious systemic diseases which would interfere with study conduct or study results interpretation per the Investigator.
16. Treatment with immunosuppressive or immunomodulatory medications within 5 half-lives prior to screening. Patients on replacement therapy for adrenal insufficiency will be allowed. Patients on stable (> 3 months) low dose corticosteroid ≤ 5 mg Prednisone will be allowed.
17. History of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible
18. Ongoing use of CCR5 antagonist
19. Inability to provide informed consent or to comply with test requirements
20. Consideration by the investigator, for safety reasons, that the subject is an unsuitable candidate to receive study treatment
21. Pregnancy or breast feeding

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22. Participating in another study for an investigational treatment	

Statistical Considerations:

Sample Size Determination and Rationale

A total of 50 subjects will be randomized 1:1 in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this exploratory 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 study treatment (leronlimab 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 mITT 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 study treatment (leronlimab or placebo). This population will be used for the analysis of safety parameters or measurements.

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
CCR5	C-C chemokine receptor type 5
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
Cmax	Maximal Concentration
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
CV	Curriculum Vitae
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FDP	Finished Drug Product
FUV	Follow-up Visit
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IC	Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviation	Term
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reaction
ITT	Intent to Treat
IV	Intravenous
IWRS	Interactive Web Based Response System
LAR	Legally Authorized Representative
LTF	Lost to Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	Maximum Tolerated Dose
NEWS	National Early Warning Score 2
OBT	Optimized Background Therapy
PD	Pharmacodynamic
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
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

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral cause of coronavirus disease 2019 (Covid-19) was first identified in late 2019 in Wuhan, Hubei province, China. On 11 March 2020, the World Health Organization declared the disease a global pandemic. The global burden of SARS CoV-2 infection continues to increase with estimates of more than 37 million people infected and over one million deaths as of October 2020.

While some individuals infected with SARS-CoV-2 may be asymptomatic, the majority of people display symptomatic disease varying from mild to critical in severity. Severe-to-critical illness is typically marked by hypoxemic respiratory failure requiring ventilatory support. Morbidity and mortality rates are elevated among patients with pre-existing co-morbidities such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, hypertension and cancer. The observed case fatality ratio (CFR) varies considerably from country to country and over time. However, the CFR in the USA has been estimated at 2.8%. While public discourse on COVID-19 has largely centered around patients with severe or fatal illness, it has become apparent that a growing number of patients experience mild to moderate symptoms for a prolonged period of time.

A patients and survivors of COVID-19 from the Body Politic COVID-19 Support Group created and analyzed a survey targeted at patients experiencing symptoms for over two weeks. Responses from 640 patients were collected between April 21 and May 2, 2020 (https://patientresearchcovid19.com/research/report-1/).

Key findings were symptoms are not limited to cough, fever, and shortness of breath. Other widely reported symptoms span neurological, gastrointestinal, cardiovascular, and other systems and include fatigue (reported by 81.3% of respondents), chills/sweats (75.9%), body aches (73.9%), headache (72.2%), brain fog and concentration issues (68.6%), gastrointestinal issues (66.9%), trouble sleeping (66.1%), and dizziness (60.6%). An elevated temperature under 100.1°F was reported by 72.2% of respondents while a fever over 100.1°F was reported by only 47.8% of respondents. The other key finding was recovery is volatile, includes relapses, and can take six or more weeks. At the time respondents took the survey, 90.6% reported not being recovered and were, on average, on day 40 of experiencing symptoms. 89% of respondents said that their

symptoms fluctuated in intensity and frequency, and 70% reported new symptoms appearing at different stages of their illness. Based on textual responses and anecdotes from the support group, patients may feel better for days or weeks only to relapse into old or new symptoms soon after.

The aim of this study is to test efficacy and safety of leronlimab (PRO140) for treatment of adult patients with prolonged symptoms of Coronavirus disease 2019 (COVID-19).

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, Coronavirus disease 2019 (COVID-19), cancer, and other diseases, including Graft versus host disease (GVHD) and Nonalcoholic steatohepatitis (NASH).

Leronlimab (PRO 140) has been administered intravenously or subcutaneously to more than 1000 patients across multiple studies. Leronlimab has been generally well-tolerated and no patterns of drug-related toxicities have been observed.

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 ten completed and nine 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 remarkable 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 included 52 adult patients with a documented history of genotypic or phenotypic resistance to ART drugs within two or more drug classes who demonstrated evidence of HIV-1 replication despite ongoing antiretroviral therapy and had 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 were to 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 were to 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.

This clinical study has been completed.

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.

This clinical study is pending start-up.

1.4.2.16. CD07_Compassionate Use

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

This clinical study is currently ongoing.

1.4.2.17. CD09_Basket Study

CD09_Basket study (open-label, 30 subjects, multi-center) seeks to evaluate the anti-tumor activity of leronlimab (PRO 140) in patients with CCR5+, locally advanced or metastatic solid tumors who have disease progression on standard therapy, or receiving a standard anticancer treatment but no

subsequent approved treatment would be available upon progression, or unable to receive standard therapy, or for whom standard therapy does not exist.

This clinical study is currently ongoing.

1.4.2.18. CD10_COVID-19

CD10_COVID-19 (two-arm, randomized, double blind, placebo controlled) study seeks to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection. Patients were randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo via subcutaneous injection.

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

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

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

- Day 3 total symptom score results:

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

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

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

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

This clinical study has been completed.

1.4.2.19. CD12_COVID-19

CD12_COVID-19 (two-arm, randomized, double blind, placebo controlled, adaptive design) seeks to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with severe or critical COVID-19.

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
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.

Protocol Number	Phase	No. of Subjects (Planned/ Analyzed)	Doses	Subject Population	Comments
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
PRO 140 CD06	PK	80/79	Single dose PK study with 350 mg SC dose	Healthy	This clinical study is completed.
CD10_COVID-10	Phase 2	75/86	700 mg SC weekly dose or placebo	Mild to moderate COVID_19	This clinical study is completed and pending final database lock.

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,	This clinical study is currently ongoing.

Protocol Number	Phase	No. of Subjects (Planned/ To be analyzed)	Doses	Subject Population	Comments
				treatment experienced	
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 or combination with Treatment of Physician's Choice)	Triple negative breast cancer	This clinical study is currently ongoing.
CD09_Basket	2	30/TBD	350 or 525 or 700 mg SC weekly dose (as monotherapy)	CCR5+, Locally Advanced or Metastatic Solid Tumors	This clinical study is currently ongoing.

Protocol Number	Phase	No. of Subjects (Planned/ To be analyzed)	Doses	Subject Population	Comments
CD12_COVID-10	Phase 2b/3	390/TBD	700 mg SC weekly dose or placebo	Severe or critical COVID_19	This clinical study is currently ongoing.

1.5. STUDY RATIONALE

Viral infections incite a pro-inflammatory response with increased production of cytokines and chemokines [Mogensen & Paludan, 2001; Quin et al., 2020; Law et al., 2005; Yen et al., 2006]. Long-term COVID-19 symptoms may be attributed to dysregulated immune inflammatory response both peripherally and centrally. Potential mechanisms of action for leronlimab in the Long COVID population may involve reduction of cytokine storm and inhibition of chemotaxis.

A focus on "cytokine storm" is clinically relevant in the severe COVID-19 population, but cytokine release of a less severe nature can also play a role in the symptoms of less severe disease, including those of Long COVID patients. A Cytokine Release Syndrome (CRS) provides a potential presentation of the spectrum of symptoms in patients with clinical manifestations of elevated peripheral and central cytokine production [Lee et al., 2014; Alexander et al., 2018]. Intermittent fatigue, Post Exertional Malaise (PEM), CNS symptoms with "brain fog," arthralgias, paresthesias, can be attributed to central cytokines while those with GI, pulmonary, hepatic, renal and cardiac can all be attributed to elevated peripheral cytokines. Many Long COVID patients report that their symptoms are substantially exacerbated by physical exercise or mental stress/exertion and are precipitated by a "storm" of recurrent symptoms, with the onset measured in days following the activity. In addition, known COVID-19 comorbidities such as aging, obesity, diabetes mellitus and hypertension are associated with increased proinflammatory cytokines and a worse COVID-19 prognosis [Aldinucci & Colomatti, 2018; Palaiodimos et al., 2020].

The chronic and relapsing symptoms of the Long COVID patients have been compared to those of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). An immune-inflammatory model in the pathogenesis ME/CFS involves elevated proinflammatory cytokines [Montoya et al., 2017; Morris et al., 2019]. This disturbance leads to a build-up of pro-inflammatory agents, especially post-infectious cytokines such as interferon gamma, and interleukin-7 [Perrin et al., 2020]. A hypothesis is developing in which these pro-inflammatory cytokines affect the neurological control in the brain, as observed in CFS/ME. The accumulation of cytokines in the CNS may lead to post-viral symptoms caused by pro-inflammatory cytokines passing through the blood-brain barrier in organs such as the hypothalamus, resulting in autonomic dysfunction manifesting acutely as a high fever and in dysregulation of the sleep/wake cycle, cognitive dysfunction and profound unremitting anergia, characteristic of CFS/ME. Separately, DNA polymorphisms and viral-induced epigenetic

changes to cytokine gene expression may lead to chronic inflammation in Long COVID patients, predisposing development of autoimmunity [de Vega et al., 2020; Rasa et al., 2018]. An autoimmune model for post-infectious ME/CFS is increasingly recognized [Steiner et al., 2018; Sotzny et al., 2018] and could be a determining factor in the progression from post-viral syndrome to ME/CFS.

It is likely that chemotaxis induced by CCL5 (RANTES) or other circulating cytokines following the binding to the CCR5 receptor contributes to the excessive lung inflammation seen in COVID-19. Disruption of the CCL5-CCR5 axis via leronlimab-mediated CCR5 blockade might prevent pulmonary trafficking of proinflammatory leukocytes and dampen pathogenic immune activation in COVID-19 [Patterson et al., 2020]. In Long COVID, dysregulation and chronic activation of cytokine signaling can cause prolonged CNS effects. Direct or indirect viral effects on the CNS can trigger neuroinflammation—a chronic immune response within the brain involving long-term activation of microglia (brain macrophages) and local release of inflammatory cytokines [Lavi & Cong, 2020; Barbosa-Silva et al., 2020]. Recent data from macaques is significant in suggesting that leronlimab may cross the blood-brain barrier, creating high CCR5 receptor occupancy on CD4+ T cells in brain tissue and resulting in detectable free leronlimab in multiple brain regions in macaques after subcutaneous dosing [Chang et al., n.d.].

Post-mortem SARS research indicated the virus had crossed the blood brain barrier into the hypothalamus via the olfactory pathway [Moldofsky & Patcai, 2011]. The pathway of the virus seemed to follow that previously suggested in CFS/ME patients, involving disturbance of lymphatic drainage from the microglia in the brain [Hives et al., 2017]. One of the main pathways of the lymphatic drainage of the brain is via the perivascular spaces along the olfactory nerves through the cribriform plate into the nasal mucosa [Kida et al., 1993]. If the pathogenesis of coronavirus affects a similar pathway, it could explain the anosmia (lack of smell) observed in a proportion of COVID-19 patients.

The build-up of cytokines in the CNS may lead to post-viral symptoms due to pro-inflammatory cytokines passing through the blood brain barrier in circumventricular organs such as the hypothalamus, leading to autonomic dysfunction manifesting acutely as a high fever and in the longer term to dysregulation of the sleep/wake cycle, cognitive dysfunction and profound unremitting anergia, all characteristic of CFS/ME. As happened after the SARS outbreak, a proportion of COVID-19 affected patients may go on to develop a severe post viral syndrome we term ‘Post COVID-19 Syndrome’ – a long term state of chronic fatigue characterized by post-exertional neuroimmune exhaustion.

In conclusion, there is ample evidence that cytokine release and the attendant downstream effects play a role in low-grade and long-term COVID-19 pathology, and cytokine-induced chemotaxis is a known response to cytokine release.

1.6. RISKS / BENEFITS ASSESSMENT

Allergic Reaction

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

Immune Response

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

Pregnancy

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

Venipuncture

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

Unknown Risks

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

Theoretical risk for increased severity of West Nile virus infection

Individuals who lack a functional CCR5 gene are at increased risk for severe infection by West Nile virus [Thompson, 2009]. Because of this, treatment with CCR5 co-receptor antagonists poses a theoretical risk for increased severity of West Nile virus infection. However, this concern is mitigated by several factors. First, no increased risk was observed for individuals who possess one functional and one non-functional CCR5 gene, indicating that an intermediate amount of

CCR5 is sufficient for defense against West Nile virus [Thompson, 2009]. Second, use of CCR5 co-receptor antagonists is unlikely to completely abrogate CCR5 function, and there has been no association reported to date between CCR5 co-receptor use and severe West Nile virus. Additionally, leronlimab (PRO 140) weakly antagonizes the natural activity of CCR5 and thus is less likely to adversely affect immune function. However, patients enrolled in this study may have immune suppression and therefore, DSMB and the investigators will be alerted to risks of West Nile infections. Furthermore, this has not been established to be a risk with maraviroc, the other FDA-approved anti-CCR5 drug already.

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

2. STUDY OBJECTIVES

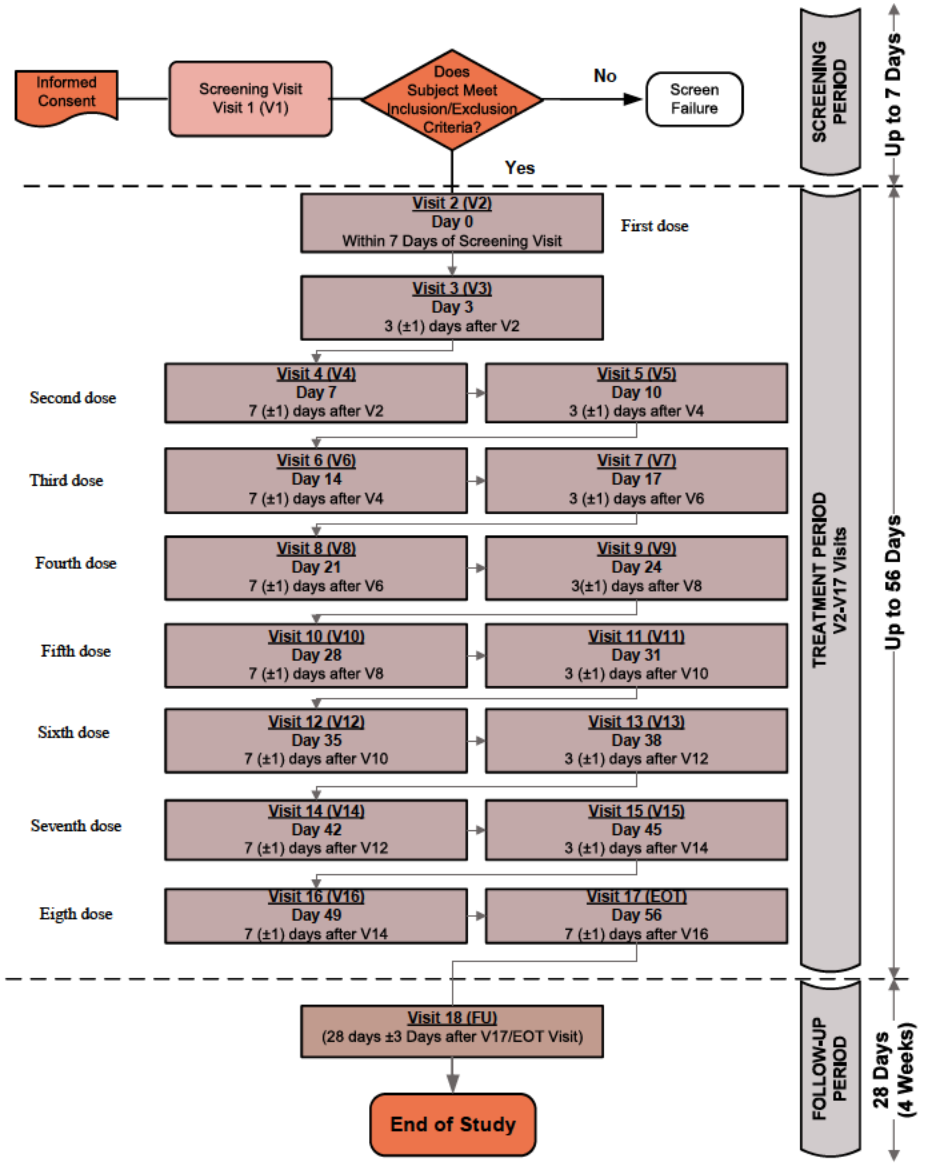
The purpose of this study is to assess the safety and efficacy of leronlimab (PRO 140) administered as weekly subcutaneous injection in subjects experiencing prolonged symptoms (> 12 weeks) of COVID-19.

3. STUDY 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 prolonged symptoms caused by coronavirus 2019 infection (COVID-19). Patients will be randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection.

The study will have three phases: Screening Period, Treatment Period, and Follow-Up Period. The study flow diagram is presented in Figure 3-1.

Figure 3-1: Study Schematic



3.1. STUDY CENTER

Up to 5 multinational centers. Centers must have the capability of implementing appropriate infection-control measures to prevent infection of study staff and others who share the clinical site space.

3.2. STUDY POPULATION

The target population for this study is adult patients with prolonged symptoms of Coronavirus disease 2019 (COVID-19).

3.3. ELIGIBILITY CRITERIA

3.3.1. Inclusion Criteria

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

1. Male or female adult ≥ 18 years of age at time of enrollment.
2. Prior confirmed COVID-19 diagnosis by standard RT-PCR assay or equivalent testing
3. Clinical Symptom Score of ≥6 AND at least two symptoms of moderate or higher severity as listed below at the time of Screening and currently experiencing two or more of the following symptoms consistent with COVID-19 infection for a prolonged period of time (>12 weeks).

   Clinical symptoms include the following:

   - Respiratory symptoms such as cough, sore throat, stuffy or runny nose, shortness of breath (difficulty breathing), tightness of chest.
   - Neurological symptoms such as difficulty in concentration (brain fog), sleep disturbance/insomnia, headache, dizziness, anxiety, tingling or numbness, loss of sense of smell or taste.
   - Cardiovascular and Gastrointestinal symptoms such as feeling of fast heartbeat, nausea, vomiting, diarrhea.
   - Musculoskeletal symptoms such as muscle aches/cramps, muscle weakness, joint pain/swelling.
   - General immune response symptoms such as fatigue (low energy or tiredness), chills or shivering, feeling hot or feverish, or exertional malaise (feeling of discomfort, illness, or lack of well-being after physical activity or mental stress).

   Note: Clinical Symptom Score is obtained from the patient diary (refer to Appendix 1 for scoring instructions).
4. Electrocardiogram (ECG) with no clinically significant findings as assessed by the Investigator.

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

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

5. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
6. Men and women of childbearing potential and their partner must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, bilateral tubal occlusion, or vasectomy) or must practice complete sexual abstinence for the duration of the study (excluding women who are not of childbearing potential and men who have been sterilized).
7. Females of child-bearing potential must have a negative urine pregnancy test at Screening Visit and prior to receiving the first dose of study drug; and Male participants must agree to use contraception and refrain from donating sperm for at least 90 days after the last dose of study intervention.
8. Subject is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions

3.3.2. Exclusion Criteria

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

1. Exhibiting signs of moderate or severe pulmonary disease (such as COPD, asthma, or pulmonary fibrosis)
2. Ongoing requirement of oxygen therapy
3. Pulse oxygen saturation (SpO2) of <94% on room air at the time of screening
4. History of splenectomy
5. Liver cirrhosis or patient showing signs of clinical jaundice at the time of screening
6. Chronic kidney disease stage 4 or requiring dialysis at the time of screening

7. NYHA Class III or IV congestive heart failure (CHF)
8. Exhibiting signs of uncontrolled hypo-or hyper- thyroidism at the time of Screening
9. Uncontrolled rheumatologic disorders at the time of screening
10. History of organ transplantation or are candidates for organ transplantation at the time of screening
11. History of Chronic Fatigue Syndrome prior to COVID19 infection
12. History of fibromyalgia prior to COVID-19 infection
13. History of major psychiatric disorder including bipolar disorders, schizophrenia, schizoaffective disorder, major depression. Patients with major depression can be enrolled if patient has had no episode within the past year or is considered in remission or controlled by treatment.
14. Any malignancy within the past 5 years, excluding successfully treated basal cell carcinoma or squamous cell carcinoma without evidence of metastases.
15. Any other clinically significant serious systemic diseases which would interfere with study conduct or study results interpretation per the Investigator.
16. Treatment with immunosuppressive or immunomodulatory medications within 5 half-lives prior to screening. Patients on replacement therapy for adrenal insufficiency will be allowed. Patients on stable (> 3 months) low dose corticosteroid ≤ 5 mg Prednisone will be allowed.
17. History of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible
18. Ongoing use of CCR5 antagonist
19. Inability to provide informed consent or to comply with test requirements
20. Consideration by the investigator, for safety reasons, that the subject is an unsuitable candidate to receive study treatment
21. Pregnancy or breast feeding
22. Participating in another study for an investigational treatment

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, vital signs, pulse oxygen saturation, physical examination, electrocardiogram (ECG), clinical symptom score assessment, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, and 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 (56 Days ± 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) days after V2
- Visit 4 (V4) [second treatment]: 7 (±1) days after V2
- Visit 5 (V5): 3 (±1) days after V4
- Visit 6 (V6) [third treatment]: 7 (±1) days after V4
- Visit 7 (V7): 3 (±1) days after V6
- Visit 8 (V8) [fourth treatment]: 7 (±1) days after V6
- Visit 9 (V9): 3 (±1) days after V8
- Visit 10 (V10) [fifth treatment]: 7 (±1) days after V8
- Visit 11 (V11): 3 (±1) days after V10
- Visit 12 (V12) [sixth treatment]: 7(±1) days after V10
- Visit 13 (V13): 3 (±1) days after V12
- Visit 14 (V14) [seventh treatment]: 7(±1) days after V12
- Visit 15 (V15): 3 (±1) days after V14
- Visit 16 (V16) [eight treatment]: 7(±1) days after V14
- Visit 17 (V17) / End of Treatment (EOT) Visit: 7 (±1) days after V16.

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,

vital signs, pulse oxygen saturation, physical examination, PROMIS® Fatigue Scale, PROMIS® Cognitive Function, PROMIS® Sleep Disturbance, and blood sample collection for CD4+ and CD8+ T cell count and serum cytokine and chemokine levels.

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. Subjects will be given a diary to record all symptoms daily throughout the entire treatment period starting at baseline.

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 V2, V4, V6, V8, V10, V12, V14, and V16.

The following assessments will be performed at V4, V6, V8, V10, V12, V14, V16, and V17(EOT): vital signs, pulse oxygen saturation, physical examination, electrocardiogram (ECG (V17 only), PROMIS® Fatigue Scale, PROMIS® Cognitive Function- Short Form 4a, PROMIS® Sleep Disturbance – Short Form 4a, Global Health Assessment (V17 only), blood sample collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V10 and V17). CD4+ and CD8+ T cell count and serum cytokine and chemokine levels (V10 and V17), assessment for the requirement of hospitalization and patient compliance to daily diary completion will be checked by the site staff.

Additionally, telephone or video contact visits will be performed 3 days (±1 day) after each treatment administration visit. The requirement of hospitalization and patient compliance to daily diary completion will be checked during V3, V5, V7, V9, V11, V13, and V15 via telephone.

Adverse events and concomitant medications will be monitored throughout the study.

Follow Up Period (4 weeks after EOT± 3 days)

Follow-up visit (V18) will be performed 4 weeks after the End of Treatment (EOT) visit. The following assessments will be performed at V18: vital signs, physical examination, pulse oxygen saturation, blood sample collection for immunophenotypic biomarker analysis, assessment for the requirement of hospitalization, review of adverse events and concomitant medications.

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.

Table 4-2: Schedule of Assessments

Procedure/Assessments	Screening Visit	Treatment Phase																Follow-Up
Visit	V1	V2 [16]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 (EOT)	V18 (FU)
Day		**Day 0**	Day 3	**Day 7**	Day 10	**Day 14**	Day 17	**Day 21**	Day 24	**Day 28**	Day 31	**Day 35**	Day 38	**Day 42**	Day 45	**Day 49**	Day 56	**Day 84**
Visit Type [17]	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic
Window Period		Within 7 days of the Screening Visit	3(±1) days after V2	7(±1) days after V2	3(±1) days after V4	7(±1) days after V4	3(±1) days after V6	7(±1) days after V6	3(±1) days after V8	7(±1) days after V8	3(±1) days after V10	7(±1) days after V10	3(±1) days after V12	7(±1) days after V12	3(±1) days after V14	7(±1) days after V14	7(±1) days after V16	28(±3) days after V17
Informed Consent [1]	X																	
Eligibility Evaluation [2]	X	X																
Subject Demographics	X																	
Medical History [3]	X																	
Vital Signs [5]	X	X		X		X		X		X		X		X		X	X	X
Pulse oxygen saturation (SpO2) [5]	X	X		X		X		X		X		X		X		X	X	X
Physical Examination	X	X		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]	X	X
ECG	X																X	
COVID-19 Related Symptom Assessment																		
Clinical Symptom Score Assessment [6]	X	X																
Patient Symptom Diary [7] - EVERYDAY		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Patient compliance to diary completion			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Questionnaires [8]																		
PROMIS® Fatigue Scale		X		X		X		X		X		X		X		X	X	
PROMIS® Cognitive Function- Short Form 4a		X		X		X		X		X		X		X		X	X	
PROMIS® Sleep Disturbance – Short Form 4a		X		X		X		X		X		X		X		X	X	
Global Health Assessment Questionnaire																	X	
Laboratory tests:																		
Complete Blood Count [9]	X									X							X	
Biochemistry [10]	X									X							X	
Coagulation Indices [11]	X									X							X	

Procedure/Assessments	Screening Visit	Treatment Phase																Follow-Up
Visit	V1	V2 [16]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 (EOT)	V18 (FU)
Day		Day 0	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21	Day 24	Day 28	Day 31	Day 35	Day 38	Day 42	Day 45	Day 49	Day 56	Day 84
Visit Type [17]	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic
Window Period		Within 7 days of the Screening Visit	3(±1) days after V2	7(±1) days after V2	3(±1) days after V4	7(±1) days after V4	3(±1) days after V6	7(±1) days after V6	3(±1) days after V8	7(±1) days after V8	3(±1) days after V10	7(±1) days after V10	3(±1) days after V12	7(±1) days after V12	3(±1) days after V14	7(±1) days after V14	7(±1) days after V16	28(±3) days after V17
Urine Pregnancy Test [12]	X	X								X							X	
Urinalysis [13]	X									X							X	
CD4+ and CD8+ T cell count		X								X							X	
Serum cytokine and chemokine levels [14]		X								X							X	
CCR5 Receptor Occupancy		X								X							X	
Immunophenotypic Biomarker Analysis		X								X							X	X
Randomization [15]		X																
PRO 140 (700 mg) or Placebo Administration		X		X		X		X		X		X		X		X		
Assessment for Requirement of Hospitalization			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	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] Pre-treatment and post-treatment vital signs and SpO2 will be recorded at V2. Post-treatment vital signs and SpO2 will be recorded at V4, V6, V8, V10, V12, V14, and V16. Vital Signs will include blood pressure, heart rate, respiration rate, temperature, weight, and height. (Note: Height will be measured only at V1).
[6] Symptom Score will be assessed for patient eligibility based on symptom score for following symptoms consistent with COVID-19 as a result of confirmed SARS-CoV-2 infection for a prolonged period of time (>12 weeks) (Total Clinical Symptom Score of ≥6 with at least two symptoms of moderate or higher severity at the time of Screening (at V1) and prior to Randomization (at V2)
[7] Patients will be asked to complete a daily diary during the treatment phase to record symptoms.
[8] All three questionnaires, PROMIS® Fatigue Scale, PROMIS® Cognitive Function, and PROMIS® Sleep Disturbance will be evaluated before study drug administration. .
[9] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.
[10] Biochemistry

Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, Lactate dehydrogenase (LDH)
Renal function indicators: Serum creatinine, eGFR
Electrolytes: sodium, potassium, chloride, calcium and bicarbonate
Other: glucose (random), cholesterol (total), Creatine kinase, C-reactive protein, Serum ferritin

[11] Prothrombin time (PT) and International Normalized Ratio (INR)
[12] ONLY performed on women of childbearing potential.
[13] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.
[14] Refer to Table 7-1 for details.
[15] Randomization via WebView CTMS system
[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] Visits listed as clinic will take place at the study center. The remaining visits are to be conducted as telephone or video contact visits.

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),
- Pulse oxygen saturation (SpO2) (See Section 7.10)
- 12-lead electrocardiogram (see Section 7.11);
- Clinical Symptom Score Assessment (see Section 7.14)
- Collection of laboratory specimens (see Section 7.8) for
    - Complete blood count;
    - Biochemistry;
    - Coagulation indices;
    - Urine pregnancy test, for female subjects of childbearing potential; and
    - Urine sample for urinalysis parameters.
- Prior and concomitant 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),
- Pulse oxygen saturation (SpO2) (see Section 7.10);
- Clinical Symptom Score Assessment (see Section 7.14)
- PROMIS® Fatigue Scale (see Section 7.16);
- PROMIS® Cognitive Function(see Section 7.17);
- PROMIS® Sleep Disturbance (see Section 7.18);
- Collection of blood specimens (see Section 7.8) for
    - CD4+ and CD8+ T cell count;
    - Serum cytokine and chemokine levels;
    - CCR5 receptor occupancy;
    - Immunophenotypic biomarker analysis.
- Urine pregnancy test, for female subjects of childbearing potential

Subjects will be randomized 1:1 via WebView CTMS system to Leronlimab (PRO 140) or Placebo (see Section 7.13).

- 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),
- Pulse oxygen saturation (SpO2) (see Section 7.10),
- Concomitant medications assessment (see Section 7.7),
- Review of adverse events (see Section 9)

4.2.2. Visits 3, 5, 7, 9, 11, 13, and 15 (V3, V5, V7, V9, V11, V13, and V15)

Telephone or video contact visits will be performed 3 days (±1 day) after each treatment administration visit. The following assessments will be performed:

- Patient Symptom Diary (see Section 7.15);

  Note: Patient compliance to daily diary completion will be checked by site staff.
- Assessment for the requirement of hospitalization (see Section 7.12);
- Prior and concomitant medications assessment (see Section 7.7); and
- Review of adverse events (see Section 9).

4.2.3. Visits 4, 6, 8, 10, 12, 14, and 16 (V4, V6, V8, V10, V12, V14, and V16)

The following assessments will be performed:

- Physical examination (see Section 7.5);
- Vital Signs (see Section 7.6),
- Pulse oxygen saturation (SpO2) (see Section 7.10);
- Patient Symptom Diary (see Section 7.15);

  Note: Patient compliance to daily diary completion will be checked by site staff.
- PROMIS® Fatigue Scale (see Section 7.16);
- PROMIS® Cognitive Function (See Section 7.17);
- PROMIS® Sleep Disturbance (see Section 7.18);
- Collection of laboratory specimens at V10 only (see Section 7.8) for

- Complete blood count;
- Biochemistry;
- Coagulation indices;
- Urine sample for urinalysis parameters;
- CD4+ and CD8+ T cell count;
- Serum cytokine and chemokine levels;
- CCR5 receptor occupancy; and
- Immunophenotypic biomarker analysis .

- Urine pregnancy test, for female subjects of childbearing potential – V10 only
- Leronlimab (700 mg) or Placebo Administration
- Assessment for the requirement of hospitalization (see Section 7.12);
- Prior and concomitant medications assessment (see Section 7.7); and
- Review of adverse events (see Section 9).

4.2.4. End of Treatment – EOT (V17)

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),
- Pulse oxygen saturation (SpO2) (see Section 7.10);
- 12-lead electrocardiogram (see Section 7.11);
- Patient Symptom Diary (see Section 7.15);

  Note: Patient compliance to daily diary completion will be checked by site staff.
- PROMIS® Fatigue Scale (see Section 7.16);
- PROMIS® Cognitive Function (see Section 7.17);
- PROMIS® Sleep Disturbance (see Section 7.18);
- Global Health Assessment (see Section 7.19);
- Collection of laboratory specimens (see Section 7.8) for
  - Complete blood count;

- Biochemistry;
- Coagulation indices;
- Urine pregnancy test, for female subjects of childbearing potential;
- Urine sample for urinalysis parameters;
- CD4+ and CD8+ T cell count;
- Serum cytokine and chemokine levels;
- CCR5 receptor occupancy; and
- Immunophenotypic biomarker analysis.

- Assessment for the requirement of hospitalization (see Section 7.12);
- Prior and concomitant medications assessment (see Section 7.7); and
- Review of adverse events (see Section 9).

4.3. FOLLOW-UP PHASE

The follow-up visit is scheduled 28(±3) days after EOT Visit.

4.3.1. Visit 18

The assessments performed at these visits will include:

- Vital Signs (see Section 7.6),
- Pulse Oxygen Saturation (see Section 7.10)
- Physical examination (see Section 7.5);
- Collection of blood specimens (see Section 7.8) for
  - Immunophenotypic biomarker analysis
- Assessment for the requirement of hospitalization (see Section 7.12);
- Prior and concomitant 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 and other global regulatory authority will be notified. The study will be stopped if any of these stopping criteria are met unless, after reviewing the safety events of interest, the medical monitor and Sponsor, agree to allow the study to proceed. The FDA and other global regulatory authority will be consulted for any protocol amendment before restarting the trial if a stopping rule is met.

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

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

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

- Subject experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the subject's best interest
- Subject becomes pregnant
- Subject becomes lost to follow-up (LTF)
- Subject will be withdrawn from the study if 2 consecutive doses 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 (8 doses)
Placebo	0 mg	SC	Weekly (8doses)

6.1. LERONLIMAB (PRO 140)

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

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

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

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

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

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

IP Dosage	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
PRO 140 700 mg	Parenteral solution	175 mg/mL	2 injections of PRO 140 (2 mL/inj.) per week on opposite sides of abdomen for eight 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 eight 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 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), and kit labels (Figure 6-2) designated for use in this clinical protocol. Each kit contains two labeled vials.

Figure 6-1: Investigational Product - Vial Label

Protocol: CD15_COVID-19 Kit No. xxx Subject No. _____ Single use 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA	Protocol: CD15_COVID-19 Kit No. xxx Subject No. _____ Single use 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) 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 - Kit Label

Protocol: CD15_COVID-19 Kit No. xxx Site No. _____ Subject No. _____ This kit contains 2 single-use vials Each 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

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

6.1.2. Leronlimab (PRO 140) - Storage and Handling

Study drug will be shipped at 2°C to 8°C (refrigerated [36°F to 46°F]) to the investigator's site. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored at 2°C to 8°C (refrigerated [36°F to 46°F]). The contents of the

vial should appear as a clear to opalescent, colorless to yellow solution; fine translucent particles may be present. This is normal.

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

6.1.3. Leronlimab (PRO 140) - Administration

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

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

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

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

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

IP should be administered slowly over 15 seconds per mL.

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

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

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 Management
Grade 1 Mild	No dose adjustment is required.
Grade 2 Moderate	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 Severe	Withhold treatment until symptoms resolve to: • Grade 1 or less
Grade 4 Life Threatening	Study treatment will be permanently discontinued

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

CTCAE Grade (attributable to leronlimab)	Treatment Management
Grade 1 Mild	No dose adjustment is required.
Grade 2 Moderate	Withhold treatment until symptoms resolve to: • Grade 1 or less or baseline;
Grade 3 Severe	Study treatment will be permanently discontinued
Grade 4 Life Threatening	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 (only at V1)
- Weight
  Note: Body Mass Index (BMI) will be auto-calculated using height and weight information in the EDC.

7.7. CONCOMITANT MEDICATIONS

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

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

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).

- **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*

- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

7.7.1. Excluded Medications

The following medications are prohibited while on study drug:

- Hydroxychloroquine, oral or parenteral corticosteroids, immunosuppressants, or immunomodulating agents
- Albuterol as nebulizer for treatment of COVID-19
- Other CCR5 antagonists
- Other investigational products

7.7.2. Allowable Medications and Therapies

The following medications and therapies are allowed:

- Empirical antibiotic treatment for secondary bacterial infections is allowed during the course of study.

7.8. Clinical Laboratory Assessments

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

- Biochemistry, Complete Blood Count (CBC), Coagulation indices and Urinalysis: At Screening (V1), V10, and V17 (EOT).
- CD4+ and CD8+ T cell count: At V2, V10, and V17 (EOT).
- Serum cytokine and chemokine levels: At V2, V10, and V17 (EOT).
- CCR5 Receptor Occupancy: At V2, V10, and V17 (EOT).
- Immunophenotypic Biomarker Analysis: At V2, V10, V17 (EOT), and V18 (FU).
- Urine pregnancy test (for female subjects of childbearing potential): At Screening (V1), V2, V10, and V17 (EOT).

All laboratory reports will be reviewed by the Investigator. Abnormal results that are considered by the Investigator to be clinically significant will be recorded as adverse events. If in the Investigator judgment, in order to make the determination of clinical significance the testing may be needed to

be repeated. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

Table 7-1: Lab Parameters

CBC Parameters	Biochemistry Parameters	Urinalysis
Hemoglobin (g/dL) 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 (%)	**Liver Function Tests** 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) **Renal Function Tests** Serum creatinine eGFR **Electrolytes** Sodium (mEq/L) Potassium (mEq/L) Chloride (mEq/L) Calcium (mg/dL) Bicarbonate (mEq/L) **Other:** Glucose, Random (mg/dL) Cholesterol, Total (mg/dL) Creatine kinase, C-reactive protein Serum ferritin **Coagulation Parameters** Prothrombin time (PT) International Normalized Ratio (INR)	pH Specimen Appearance Color Specific Gravity Ketones Bilirubin Occult Blood Glucose Protein Nitrite Urobilinogen (mg/dL) Leukocyte Esterase Leukocytes(/HPF)
Miscellaneous		**Cytokine and Chemokine Panel**
Urine pregnancy test (for female subjects of childbearing potential) CD4+ and CD8+ T cell count CCR5 receptor occupancy Immunophenotypic biomarker analysis		sCD40L, EGF, Eotaxin (CCL11), FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO alpha (CXCL1), IFN-alpha2, IFN-gamma, IL-1 alpha, IL-1 beta, IL-1RA, IL-2, IL-2R, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-12 (p40/p70) IL-13, IL-15, IL-17A, IL-17E/IL-25, IL-17F, IL-18, IL-22, IL-27, IP-10 (CXCL10), MCP-1 (CCL2), MCP-3, M-CSF, MDC (CCL22), MIG (CXCL9), MIP-1 alpha (CCL3), MIP-1 beta (CCL4), PDGF-AA, PDGF-AB/BB, RANTES (CCL5), TGF-alpha, TNF-alpha, TNF-beta, VEGF-A, TGF beta 1, Melanocyte stimulating hormone and C4A.

7.9. Study Treatment Application

Refer to Section 6.1.3 for details.

7.10. Pulse Oxygen Saturation (SpO2)

Pulse Oxygen Saturation (SPO2) will be measured at Screening and V2 (pre-dose and post-dose), V4, V6, V8, V10, V12, V14, V16, V17 (EOT), and V18 (Follow-Up).

Note: Post-dose values will be recorded at V4, V6, V8, V10, V12, V14, and V16.

7.11. 12-Lead Electrocardiogram

A resting supine 12-lead ECG will be conducted at the Screening Visit (V1), and Visit 17 (EOT). 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.

7.12. Requirement of Hospitalization

The incidence and duration, in days, of subjects' hospitalization will be assessed at beginning at V3 through V18 (Follow-Up).

7.13. Randomization

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

7.14. Clinical Symptom Score

Clinical symptom score will be assessed at Screening (V1) and baseline (V2) based on following commonly reported symptoms consistent with COVID-19 infection for a prolonged period of time (>12 weeks):

- Respiratory symptoms such as cough, sore throat, stuffy or runny nose, shortness of breath (difficulty breathing), tightness of chest etc.
- Neurological symptoms such as difficulty in concentration (brain fog), sleep disturbance/insomnia, headache, dizziness, anxiety, tingling or numbness, loss of sense of smell or taste.
- Cardiovascular and Gastrointestinal symptoms such as feeling of fast heartbeat, nausea, vomiting, diarrhea.

- Musculoskeletal symptoms such as muscle aches/cramps, muscle weakness, joint pain/swelling.
- General immune response symptoms such as fatigue (low energy or tirednesschills or shivering, feeling hot or feverish or exertional malaise (feeling of discomfort, illness, or lack of well-being after physical activity or mental stress).

Note: Clinical Symptom Score is obtained from the patient diary (refer to Appendix 1 for scoring instructions).

7.15. PATIENT SYMPTOM DIARY

After receiving treatment, subjects will be given a diary to record all symptoms daily throughout the entire treatment period. See Appendix 1.

7.16. PROMIS® FATIGUE SCALE

This score is based on questions focused on physical fatigue and psychological fatigue. The assessment will be performed (self-administered by the subject) at V2, V4, V6, V8, V10, V12, V14, V16, and V17 (EOT). See Appendix 3.

7.17. PROMIS® COGNITIVE FUNCTION

The brief mental fatigue questionnaire evaluates subject cognitive symptoms. The assessment will be performed (self-administered by the subject) at V2, V4, V6, V8, V10, V12, V14, V16, and V17 (EOT). See Appendix 4.

7.18. PROMIS® SLEEP DISTURBANCE

The brief questionnaire evaluates subjects' sleep quality. The assessment will be performed (self-administered by the subject) at V2, V4, V6, V8, V10, V12, V14, V16, and V17 (EOT). See Appendix 5.

7.19. GLOBAL HEALTH ASSESSMENT

The brief questionnaire evaluates general health (physical and mental health) and quality of life. This is an exploratory (non-validated) assessment developed (based on PROMIS® Scale v1.2 – Global Health) with an intent to assist in identifying more appropriate global health measurement for the future studies in long-hauler COVID-19 population and will not be used for labeling claims. The assessment will be performed (self-administered by the subject) at V17 (EOT/Day 56). See Appendix 6.

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:

- Leronlimab (PRO 140) 700 mg
- Placebo

8.2. DESCRIPTION OF STUDY OUTCOMES (ENDPOINTS)

8.2.1. Primary Endpoint

The primary endpoint for the study is:

- Changes from baseline in daily COVID-19-related symptom severity score through day 56

  Note: A set of common COVID-19-related symptoms (see patient diary template) will be evaluated daily by the patient regardless of which symptoms a subject had at baseline, as new symptoms may appear following the baseline assessment.

8.2.2. Secondary Endpoints

The secondary efficacy endpoints for the study are:

- Duration of COVID-19 associated symptoms from start of study treatment (Day 0) based on self-assessment using daily symptom diary.

  Duration is defined as number of days when any symptoms scored as

  - *moderate or severe is defined as number of days are still scored as moderate or severe (i.e., not mild or absent) through Day 56, or*
  - *mild or absent at study entry are scored as mild or worse (i.e., not absent) through Day 56.*
- Number of symptom-free days of COVID-19 associated symptoms that were present at the start of study treatment (Day 0) based on self-assessment using daily symptom diary.

  Symptom-free days are defined as number of days when any symptoms scored as mild, moderate or severe at baseline are scored as absent (or none) through Day 56.

- Progression (or worsening) of COVID-19-associated symptoms through Day 56 compared to baseline.

  Progression or symptom worsening is defined as number of days when any symptoms scored as

  - *moderate at baseline are scored as severe through Day 56.*
  - *mild at baseline are scored as moderate or severe through Day 56.*
  - *absent at baseline are scored as mild, moderate or worse through Day 56.*
- Change from baseline in PROMIS® Fatigue Score at Days 28 and 56.
- Change from baseline in PROMIS® Cognitive Function Score at Days 28 and 56.
- Change from baseline in PROMIS® Sleep Disturbance Score at Days 28 and 56.
- Incidence of hospitalization during the treatment phase
- Duration (days) of hospitalization during the treatment phase

8.2.3. Exploratory Outcome Measures (Endpoints)

- Change from baseline in pulse oxygen saturation (SpO2) at Day 7, 14, 21, 28, 35, 42, 49, and 56.
- Change from baseline in serum cytokine and chemokine levels on Days 28 and 56.
- Change from baseline in CD4+ and CD8+ T cell count on Days 28 and 56.
- Change from baseline in Transgrowth factor beta 1 (TGF beta1) on Days 28and 56.
- Change from baseline in CRP on Days 28and 56.
- Change from baseline in CCR5 receptor occupancy on Days 28 and 56.
- To explore biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of leronlimab.
- Evaluation of Global Health Assessment at Day 56.

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 50 subjects will be randomized 1:1 in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this exploratory study.

8.4. RANDOMIZATION

This is a multi-center randomized clinical trial. An individual, independent of the clinical trial team, will develop the randomization schedules. The actual randomization assignment will be made through an Interactive Web Based Response System (IWRS) called WebView®. Subjects who have provided written informed consent and have met all the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment groups.

8.5. STRATIFICATION

Randomization will be stratified by symptom duration (defined as time from first reported symptom onset to the time of randomization) of 12 – 24 weeks or > 24 weeks.

8.6. BLINDING

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

The 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).

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

8.7. TIME TO UNBLINDING

8.7.1. Emergency Unblinding

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

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

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

8.7.2. Final Analysis

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

8.8. INTERIM ANALYSIS

There will be no interim analysis performed in this study

8.9. GENERAL STATISTICAL CONSIDERATIONS

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

8.9.1. Analysis Populations

8.9.1.1. Modified 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 study treatment (leronlimab or placebo). This population will be used as the primary analysis population for analysis of the primary and secondary efficacy endpoints.

8.9.1.2. PP Population

The **Per Protocol (PP) population** is defined as the set of subjects who meet the ITT Population requirements and are not associated with any major protocol violations. This population will be identified before the database lock. This population will be used as the supportive analysis population for analysis of the primary and secondary efficacy endpoints.

8.9.1.3. Safety Population

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

8.9.2. Covariates

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

8.9.3. Missing Data

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

For efficacy evaluations, multiple imputation methods will be used to handle missing data. This imputation method is a robust method to impute missing measurements. The imputation will be carried out in SAS version 9.4 or later using PROC MI. Each imputation model will include the stratification factor as a covariate in the model. The details of multiple imputation will be included in the statistical analysis plan.

8.10. ANALYSIS METHODS

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

8.10.1. Subject Disposition

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

8.10.2. Demographic and Baseline Characteristics

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

8.10.3. Concomitant Medications/Therapies

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

8.10.4. Efficacy Analyses

Primary Analysis

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

Primary Endpoint

The primary endpoint for this study is the change from baseline in Fatigue Severity Score at Day 28.

Secondary Endpoints

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

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

- Continuous data summaries will include:
    - If the Normality assumption is met, Analysis of Covariance (ANCOVA) would be used.
    - If the Normality assumption is not met, a non-parametric method or a rank – ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.
- Categorical data summaries will be based on Logit model will be used.
- Time-dependent data: Cox proportional hazards model will be used to analyze time dependent data and to depict the time to event data.

8.10.5. Supportive Analysis

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

8.10.6. Subgroup Analysis

Subgroup analyses will be conducted for the predefined stratification factors (Section 8.5) for the study. Additional exploratory subgroup analysis will be conducted using the baseline clinical characteristics and laboratory parameters. The details will be prospectively specified in the SAP.

Safety Summaries

8.10.6.1. Adverse Events

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

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

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

8.10.6.2. Clinical Laboratory Data

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

8.10.6.3. ECG

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

8.10.6.4. Vital Signs

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

8.10.6.5. Physical Examination

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

9. ADVERSE EVENTS (DEFINITIONS AND REPORTING)

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

9.1. ADVERSE EVENT (AE)

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

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

9.2. REPORTING OF ADVERSE EVENTS

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

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

9.2.1. Impact on Study Treatment

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

9.2.2. CTCAE Grade (Intensity) Assessment

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

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

Table 9-1: CTCAE v5.0 General Guidelines

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

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

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

9.2.3. Causality Assessment

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

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

treatment.

3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
4. **Unlikely 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. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Medical Monitor within 24 hours.

Medical Monitor	[redacted]

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

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

9.5. SAE FOLLOW-UP

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

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

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

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

9.6. EXPECTED/ANTICIPATED EVENTS

Refer to Investigator Brochure for the expected/anticipated events.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

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

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

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. MONITORING REQUIREMENTS

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

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

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

11.2. ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

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

11.3. MODIFICATION OF PROTOCOL

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

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

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

11.4. REPORTING PROTOCOL DEVIATIONS

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

11.4.1. Major Protocol Deviation or Violation

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

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

11.4.2. Minor Protocol Deviation or Violation

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

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

12. DATA SAFETY MONITORING COMMITTEE (DSMC)

This section is not applicable for this study.

13. ETHICS AND REGULATORY REQUIREMENTS

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

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

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

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

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

13.2. INVESTIGATOR'S RESPONSIBILITIES

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

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

13.3. SUBJECT INFORMED CONSENT REQUIREMENTS

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

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

14. DATA HANDLING AND RECORD KEEPING

14.1. RECORDING AND COLLECTION OF DATA

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

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

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

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

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

14.2. CLINICAL DATA MANAGEMENT

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

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

14.3. ARCHIVING

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

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

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

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

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

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

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

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

15. PUBLICATION PLAN

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

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

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

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17. APPENDICES

17.1. APPENDIX 1: PATIENT DIARY TEMPLATE

Assessment of COVID-19-related symptoms

Subject Number: _____ Date and time of Assessment: _____

1. What was the severity of your **cough** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

2. What was the severity of your **sore throat** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

3. What was the severity of your **stuffy or runny nose** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

4. What was the severity of your **shortness of breath (difficulty breathing)** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

5. What was the severity of your **feeling of tightness of chest** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

6. What was the severity of your **feeling of fast heartbeat** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

7. What was the severity of your **fatigue (low energy or tiredness)** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

8. What was the severity of your **exertional malaise (feeling of discomfort, illness, or lack of well-being)** after physical activity or mental stress over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

9. What was the severity of your **muscle aches/cramps** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

10. What was the severity of your **muscle weakness** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

11. What was the severity of your **joint pain/swelling** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

12. What was the severity of your **chills or shivering** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

13. What was the severity of your **feeling hot or feverish** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

14. What was the severity of your **difficulty in concentration (brain fog)** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

15. What was the severity of your **sleep disturbance (insomnia)** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

16. What was the severity of your **headache** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

17. What was the severity of your **dizziness** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

18. What was the severity of your **anxiety** at its worst over the last 24 hours?

☐ None ☐ Mild ☐ Moderate ☐ Severe

19. What was the severity of your **feeling of tingling or numbness** in at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

20. What was the severity of your **nausea (feeling like you wanted to throw up)** at its worst over the last 24 hours?
☐ None ☐ Mild ☐ Moderate ☐ Severe

21. How many times did you **vomit (throw up)** in the last **24 hours**?*
☐ I did not vomit at all ☐ one or two times ☐ three or four times ☐ five or more times

22. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?*
☐ I did not have diarrhea at all ☐ one or two times ☐ three or four times ☐ five or more times

23. Rate your sense of **smell** in the last **24 hours**
☐ My sense of smell is THE SAME AS usual ☐ My sense of smell is LESS THAN usual
☐ I have NO sense of smell

24. Rate your sense of **taste** in the last **24 hours**
☐ My sense of taste is THE SAME AS usual ☐ My sense of taste is LESS THAN usual
☐ I have NO sense of taste

*The response options shown for items 19 and 20 are intended only for use with a 24-hour recall period.

Score Table

(For reference – Not included as part of Patient Diary)

Subjects' Rating

*Each symptom is scored individually using the scoring values mentioned in **italics** below.*

1. What was the severity of your **cough** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

2. What was the severity of your **sore throat** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

3. What was the severity of your **stuffy or runny nose** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

4. What was the severity of your **shortness of breath (difficulty breathing)** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

5. What was the severity of your **feeling of tightness of chest** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

6. What was the severity of your **feeling of fast heartbeat** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

7. What was the severity of your **fatigue (low energy or tiredness)** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

8. What was the severity of your **exertional malaise (feeling of discomfort, illness, or lack of well-being)** after physical activity or mental stress over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

9. What was the severity of your **muscle aches/cramps** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

10. What was the severity of your **muscle weakness** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

11. What was the severity of your **joint pain/swelling** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

12. What was the severity of your **chills or shivering** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

13. What was the severity of your **feeling hot or feverish** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

14. What was the severity of your **difficulty in concentration (brain fog)** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

15. What was the severity of your **sleep disturbance (insomnia)** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

16. What was the severity of your **headache** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

17. What was the severity of your **dizziness** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

18. What was the severity of your **anxiety** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

19. What was the severity of your feeling of **tingling or numbness** in at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

20. What was the severity of your **nausea (feeling like you wanted to throw up)** at its worst over the last 24 hours?
None = 0, Mild = 1, Moderate = 2, Severe = 3

21. How many times did you **vomit (throw up)** in the last **24 hours**?*
I did not vomit at all = 0, one or two times = 1, three or four times = 2, five or more times = 3

22. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?*
I did not have diarrhea at all = 0, one or two times = 1, three or four times = 2, five or more times = 3

23. Rate your sense of **smell** in the last **24 hours**
My sense of smell is THE SAME AS usual = 0,
My sense of smell is LESS THAN usual = 1
I have NO sense of smell = 2

24. Rate your sense of **taste** in the last **24 hours**
My sense of taste is THE SAME AS usual = 0
My sense of taste is LESS THAN usual = 1
I have NO sense of taste = 2

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

For complete detailed information please refer to the link below:

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

17.3. APPENDIX 3: PROMIS® FATIGUE SCALE

PROMIS® Item Bank v1.0 –Fatigue – Short Form 4a

Fatigue – Short Form 4a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
H7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

17.4. APPENDIX 4: PROMIS® COGNITIVE FUNCTION- SHORT FORM 4A

PROMIS® Item Bank v2.0 – Cognitive Function- Short Form 4a

Cognitive Function- Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days...	**Never**	**Rarely (Once)**	**Sometimes (Two or three times)**	**Often (About once a day)**	**Very often (Several times a day)**
PC2r	My thinking has been slow	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC35r	It has seemed like my brain was not working as well as usual	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC36r	I have had to work harder than usual to keep track of what I was doing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC42r	I have had trouble shifting back and forth between different activities that require thinking	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

17.5. APPENDIX 5: PROMIS® SLEEP DISTURBANCE – SHORT FORM 4A

PROMIS Item Bank v1.0 –Sleep Disturbance – Short Form 4a

Sleep Disturbance – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

17.6. APPENDIX 6 – GLOBAL HEALTH QUESTIONNAIRE

Global Health Assessment

(Based on PROMIS® Scale v1.2 – Global Health)

Please respond to each question or statement by marking one box per row.

	Significantly Improved	Improved	Minimal or No change	Worse	Significantly Worse
In general, since you started on this trial, how would you rate the change in your **health**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, since you started on this trial, how would you rate the change in your **physical health**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, since you started on this trial, how would you rate the change in your **mental health, including your mood and your ability to think**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, since you started on this trial, how would you rate the change in your **quality of life**?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

[redacted]

STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CD15_COVID-19

Sponsor:

CytoDyn, Inc.
1111 Main Street, Suite 660
Vancouver, Washington
98660

(360) 980-8524-Work
(360) 980-8549-Fax
www.cytodyn.com

Protocol Number: **CD15_COVID-19**

Protocol Title: A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab in Patients Experiencing Prolonged Coronavirus Disease 2019 (COVID-19) Symptoms [Long-Haulers]

Protocol Version / Date: Version 5.0 / 26 May 2021

SAP Author: [redacted]

Plan Version: SAP – Final Version 1.0

Plan Date: 11 Jun 2021

Protocol Number:	**CD15_COVID-19**
Protocol Version:	Version 5.0
Protocol Name:	A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab in Patients Experiencing Prolonged Coronavirus Disease 2019 (COVID-19) Symptoms [Long-Haulers]
Sponsor:	CytoDyn, Inc. 1111 Main Street, Suite 660 Vancouver, Washington 98660
Prepared by:	[redacted]
SAP Version:	Final Version 1.0
SAP Date:	11 Jun 2021

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

[redacted]

Jun 14, 2021
Date

Jun 11, 2021
Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Transaminase
ARDS	Acute Respiratory Distress Syndrome
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
CCR5	C-C chemokine receptor type 5
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
Cmax	Maximal Concentration
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
CV	Curriculum Vitae
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FDP	Finished Drug Product
FUV	Follow-up Visit
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IC	Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug

Abbreviation	Term
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reaction
ITT	Intent to Treat
IV	Intravenous
IWRS	Interactive Web Based Response System
LAR	Legally Authorized Representative
LTF	Lost to Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	Maximum Tolerated Dose
NEWS	National Early Warning Score 2
OBT	Optimized Background Therapy
PD	Pharmacodynamic
PK	Pharmacokinetic
PI	Principal Investigator
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SOP	Standard Operating Procedure
SpO2	Peripheral Capillary Oxygen Saturation
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
TNBC	Triple Negative Breast Cancer
Treg	T regulatory cell
VL	Viral Load

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol CD15_COVID-19, sponsored by CytoDyn Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objective of this plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

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

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

- Protocol Version 5.0 / 26 May 2021
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

2. PROTOCOL DESIGN AND OBJECTIVES

2.1 Study Objectives

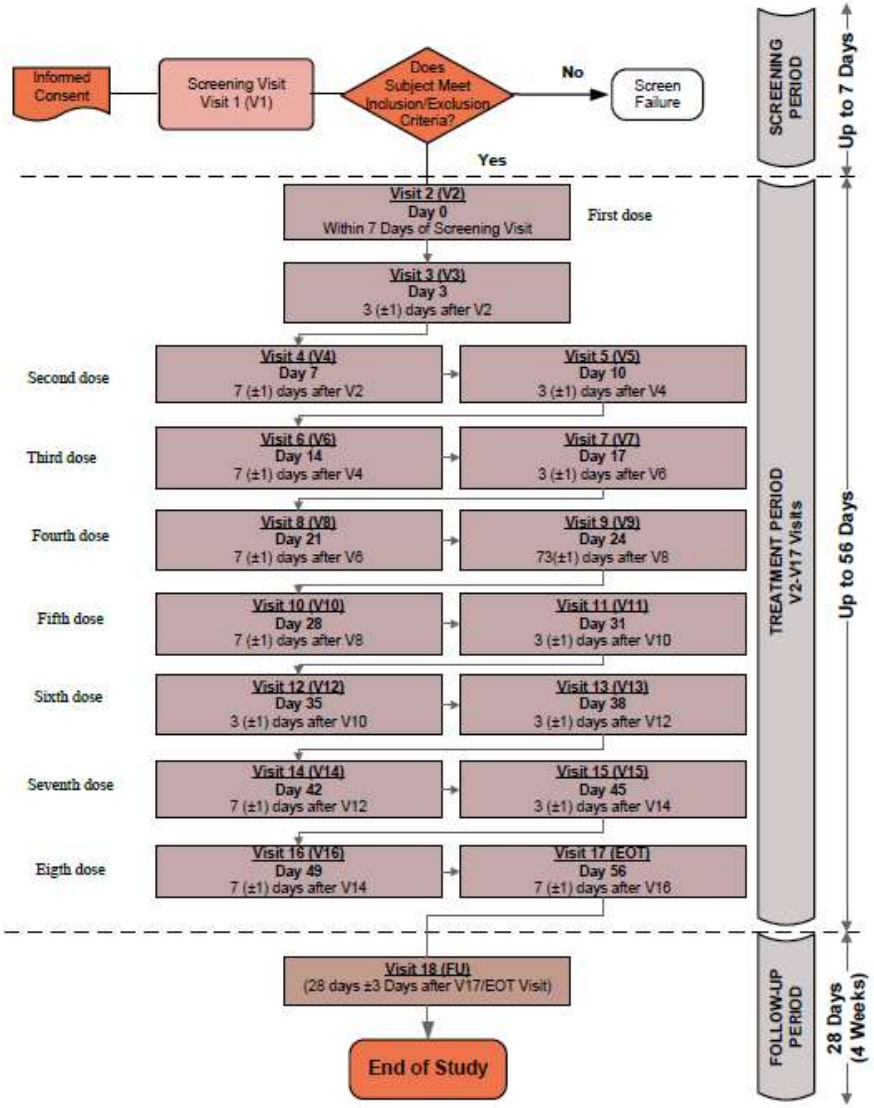
The purpose of this study is to assess the safety and efficacy of leronlimab (PRO 140) administered as weekly subcutaneous injection in subjects experiencing prolonged symptoms (> 12 weeks) of COVID-19.

2.2 Design Overview

This is a Phase 2, two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with prolonged symptoms caused

by COVID-19. Patients will be randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection. The study flow diagram is presented in Figure 2-1.

Figure 2-1: Study Schematic



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

Screening Period (up to 1 week):

Screening assessments will commence at Visit 1 (V1) after obtaining signed informed consent, and will include review of medical and medication history, eligibility evaluation, vital signs, pulse oxygen saturation, physical examination, electrocardiogram (ECG), clinical symptom score assessment, and laboratory sample collection for routine serum biochemical, hematologic, coagulation, urinalysis, and 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 (56 Days ± 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) days after V2
- Visit 4 (V4) [second treatment]: 7 (±1) days after V2
- Visit 5 (V5): 3 (±1) days after V4
- Visit 6 (V6) [third treatment]: 7 (±1) days after V4
- Visit 7 (V7): 3 (±1) days after V6
- Visit 8 (V8) [fourth treatment]: 7 (±1) days after V6
- Visit 9 (V9): 3 (±1) days after V8
- Visit 10 (V10) [fifth treatment]: 7 (±1) days after V8
- Visit 11 (V11): 3 (±1) days after V10
- Visit 12 (V12) [sixth treatment]: 7(±1) days after V10
- Visit 13 (V13): 3 (±1) days after V12
- Visit 14 (V14) [seventh treatment]: 7(±1) days after V12
- Visit 15 (V15): 3 (±1) days after V14
- Visit 16 (V16) [eight treatment]: 7(±1) days after V14
- Visit 17 (V17) / End of Treatment (EOT) Visit: 7 (±1) days after V16.

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, vital signs, pulse oxygen saturation, physical examination, PROMIS® Fatigue Scale, PROMIS® Cognitive Function, PROMIS® Sleep Disturbance, and blood sample collection for CD4+ and CD8+ T cell count and serum cytokine and chemokine levels.

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. Subjects will be given a diary to record all symptoms daily throughout the entire treatment period starting at baseline.

At V2, subjects will be randomized to receive leronlimab (PRO 140) or placebo which will be administered subcutaneously weekly at V2, V4, V6, V8, V10, V12, V14, and V16.

The following assessments will be performed at V4, V6, V8, V10, V12, V14, V16, and V17(EOT): vital signs, pulse oxygen saturation, physical examination, electrocardiogram (ECG (V17 only), PROMIS® Fatigue Scale, PROMIS® Cognitive Function- Short Form 4a, PROMIS® Sleep Disturbance – Short Form 4a, Global Health Assessment (V17 only), blood sample collection for routine serum biochemical, hematologic, coagulation and urine laboratory assessments (V10 and V17). CD4+ and CD8+ T cell count and serum cytokine and chemokine levels (V10 and V17), assessment for the requirement of hospitalization and patient compliance to daily diary completion will be checked by the site staff.

Additionally, telephone or video contact visits will be performed 3 days (±1 day) after each treatment administration visit. The requirement of hospitalization and patient compliance to daily diary completion will be checked during V3, V5, V7, V9, V11, V13, and V15 via telephone.

Adverse events and concomitant medications will be monitored throughout the study.

Follow Up Period (4 weeks after EOT± 3 days)

Follow-up visit (V18) will be performed 4 weeks after the End of Treatment (EOT) visit. The following assessments will be performed at V18: vital signs, physical examination, pulse oxygen saturation, blood sample collection for immunophenotypic biomarker analysis, assessment for the requirement of hospitalization, review of adverse events and concomitant medications.

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.

Table 2-1: Schedule of Assessments

Procedure/Assessments	Screening Visit	Treatment Phase																Follow-Up
Visit	V1	V2 [16]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 (EOT)	V18 (FU)
Day		Day 0	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21	Day 24	Day 28	Day 31	Day 35	Day 38	Day 42	Day 45	Day 49	Day 56	Day 84
Visit Type [17]	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic
Window Period		Within 7 days of the Screening Visit	3(±1) days after V2	7(±1) days after V2	3(±1) days after V4	7(±1) days after V4	3(±1) days after V6	7(±1) days after V6	3(±1) days after V8	7(±1) days after V8	3(±1) days after V10	7(±1) days after V10	3(±1) days after V12	7(±1) days after V12	3(±1) days after V14	7(±1) days after V14	7(±1) days after V16	28(±3) days after V17
Informed Consent [1]	X																	
Eligibility Evaluation [2]	X	X																
Subject Demographics	X																	
Medical History [3]	X																	
Vital Signs [5]	X	X		X		X		X		X		X		X		X	X	X
Pulse oxygen saturation (SpO2) [5]	X	X		X		X		X		X		X		X		X	X	X
Physical Examination	X	X		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]	X	X
ECG	X																X	
COVID-19 Related Symptom Assessment																		
Clinical Symptom Score Assessment [6]	X	X																
Patient Symptom Diary [7] - EVERYDAY		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Patient compliance to diary completion			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Questionnaires [8]																		
PROMIS® Fatigue Scale		X		X		X		X		X		X		X		X	X	
PROMIS® Cognitive Function-Short Form 4a		X		X		X		X		X		X		X		X	X	
PROMIS® Sleep Disturbance – Short Form 4a		X		X		X		X		X		X		X		X	X	
Global Health Assessment Questionnaire																	X	
Laboratory tests:																		

Procedure/Assessments	Screening Visit	Treatment Phase																Follow-Up
Visit	V1	V2 [16]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 (EOT)	V18 (FU)
Day		Day 0	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21	Day 24	Day 28	Day 31	Day 35	Day 38	Day 42	Day 45	Day 49	Day 56	Day 84
Visit Type [17]	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Clinic	Clinic
Window Period		Within 7 days of the Screening Visit	3(±1) days after V2	7(±1) days after V2	3(±1) days after V4	7(±1) days after V4	3(±1) days after V6	7(±1) days after V6	3(±1) days after V8	7(±1) days after V8	3(±1) days after V10	7(±1) days after V10	3(±1) days after V12	7(±1) days after V12	3(±1) days after V14	7(±1) days after V14	7(±1) days after V16	28(±3) days after V17
Complete Blood Count [9]	X									X							X	
Biochemistry [10]	X									X							X	
Coagulation Indices [11]	X									X							X	
Urine Pregnancy Test [12]	X	X								X							X	
Urinalysis [13]	X									X							X	
CD4+ and CD8+ T cell count		X								X							X	
Serum cytokine and chemokine levels [14]		X								X							X	
CCR5 Receptor Occupancy		X								X							X	
Immunophenotypic Biomarker Analysis		X								X							X	
Randomization [15]		X																
PRO 140 (700 mg) or Placebo Administration		X		X		X		X		X		X		X		X		
Assessment for Requirement of Hospitalization			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	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] Pre-treatment and post-treatment vital signs and SpO2 will be recorded at V2. Post-treatment vital signs and SpO2 will be recorded at V4, V6, V8, V10, V12, V14, and V16. Vital Signs will include blood pressure, heart rate, respiration rate, temperature, weight, and height. (Note: Height will be measured only at V1).

[6] Symptom Score will be assessed for patient eligibility based on symptom score for following symptoms consistent with COVID-19 as a result of confirmed SARS-CoV-2 infection for a prolonged period of time (>12 weeks) (Total Clinical Symptom Score of ≥6 with at least two symptoms of moderate or higher severity at the time of Screening (at V1) and prior to Randomization (at V2)

[7] Patients will be asked to complete a daily diary during the treatment phase to record symptoms.

[8] All three questionnaires, PROMIS® Fatigue Scale, PROMIS® Cognitive Function, and PROMIS® Sleep Disturbance will be evaluated before study drug administration. .

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

[10] Biochemistry

Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, Lactate dehydrogenase (LDH)
Renal function indicators: Serum creatinine, eGFR
Electrolytes: sodium, potassium, chloride, calcium and bicarbonate
Other: glucose (random), cholesterol (total), Creatine kinase, C-reactive protein, Serum ferritin

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

[12] ONLY performed on women of childbearing potential.

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

[14] Refer to Table 7-1 for details.

[15] Randomization via WebView CTMS system

[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] Visits listed as clinic will take place at the study center. The remaining visits are to be conducted as telephone or video contact visits.

2.3 Study Duration

A subject will be in this trial at maximum of around 91 Days.

- **Screening Period** (Screening to Baseline): Up to 7 days (1 Week)
- **Treatment Period:** 56 Days
- **Follow-up Phase:** 28 Days (4 weeks)

2.4 Study Treatments

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

Table 2-2: Treatment Groups

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

2.5 Randomization

This is a multi-center randomized clinical trial. Subjects will be randomized 1:1 to the leronlimab group and placebo group. Symptom duration (defined as time from first reported symptom onset to the time of randomization) will be used as a stratification factor to ensure balance between each treatment group in this stratum. An individual, independent of the clinical trial team, will develop the randomization schedules. The actual randomization assignment will be made through an Interactive Web Based Response System (IWRS) called WebView®. Subjects who have provided written informed consent and have met all the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment groups.

2.6 Stratification

Randomization will be stratified into one of the two categories based on symptom duration (defined as time from first reported symptom onset to the time of randomization):

- Symptom duration >=12 weeks and <= 24 weeks
- Symptom duration > 24 weeks

2.7 Blinding

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

The [redacted] Information Technology department will be unblinded to treatment. As noted above, the

[redacted] Technology department is not otherwise involved with the study.

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

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

2.8 Time to Unblinding

2.8.1 Emergency Unblinding

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

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

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

2.8.2 Final Analysis

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

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoint is:

- Changes from baseline in daily COVID-19-related symptom severity score through Day 56
  Note: A set of common COVID-19-related symptoms (see patient diary template) will be evaluated daily by the patient regardless of which symptoms a subject had at baseline, as new symptoms may appear following the baseline assessment.

3.2 Secondary Endpoints

The secondary endpoints for the study are:

- Duration of COVID-19 associated symptoms from start of study treatment (Day 0) based on self-assessment using daily symptom diary

  Duration is defined as number of days when any symptoms scored as

  - *2 or 3 at baseline are still scored as 2 or 3 (i.e., not 0 or 1) through Day 56, or*
  - *1 or 0 at study entry are scored as 1 or worse (i.e., not 0) through Day 56.*
- Number of symptom-free days of COVID-19 associated symptoms that were present at the start of study treatment (Day 0) based on self-assessment using daily symptom diary
  Symptom-free days are defined as number of days when any symptoms scored as 1, 2 or 3 at baseline are still scored as 0 through Day 56 .
- Progression (or worsening) of COVID-19-associated symptoms through Day 56 compared to baseline

  Progression or symptom worsening is defined as number of days when any symptoms scored as

  - *2 at baseline are still scored as 3 through Day 56, or*
  - *1 at baseline are still scored as 2 or 3 through Day 56, or*
  - *0 at study entry are scored as worse (i.e., not 0) through Day 56.*
- Change from baseline in PROMIS® Fatigue Score at Days 28 and 56
- Change from baseline in PROMIS® Cognitive Function Score at Days 28 and 56
- Change from baseline in PROMIS® Sleep Disturbance Score at Days 28 and 56
- Incidence of hospitalization during the treatment phase
- Duration (days) of hospitalization during the treatment phase

3.3 Exploratory Endpoints

- Change from baseline in pulse oxygen saturation (SpO2) at Day 7, 14, 21, 28, 35, 42, 49, and 56

- Change from baseline in serum cytokine and chemokine levels on Days 28 and 56
- Change from baseline in CD4+ and CD8+ T cell count on Days 28 and 56
- Change from baseline in Transgrowth factor beta 1 (TGF beta1) on Days 28 and 56
- Change from baseline in CRP on Days 28 and 56
- Change from baseline in CCR5 receptor occupancy on Days 28 and 56.
- To explore biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of leronlimab.
- Evaluation of Global Health Assessment at Day 56

3.4 Safety Measures

Safety will be assessed using:

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

4. SAMPLE SIZE DETERMINATION AND RATIONALE

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

A total of 50 subjects will be randomized in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this exploratory study.

5. INTERIM ANALYSIS

There will be no interim analysis performed in this study.

6. ANALYSIS POPULATIONS

6.1 Modified 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 study treatment (leronlimab or placebo). This population will be used as

the primary analysis population for analysis of the primary and secondary efficacy endpoints..

6.2 PP Population

The **Per Protocol (PP) population** is defined as the set of subjects who meet the mITT Population requirements and are not associated with any major protocol violations. This population will be identified before the database lock. This population will be used as the supportive analysis population for analysis of the primary and secondary efficacy endpoints.

6.3 Safety Population

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

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before the randomized treatment.

7.2 Duplicate Data

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

7.3 Handling of Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized to minimize missing data. Missing data will not be imputed.

7.4 Multiple Comparisons and Type I Error Rate Multiplicity adjustments

There will be no adjustment for multiple testing or multiplicity for this phase II trial. For all effectiveness endpoints, inference will be based on type I error rate of 0.05.

7.5 Covariates and Prognostic Factors

In the efficacy analysis, the stratification factors and baseline values will be used as covariates in the analysis of all the primary, secondary, and explorartory endpoints.

7.6 Subgroups

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

- Symptom duration >=12 weeks and <= 24 weeks
- Symptom duration > 24 weeks

Additional exploratory subgroup analysis may be conducted using the baseline clinical characteristics (such as COVID-19 vaccination status) and laboratory parameters.

7.7 Standard Calculations

7.7.1 Age

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

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

7.7.2 Body Mass Index (BMI)

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

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

7.7.3 Change from Baseline

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

Change from baseline = Post Baseline Measurement – Baseline Measurement

7.7.4 Censoring rule for subjects with outcome of Death

For analyses of duration of hospitalization, all deaths within 56 days will be considered censored at Day 56. Conceptually, a death corresponds to an infinite length of stay support but censoring at any time greater than or equal to Day 56 gives the same answer as censoring at Day 56; both correspond to giving deaths the worst rank.

8. STATISTICAL METHODS

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

8.1 Summarizing and Tabulating the Collected Data

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

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

8.1.1 Subject Disposition and Withdrawals

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

8.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major before un-blinding.

Protocol deviations for all randomized subjects will be listed as by-subject listing and major deviations will be summarized descriptively according to the following categories:

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

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Race, Gender , Tobacco use history etc.) will be summarized using appropriate descriptive statistics.

Medical history of the subjects will be provided as a by-subject listing.

8.1.4 Prior and Concomitant Medications

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

8.1.5 Treatment Exposure

All data from administration of study drug will be presented.

In addition, extent of exposure will be summarized using total number of injections received during the treatment phase for all subjects, including n, median, mean, SD, min, max. The duration (days) of exposure from the treatment start date to the treatment end date will be summarized.

8.2 Analysis of Efficacy Data

The primary analysis will be conducted on the mITT population. The PP population will be used as the supportive analysis population for analysis of the primary and secondary efficacy endpoints.

8.2.1 *Primary Efficacy Endpoint*

The primary endpoint for the study is changes from baseline in daily COVID-19-related symptom severity score through day 56.

Daily COVID-19 related symptom score is the sum of score from Assessment of COVID-19-related symptoms.

For this endpoint, proportions of subjects in each category will be summarized and compared using proportional odds model, adjusting for baseline COVID-19 related symptom score and stratification factors. Odds Ratio estimates and 95% Confidence Interval will also be calculated.

8.2.2 *Secondary Efficacy Endpoint*

8.2.2.1 Duration of COVID-19 associated symptoms from start of study treatment (Day 0) based on self-assessment using daily symptom diary.

Duration is defined as number of days when any symptoms scored as

- 2 or 3 at baseline are still scored as 2 or 3 (i.e., not 0 or 1) through Day 56, or
- 1 or 0 at study entry are scored as 1 or worse (i.e., not 0) through Day 56.

The duration (days) of COVID-19 associated symptoms will be compared between the treatment groups using the a non-parametric method or a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data.

8.2.2.2 Number of symptom-free days of COVID-19 associated symptoms that were present at the start of study treatment (Day 0) based on self-assessment using daily symptom diary.

Symptom-free days are defined as number of days when any symptoms scored as 1, 2 or 3 at baseline are still scored as 0 through Day 56 .

The number of symptom-free days of COVID-19 associated symptoms will be compared between the treatment groups. Similar analysis methods used for the section 8.2.2.1 will be applied to analyze the data from this endpoint.

8.2.2.3 Progression (or worsening) of COVID-19-associated symptoms through Day 56 compared to baseline.

Progression or symptom worsening is defined as number of days when any symptoms scored as

- 2 at baseline are still scored as 3 through Day 56, or
- 1 at baseline are still scored as 2 or 3 through Day 56, or
- 0 at study entry are scored as worse (i.e., not 0) through Day 56.

The progression (or worsening) of COVID-19-associated symptoms will be compared between the

treatment groups.. Similar analysis methods used for section 8.2.2.1 will be applied to analyze the data from this endpoint.

8.2.2.4 Change from baseline in PROMIS® Fatigue Score at Days 28 and 56.

The change from baseline in PROMIS® Fatigue Score will be compared between the treatment groups will be presented and summarized descriptively by treatment group using ANCOVA adjusting for stratification factors. If the data is not normally distributed, a non-parametric method or a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

8.2.2.5 Change from baseline in PROMIS® Cognitive Function Score at Days 28 and 56.

The change from baseline in PROMIS® Cognitive Score will be compared between the treatment groups. Similar analysis methods used for section 8.2.2.4 will be applied to analyze the data from this endpoint.

8.2.2.6 Change from baseline in PROMIS® Sleep Disturbance Score at Days 28 and 56.

The change from baseline in PROMIS® Sleep Score will be compared between the treatment groups.. Similar analysis methods used for section 8.2.2.4 will be applied to analyze the data from this endpoint.

8.2.2.7 Incidence of hospitalization during the treatment phase

The Incidence of hospitalization will be compared between the treatment groups. Similar analysis methods used for section 8.2.2.1 will be applied to analyze the data from this endpoint.

8.2.2.8 Duration (days) of hospitalization during the treatment phase

The duration of hospitalization will be compared between the treatment groups. Similar analysis methods used for section 8.2.2.1 will be applied to analyze the data from this endpoint.

8.2.3 *Exploratory Endpoints*

- Change from baseline in pulse oxygen saturation (SpO2) at Day 7, 14, 21, 28, 35, 42, 49, and 56

The Change from baseline in pulse oxygen saturation (SpO2) will be presented and summarized descriptively by treatment group using similar analysis methods used for section 8.2.2.4.

- Change from baseline in serum cytokine and chemokine levels on Days 28 and 56

The Change from baseline in serum cytokine and chemokine levels will be presented and summarized descriptively by treatment group compared using using similar analysis methods used for section 8.2.2.4.

- Change from baseline in CD4+ and CD8+ T cell count on Days 28 and 56

The Change from baseline in CD4+ and CD8+ T cell count will be presented and summarized

descriptively by treatment group compared using similar analysis methods used for section 8.2.2.4.

- Change from baseline in Transgrowth factor beta 1 (TGF beta1) on Days 28 and 56

The Change from baseline in Transgrowth factor beta 1 (TGF beta1) will be presented and summarized descriptively by treatment group compared using using similar analysis methods used for section 8.2.2.4.

- Change from baseline in CRP on Days 28 and 56

The Change from baseline in CRP will be presented and summarized descriptively by treatment group compared using similar analysis methods used for section 8.2.2.4.

- Change from baseline in CCR5 receptor occupancy on Days 28 and 56.

The Change from baseline in CCR5 will be presented and summarized descriptively by treatment group compared using similar analysis methods used for section 8.2.2.4.

- To explore biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of leronlimab.

Biomarkers that may predict and/or act as pharmacodynamic indicators of pharmacologic activity of leronlimab will be explored.

- Evaluation of Global Health Assessment at Day 56.

The change from baseline in Global Health Assessment will be compared between the treatment groups. Similar analysis methods used for section 8.2.2.4 will be applied to analyze the data from this endpoint.

8.3 Analysis of Safety Data

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

8.3.1 *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, unlikely 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.

8.3.2 *Clinical Laboratory Evaluations*

All available results of the clinical laboratory evaluations will be listed and/or summarized. Laboratory evaluations include hematology, biochemistry, serology and urinalysis.

Laboratory data will be classified into grades according to DAIDS toxicity grading. A severity grade of 0 will be assigned when the value is within normal limits.

The following summaries will be produced for the hematology and biochemistry laboratory data (by laboratory parameter):

- Number and percentage of patients with worst post-baseline grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline
- Shift tables using DAIDS grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with DAIDS grades
- Shift tables using normal range to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters without DAIDS grades

8.3.3 *Vital Signs*

Vital sign assessments are performed in order to characterize basic body function. The parameters collected in this study are: systolic BP (mmHg), diastolic BP (mmHg), temperature (^{0}C), heart rate (bpm), respiratory rate (rpm), pulse oxygen.

8.3.3.1 Clinically notable elevated values

- Systolic BP: ≥ 160 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: ≥ 39.1°C
- Heart rate: ≥ 120 bpm with increase from baseline of ≥15 bpm
- Respiration rate: ≥ 24 breaths per minute with increase from baseline of ≥ 6 breaths per minute

8.3.3.2 Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline

- Body temperature: ≤ 35°C
- Heart rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
- Respiration rate: < 8 breaths per minute with decrease from baseline of ≥ 6 breaths per minute
- Oxygen Saturation: < 94%

Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e. both elevated and below normal values) will be summarized for heart rate, diastolic BP and systolic BP by treatment group.

8.3.4 *Electrocardiogram (ECGs)*

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

The number and percentage of patients having notable ECG interval values and newly occurring qualitative ECG abnormalities will be summarized by treatment group.

The following notable ECG interval values for each parameter will be presented as by-subject listing. Number and percentage of subjects with at least one occurrence of the below notable ECG changes will be summarized.

QT and QTc:

(1) New >450 msec

(2) New >480 msec

(3) New >500 msec

(4) Increase from baseline >30 msec

(5) Increase from baseline >60 msec

Shift tables will also be presented for the categories of QT results (<=450, >450-480, >480-500, >500) with counts and percentages of subjects, for shift (change) from baseline.

PR:

(1) An increase >25% from baseline and PR >200 msec at any post-baseline assessment

QRS:

(1) An increase >25% from baseline and QRS >110 msec at any post-baseline assessment

Ventricular rate :

(1) A decrease >25% from baseline and HR <50 bpm at any post-baseline assessment

(2) An increase >25% from baseline and HR >100 bpm at any post-baseline assessment

In addition, individual subject changes will be identified through shift tables. Shift tables will be

presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, for shift (change) from baseline.

8.3.5 *Physical Examination*

All abnormal physical examination finds will be listed.

8.3.6 Urine Pregnancy Test

All data from Urine Pregnancy test will be presented as a by-subject listing.

8.3.7 Pregnancy

All data from Outcome Description Form – Pregnancy and Notification form – pregnancy will be presented as a by-subject listing.

8.3.8 Leading Questions

All data from Leading Questions will be presented as a by-subject listing.

8.3.9 Covid-19 diagonsis

All data from covid 19 diagnosis will be presented as a by-subject listing.

9. APPENDIX – PLANNED TLG

9.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)
ELIGIBILTY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)
EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)
DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)
TREATMENT ADMINISTRATION LISTINGS (LISTINGS 16.2.5.X)
EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)
ADVERSE EVENT DATA (LISTINGS 16.2.7.X)
SAFETY DATA (LISTINGS 16.2.8.X)

9.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS
POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS
CONCOMITANT MEDICATION USAGE
EFFICACY SUMMARIES
SAFETY SUMMARIES
- ADVERSE EVENT SUMMARIES
- SERIOUS ADVERSE EVENTS
- LABORATORY
- VITAL SIGNS
- PE
- ECG
- OTHER SAFETY

10. VERSION HISTORY

This is the first version of the SAP.

11. REFERENCES

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

Signature: xuan shao

Electronically signed by: xuan shao
Reason: I have reviewed this document
Date: Jun 14, 2021 08:33 EDT

Email: xuans@amarexcro.com

RESEARCH SUBJECT INFORMATION AND CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

TITLE:	A Phase 2, Two-Part Study (8-Week, Randomized, Double Blind, Placebo Controlled Period Followed by a 4-Week, Open-Label Extension Period) to Evaluate the Efficacy and Safety of Leronlimab in Patients Experiencing Prolonged Coronavirus Disease 2019 (COVID-19) Symptoms [Long-Haulers]
PROTOCOL NO.:	CD15_COVID-19 IRB Protocol #20210354
SPONSOR:	CytoDyn, Inc.
INVESTIGATOR:	Name Address City, State Zip Country
STUDY RELATED PHONE NUMBER(S):	Phone Number Phone Number (24 hours) [24-hour number is required]

This consent form contains important information to help you decide whether to participate in a research study.

The study staff will explain this study to you. Ask questions about anything that is not clear at any time. You may take home an unsigned copy of this consent form to think about and discuss with family or friends.

- **Being in this study is voluntary – <u>your choice</u>.**
- **If you join this study, you can still <u>stop at any time</u>.**
- **No one can <u>promise</u> that a study will help you.**
- **Do not join this study unless all of your <u>questions</u> are <u>answered</u>.**

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the study;
- Any possible benefits to you;
- The possible risks to you;

- Other options you could choose instead of being in this study;
- How your personal health information will be treated during the study and after the study is over;
- Whether being in this study could involve any cost to you; and
- What to do if you have problems or questions about this study.

Please read this consent form carefully.

INTRODUCTION

You are being invited to take part in a clinical research study because you have been diagnosed with Coronavirus Disease 2019, known as COVID-19, and are experiencing prolonged symptoms of the disease. This research study is using an investigational drug as a possible treatment for this diagnosis.

The name of the investigational study drug involved in this study is:

- Leronlimab (PRO 140). It belongs to a class (group) of drugs called C-C Chemokine Receptor Type-5 (CCR5) antagonists.

For purposes of this research, you will be referred to as a "participant".

CytoDyn, Inc., a pharmaceutical company is supporting this research study by providing funding for this research study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

Before you decide to take part in this study, it is important for you to understand why the research is being done and what it will involve.

WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase 2 clinical trial. Phase 2 clinical trials test the safety and effectiveness of an investigational drug to learn whether the drug works in treating a specific disease.

Your study doctor and medical team are conducting a research study with CytoDyn, Inc. This study will help determine the safety and efficacy of Leronlimab (PRO 140) in the treatment of prolonged symptoms of coronavirus disease 2019 (COVID-19).

The safety of Leronlimab (PRO 140) has been previously evaluated in over 750 people in previous studies. The product you will be using is an investigational drug. "Investigational" means that the drug is being studied. The FDA (the U.S. Food and Drug Administration) has not approved this drug, Leronlimab (PRO 140) as a treatment for any disease. The results of these studies will be used to design future studies to improve treatment of patients suffering from COVID-19.

In Part 1 of this study, subjects will be randomly assigned (by chance, like drawing straws) to receive weekly doses of Leronlimab (PRO 140) or placebo. You have a 1 in 2 chance (50%) of receiving the study drug and 1 in 2 chance (50%) of receiving the placebo. Neither you nor the study doctor will know which one you will receive. This information can be made available in case of an emergency.

During the study, you will be asked to discontinue use of any of the following medications:

- Hydroxychloroquine, oral or parenteral corticosteroids, immunosuppressants, or immunomodulating agents
- Albuterol as nebulizer for treatment of COVID-19
- Other CCR5 antagonists
- Other investigational products (medications prescribed through another clinical study)

About 50 subjects will enroll in the study across up to 5 centers within the USA.

HOW DOES Leronlimab (PRO 140) WORK?

Leronlimab (PRO 140) belongs to the monoclonal antibody class of medicines. Monoclonal antibodies are synthetic versions of the disease-fighting proteins (antibodies) that are naturally produced by the body. Antibodies that are normally circulating in the blood typically react to any foreign organisms or materials (bacteria, viruses, etc.) that enter our body. However, Leronlimab (PRO 140) binds to a protein (CCR5) that is present on the surface of one kind of our blood cells. By doing so, it is hoped that it reduces the bad inflammation results from infection with the coronavirus, and thus might be useful in the treatment of COVID-19.

In the disease COVID-19, the body may respond to the viral infection by overproducing immune cells and their signaling molecules in a dangerous phenomenon called cytokine storm, which is often associated with a surge of activated immune cells in the body.

Leronlimab (PRO 140) does not kill the novel coronavirus. Based on in vitro data, it is our hypothesis that Leronlimab acts by blocking pro-inflammatory cytokines, which prevents cytokine storm and thus could be useful in treatment of COVID-19 symptoms.

A small Phase II study of 86 patients with mild to moderate coronavirus disease 2019 (COVID-19) did not meet its study goal to demonstrate difference between Leronlimab and placebo.

However, some additional analyses of the data indicated a possibility of benefit in more severe patients. Safety results showed no new safety risk was identified in patients receiving Leronlimab.

This document uses words such as treatment, drug, medication, and patient. Please remember this is a research study and the use of these terms does not mean the use of the Leronlimab (PRO 140) has been found to be safe or effective for your condition.

WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. You will always be free to withdraw from the study at any time. If you withdraw during the study, you will be asked to come in for a final visit for study evaluations. You do not have to give a reason for your withdrawal from the study. This will not affect the standard of care that you will receive, and it will not result in any penalty or loss of benefits to which you are entitled. The data collected up to that point will be kept with your medical records and will be kept confidential. Your identity will not be disclosed.

Instead of being in this research study, you have other options which may include the following:

- Hydroxychloroquine or chloroquine with or without azithromycin, Veklury (remdesivir), Dexamethasone (or other corticosteroids), monoclonal antibodies (such as bamlanivimab, casirivimab, imdevimab), immunomodulatory agents (such as baricitinib, sarilumab, clazakizumab, tocilizumab, anakinra), or Convalescent plasma therapy.
- Other standard supportive care to help relieve symptoms
- Taking part in another research study being explored for COVID-19 treatment

Please talk to the research doctor about your options and their risks and benefits before you decide whether you will take part in this research study.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

There are two parts to this study. If you sign this consent form, you will take part in the first part. At the end of the first part, you will then have the option to continue into the second part of the study.

IN THE FIRST PART OF THE STUDY:

- You will take once weekly dose of 700 mg Leronlimab (PRO 140) or placebo for eight weeks, for a total of eight doses.
- Leronlimab (PRO 140) or placebo will be injected via a very thin needle slightly below the surface of your skin in your stomach, by the research staff or visiting nurse. You will receive two injections (of 2 mL) on opposite sides of your abdomen every week for eight weeks.

- Your participation involves 3 periods:
    - Screening phase will take up to 1 week and will include one visit to the study clinic.
    - Treatment phase will last for eight weeks and include eight visits to the study clinic, when you will receive treatment with Leronlimab (PRO 140), as well as telephone or video "visits" in between treatment administration visits. The final visit during the treatment phase will take place one week after the final treatment administration and will be at the study clinic. There will be a total of sixteen "visits" during the treatment phase.
    - Follow-up phase is applicable only if you decide not to continue into Part 2 of the study, and will last for four weeks. The follow-up phase includes one visit to the study clinic, four weeks after the last visit in the treatment phase.
- In total, the expected Part 1 duration is 91 days (13 weeks).
- At visits conducted at the study clinic, you and the study staff will be provided the appropriate protective gear (e.g., masks, gloves) to prevent the spread of the infection.
- Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Screening Period (before the research starts):
During this part of the study you will be evaluated to determine if you would be eligible to enter the study. The screening period may last up to seven days (1 week).

After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can participate in the research study. If you have had some of these tests or procedures recently, they may not have to be repeated.

Screening Visit
After signing this consent form, the following procedures will be done at the screening visit:

- You will be asked a number of general questions about your age, race, ethnicity, your medical and surgical history, including any illnesses or health problems, and your prior or current medications.
- Your study doctor will give you a Physical Exam.
- Your height, weight, heart rate, body temperature, blood pressure, and breathing rate will also be assessed.
- Your study doctor will assess your COVID-19 clinical symptom score.
- Your doctor will perform a test (pulse oximetry) to measure your blood oxygen level
- Your study doctor will perform an ECG (electrocardiogram – a test to check your heart).
- A series of blood tests will be performed. The amount of blood needed for these tests is about 3-4 teaspoons.

  - A blood test for general health screening, such as chemistry, complete blood count and coagulation.
- If you are a female and able to become pregnant, a pregnancy test will be required. If the pregnancy test is positive, you will not be able to be in the study.
- A urine sample will be needed for lab tests.

Note that all of the procedures listed above may not be done if at any point during the evaluation, you fail eligibility. If you are not eligible for the study, your study doctor will explain the reasons and arrange for your prescribed standard care to continue.

Within this 1-week period, you will be informed if you are eligible to enter the study. If Visit 2 takes place on the same day as the Screening Visit, scheduled assessments performed under screening visit (V1) do not need to be repeated.

Treatment Period

Visit 2 (Day 0)
The treatment will start within 1 week of the Screening Visit.

Before you receive any study treatment, your study doctor will reconfirm your study eligibility by completing the following procedures:

- Your heart rate, breathing rate, body temperature, and blood pressure will be assessed.
- Your study doctor will measure your weight and give you a physical exam.
- Your study doctor will assess your COVID-19 clinical symptom score to confirm your eligibility for participation in the study.
- Your study doctor will ask a series of questions related to your fatigue and energy level.
- Your study doctor will ask a series of questions related to your concentration and ability to perform tasks requiring thinking.
- Your study doctor will ask a series of questions related to sleep quality.
- Your doctor will perform a test (pulse oximetry) to measure your blood oxygen level.
- A blood test to check the levels of immune cells (CD4/CD8 T cells), certain proteins and substances (cytokines and chemokines) in your blood cells, as well as to check the levels of CCR5 receptors and other biomarkers, will be performed. The amount of blood needed for these tests is about 6 teaspoons.
- If you are a female and able to become pregnant, a urine pregnancy test will be required. If the pregnancy test is positive, you will not be able to be in the study.
- You will be randomly assigned (by chance) to one of the two study treatment groups. The study treatment assignment will be in a 1:1 ratio to one of the following:
  - Leronlimab (PRO 140), 700mg; Or
  - Placebo

Neither you nor the study doctor will know which one you will receive. This information can be made available in case of an emergency. You will be asked to report any symptoms that you experienced.

Once all of the above assessments have been completed, your study doctor will perform for the following procedures:

- You will receive your treatment injections of Leronlimab (PRO 140) or placebo. Leronlimab (PRO 140) or Placebo will be given under your skin as two 2mL shots on opposite sides of the stomach.
- Your essential body functions like heart rate, body temperature, breathing rate, and blood pressure will be recorded. Your weight will also be measured.
- Your doctor will perform a test (pulse oximetry) to measure your blood oxygen level. You will be asked about your past or current medications.
- You will be asked to report any unfavorable signs or symptoms that you experienced.
- You will be given a diary to record all symptoms daily throughout the entire treatment phase (56 days).

<u>Visits 3, 5, 7, 9, 11, 13, and 15 (Days 3, 10, 17, 24, 31, 38, and 45)</u>
The following assessments will be performed via telephone at Visits 3, 5, 7, 9, 11, 13, and 15:

- You will be asked if you have been using your diary to record all symptoms since your last visit.
- You will be asked if there have been any hospital or ER visits since the last study visit.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.

<u>Visits 4, 6, 8, 10, 12, 14, and 16 (Days 7, 14, 21, 28, 35, 42, and 49)</u>
The following assessments will be performed at the clinic at Visits 4, 6, 8, 10, 12, 14, and 16:

- Your study doctor will give you a physical exam based on symptoms you have experienced.
- Your weight, heart rate, body temperature, blood pressure, and breathing rate will also be assessed.
- You doctor will perform a test (pulse oximetry) to measure your blood oxygen level
- You will be asked whether you have used your diary to record all symptoms you have experienced since the last visit.
- Your study doctor will ask a series of questions related to your fatigue and energy level.
- Your study doctor will ask a series of questions related to your concentration and ability to perform tasks requiring thinking.
- Your study doctor will ask a series of questions related to sleep quality.
- You will receive your treatment injections of Leronlimab (PRO 140) or placebo.

- You will be asked if there have been any hospital or ER visits since the last study visit.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.
- **At Visit 10 only**, a series of blood and urine tests will be performed. The amount of blood needed for these tests is about 8 teaspoons.

    - A blood test for general health screening, such as chemistry, complete blood count and coagulation
    - A blood test to check the levels of immune cells (CD4/CD8 T cells) and certain proteins and substances (cytokines and chemokines), as well as to check the levels of CCR5 receptors and other biomarkers.
    - A urine sample will be needed for lab tests
    - If you are a female and able to become pregnant, a urine pregnancy test will be required. If the pregnancy test is positive, you will not be able to be in the study.

Visit 17, End of Treatment (Day 56)
One week after your last treatment, you will be asked to visit the clinic for the end of treatment (EOT) visit during which the following assessments will be performed:

- Your study doctor will give you a physical exam.
- Your weight, heart rate, body temperature, blood pressure, and breathing rate will also be assessed.
- You doctor will perform a test (pulse oximetry) to measure your blood oxygen level.
- Your study doctor will perform an ECG (electrocardiogram – a test to check your heart).
- You will be asked whether you have used your diary to record all symptoms you have experienced since the last visit.
- Your study doctor will ask a series of questions related to your fatigue and energy level.
- Your study doctor will ask a series of questions related to your concentration and ability to perform tasks requiring thinking.
- Your study doctor will ask a series of questions related to sleep quality.
- A series of blood and urine tests will be performed. The amount of blood needed for these tests is about 8 teaspoons.
    - A blood test for general health screening, such as chemistry, complete blood count and coagulation.
    - A blood test to check the levels of immune cells (CD4/CD8 T cells), certain proteins and substances (cytokines and chemokines) made by a kind of your blood cells, as well as to check the levels of CCR5 receptors and other biomarkers.
    - A urine sample will be needed for lab tests
- If you are a female and able to become pregnant, a urine pregnancy test will be required. If the pregnancy test is positive, you will not be able to be in the study.
- You will be asked if there have been any hospital or ER visits since the last study visit.

- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.

Follow-Up Period (only if you decide NOT to continue into Part 2)

Follow-up Visit (Day 84)
The follow-up period will last up to four weeks and include one visit. The following assessments will be performed at the follow-up visit:

- Your heart rate, body temperature, blood pressure, breathing rate, and weight will also be assessed.
- You doctor will perform a test (pulse oximetry) to measure your blood oxygen level.
- Your study doctor will give you a physical exam.
- Your study doctor will assess your clinical status based on your hospitalization status.
- A blood test for general health screening, to check the levels of immune cells (CD4/CD8 T cells) and certain proteins and substances (cytokines and chemokines) in your blood cells, as well as to check the levels of CCR5 receptors and other biomarkers.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any symptoms that you experienced.

Unscheduled Visits
In the event that you come to the 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 study doctor.

IF YOU DECIDE TO CONTINUE TO THE SECOND PART OF THE STUDY:

- You will take once weekly dose of 350 mg Leronlimab (PRO 140) for four weeks, for a total of four doses, regardless of whether you were assigned to leronlimab (PRO 140) or placebo in Part 1.
- Leronlimab (PRO 140) will be injected via a very thin needle slightly below the surface of your skin in your stomach, by the research staff or visiting nurse. You will receive one injection (of 2 mL) every week for four weeks.
- Your participation involves 2 periods:
    - Treatment phase will last for four weeks and include four visits to the study clinic, when you will receive treatment with Leronlimab (PRO 140), as well as telephone or video “visits” in between treatment administration visits. The final visit during the treatment phase will take place one week after the final treatment administration and will be at the study clinic. There will be a total of eight “visits” during the treatment phase.

  - Follow-up phase will last for four weeks. The follow-up phase includes one visit to the study clinic, four weeks after the last visit in the treatment phase.
- In total, the expected duration of Part 2 is 56 days.
- At visits conducted at the study clinic, you and the study staff will be provided the appropriate protective gear (e.g., masks, gloves) to prevent the spread of the infection.
- Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Visit 17 (Day 56)

- Your study doctor will give you a physical exam based on symptoms you have experienced.
- Your weight, heart rate, body temperature, blood pressure, and breathing rate will also be assessed.
- Your doctor will perform a test (pulse oximetry) to measure your blood oxygen level
- Your doctor will assess your COVID-19 clinical symptom score.
- You will be asked whether you have used your diary to record all symptoms you have experienced since the last visit.
- Your study doctor will ask a series of questions related to your fatigue and energy level.
- Your study doctor will ask a series of questions related to your concentration and ability to perform tasks requiring thinking.
- Your study doctor will ask a series of questions related to sleep quality.
- You will receive your treatment injection of Leronlimab (PRO 140).
- You will be asked if there have been any hospital or ER visits since the last study visit.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.
- A blood test for general health screening, such as chemistry, complete blood count and coagulation
- A blood test to check the levels of immune cells (CD4/CD8 T cells) and certain proteins and substances (cytokines and chemokines), as well as to check the levels of CCR5 receptors and other biomarkers will be performed.
- A urine sample will be needed for lab tests
- If you are a female and able to become pregnant, a urine pregnancy test will be required. If the pregnancy test is positive, you will not be able to be in the study.

Visits 18, 20, and 22 (Days 59, 66, and 73)
The following assessments will be performed via telephone at Visits 18, 20, and 22:

- You will be asked if you have been using your diary to record all symptoms since your last visit.

- You will be asked if there have been any hospital or ER visits since the last study visit.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.

Visits 19, 21, and 23 (Days 63, 70, and 77)
The following assessments will be performed via telephone at Visits 17, 19, 21, and 23:

- Your study doctor will give you a physical exam based on symptoms you have experienced.
- Your weight, heart rate, body temperature, blood pressure, and breathing rate will also be assessed.
- Your doctor will perform a test (pulse oximetry) to measure your blood oxygen level
- You will be asked whether you have used your diary to record all symptoms you have experienced since the last visit.
- Your study doctor will ask a series of questions related to your fatigue and energy level.
- Your study doctor will ask a series of questions related to your concentration and ability to perform tasks requiring thinking.
- Your study doctor will ask a series of questions related to sleep quality.
- You will receive your treatment injection of Leronlimab (PRO 140).
- You will be asked if there have been any hospital or ER visits since the last study visit.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.
- A blood test to check the levels of immune cells (CD4/CD8 T cells) and certain proteins and substances (cytokines and chemokines), as well as to check the levels of CCR5 receptors and other biomarkers will be performed.

Visit 24, End of Treatment (Day 56)
One week after your last treatment, you will be asked to visit the clinic for the end of treatment (EOT) visit during which the following assessments will be performed:

- Your study doctor will give you a physical exam.
- Your weight, heart rate, body temperature, blood pressure, and breathing rate will also be assessed.
- You doctor will perform a test (pulse oximetry) to measure your blood oxygen level.
- Your study doctor will perform an ECG (electrocardiogram – a test to check your heart).
- You will be asked whether you have used your diary to record all symptoms you have experienced since the last visit.
- Your study doctor will ask a series of questions related to your fatigue and energy level.
- Your study doctor will ask a series of questions related to your concentration and ability to perform tasks requiring thinking.
- Your study doctor will ask a series of questions related to sleep quality.

- A series of blood and urine tests will be performed. The amount of blood needed for these tests is about 8 teaspoons.
    - A blood test for general health screening, such as chemistry, complete blood count and coagulation.
    - A blood test to check the levels of immune cells (CD4/CD8 T cells), certain proteins and substances (cytokines and chemokines) made by a kind of your blood cells, as well as to check the levels of CCR5 receptors and other biomarkers.
    - A urine sample will be needed for lab tests
- If you are a female and able to become pregnant, a urine pregnancy test will be required. If the pregnancy test is positive, you will not be able to be in the study.
- You will be asked if there have been any hospital or ER visits since the last study visit.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any unfavorable signs or symptoms that you experienced.

Follow-Up Period

Follow-up Visit (Day 112)
The follow-up period will last up to four weeks and include one visit. The following assessments will be performed at the follow-up visit:

- Your heart rate, body temperature, blood pressure, breathing rate, and weight will also be assessed.
- You doctor will perform a test (pulse oximetry) to measure your blood oxygen level.
- Your study doctor will give you a physical exam.
- Your study doctor will assess your clinical status based on your hospitalization status.
- A blood test for general health screening, to check the levels of immune cells (CD4/CD8 T cells) and certain proteins and substances (cytokines and chemokines) in your blood cells, as well as to check the levels of CCR5 receptors and other biomarkers.
- You will be asked if there have been any changes to the medications you are taking.
- You will be asked to report any symptoms that you experienced.

Unscheduled Visits
In the event that you come to the 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 study doctor.

HOW LONG WILL I BE IN THIS RESEARCH STUDY?
Part 1 of the research study lasts for a total of 91 days (including screening period, treatment period and follow-up period). Part 2 of the study lasts for an additional 56 days. You can participate for as long as you do not have serious side effects and your disease does not get worse.

You may be taken off the research study for many reasons including if:

- It is considered to be in your best interest.
- The study treatment or procedures are found to be unsafe or ineffective.
- There is any problem with following study treatments and procedures.
- Your condition worsens.
- You become pregnant.
- If you miss two consecutive doses of the investigational drug.
- The study is canceled by the sponsor or the FDA.
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study.

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

WHAT ARE THE RISKS/SIDE EFFECTS OF TAKING PART?

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your essential body functions- blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

In other studies of Leronlimab (PRO 140), possibly related side effects observed in subjects receiving the 700 mg dose included:

- Reactions at the site of the injection such as:
    - Bruising
    - Redness of the skin
    - Fluid leakage

  - Itch
  - Rash

- Headache
- Diarrhea
- Fatigue

All of these side effects occurred in less than 2% of subjects.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Side effects that you could experience during or after the Leronlimab (PRO 140) treatment:

- The most common potential study drug-related side effect that has been seen using the drug formulation that you will be using is mild headache. Other side effects likely to be related to the drug include mild to moderate diarrhea, nausea, and fatigue. There may be other side effects associated with Leronlimab (PRO 140) that we do not know about.
- Leronlimab (PRO 140) belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions (fatigue, diarrhea, fever, vomiting, headache, nausea, pain at the site of injection, low blood pressure, rash, itching, and chills) or flu-like reactions such as fever, chills, and aches. These events usually do not last long if they occur at all. Severe allergic reactions, however, can be life-threatening.
- Rare severe acute hypersensitivity reactions or anaphylaxis can occur. If anaphylaxis or severe allergic reactions occur, therapy with Leronlimab (PRO 140) will be permanently discontinued and appropriate medications (e.g., epinephrine) and supportive care will be provided.
- 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.

- Side effects that may be associated within a short period of time after receiving drugs similar to Leronlimab (PRO 140) through an injection include chills, headache, backache, overall feeling of being ill, fever, skin rash, nausea, tingling and high blood pressure. Your study doctor may give you medicine to help with these side effects.
- People who lack a functional CCR5 gene are at increased risk for severe infection by West Nile virus. Please ask your study doctor about this.
- Local pain, redness, tenderness, bruising, itching and rarely, an infection might occur at the site of injection in your stomach or at the site of the needle stick in your arm for blood draws or you may faint when blood is taken.
- Studies on Leronlimab (PRO 140) to determine its capability to cause harm to an unborn child have not been performed. If you are a woman of childbearing potential, you will be tested for pregnancy at the beginning of the study.
- It is unknown if Leronlimab (PRO 140) can pass through breast milk and it is unknown if this can cause harm to your child.

In addition to the risks or discomforts listed here, there may be other risks that are currently not known.

Reproductive Risks:
The drug used in this research study may affect and involve unforeseeable risks to a fetus. While participating in this research study, you should not become pregnant and should not nurse a baby. We can provide counseling about preventing pregnancy. You must use two medically accepted method of birth control (barrier contraceptives such as male condom, female condom, or diaphragm with a spermicidal gel, hormonal contraceptives such as implants, injectables, combined oral pills, patches or rings; intrauterine devices (IUDs), tubal ligation (two fallopian tubes that connect ovaries and uterus are blocked, tied, clamped, sealed, or cut) or sexual abstinence) throughout the course of this study. Let your doctor know immediately if you or your partner become pregnant.

Male participants with a partner who can become pregnant must also agree to use birth control methods as above, and must not donate sperm, during the study and for 90 days after the last dose of study drug.

If you or your partner become pregnant during the course of this study, the study doctor will ask to follow you or your partner until 3 months after the birth of the child. This will consist of telephone contact to determine what side effects may have happened.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future. If you receive Leronlimab and it is effective, it may help reduce the bad inflammation that resulted from COVID-19 infection.

WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

The study sponsor may reimburse you for qualifying study-related travel costs and/or expenses. Study staff will review the reimbursement plan and any requirements for reimbursement with you.

[Patients will receive $[Amount] for each completed study visit. If you do not complete the study, you will be paid for the visits which you have completed. You will be paid at the end of the designated study visits.]

OR

[You will not receive any payment for taking part in this research study.]

WHAT IF SOMETHING IS DEVELOPED FROM THIS RESEARCH?

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

ARE THERE COSTS FOR PARTICIPATING IN THIS STUDY?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for Leronlimab (PRO 140). It is possible that Leronlimab (PRO 140) may not continue to be supplied free for some reason. If this would occur, your research doctor will talk with you about your options.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services of the hospital for information. You should also check with your insurance to see what services will be covered by your insurance and what you will have to pay.

WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the study

doctor as soon as possible. The research doctor's name and phone number are listed in this consent form. The study doctor will treat you or refer you for care.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to you or your insurance company. You will be billed for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data. The information collected about you usually will not directly identify you (for example, by name, address, or social security number). Instead, your initials and a code number will be used for your information.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

If you consent to take part in this study, your medical records may be reviewed by relevant employees of CytoDyn, Inc., the company sponsoring the study, or Amarex Clinical Research, LLC (Amarex), the company to which CytoDyn has given the management of this study, for purposes of analyzing the study results and monitoring the study. Regulatory authorities such as the U.S. Food and Drug Administration (FDA), the Institutional Review Board (IRB) and other foreign regulatory bodies may review study results and subject records to check that the study is being conducted correctly. They also want to make sure that your health information has been collected the right way, or for other reasons that are allowed under the law. Your identity and medical records will be kept confidential and will not be disclosed outside of the hospital/clinic/family physician's office.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

During the course of a research study, new information may become available about your disease or the treatment that is being studied that might change your decision to be in this study. If this happens, your study doctor will discuss this with you and whether you want to continue in the study. If you decide to withdraw, your study doctor will make arrangements for your prescribed standard care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

In addition, on receiving new information your study doctor might consider it to be in your best interest to withdraw you from the study. Your study doctor will explain the reasons and arrange for your prescribed standard care to continue.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

This study is expected to start in 2021. Once the study is finished, the information will be analyzed and a clinical report will be written to record the results. This process can take about 6 months. Your study doctor will be kept informed of the results from the study, and a paper detailing these results will probably be published in an appropriate medical journal. You can also ask your study doctor for the results of the study.

RESEARCH FUNDING

The company sponsoring and funding this research is CytoDyn, Inc.

The study center and/or your study doctor are receiving financial support from the sponsor for holding this study.

CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping Leronlimab (PRO 140). In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions, concerns, or complaints about the study or problems relating to your participation in this study, please contact:

[Name] at [Number]

If, at any time, you feel you have experienced a research-related injury or reaction to the study drug, contact your study doctor:

[Name] at [Number] (24 hours)

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or researchquestions@wcgirb.com if

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

The IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

If you choose to participate in this study, please read the following and sign where indicated.

PARTICIPANT STATEMENT OF CONSENT

I confirm that I have read this consent form (or it has been read to me) and have had the opportunity to ask questions. I agree to participate in this study and comply with the requirements to the best of my ability.

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time.

By signing this consent form, I have not given up any of my legal rights. I will receive a signed and dated copy of this consent form.

_____
Printed Name of Participant

_____ _____ _____
Participant's Signature *Date* *Time*

STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

I, the undersigned, certify that to the best of my knowledge that subject named above had the study fully and carefully explained, including the nature, risks, and benefits of his/her participation in the research study; and all questions were answered to his/her satisfaction. I confirm that he/she freely and voluntarily gave consent to participate in this research study before any study-related procedures were performed. A medical problem or language or educational barrier has not precluded this understanding.

I reviewed the consent form with the subject and answered his/her questions. The subject appeared to have understood the information and was able to answer the following questions correctly:

- What is the purpose of this study?
- If you decide to be in the study, what will you be asked to do?
- What is the possible benefit of participating in this study?
- What are the possible risks of participating in this study?
- If you decide not to participate in this study, what options do you have?
- Will participating in this study cost you anything? If so, what will you have to pay for?
- Do you have to be in this study?
- If you decide to be in the study, can you leave the study when you want to?

_____ _____ _____
Signature of Person Conducting Informed Consent Discussion *Date* *Time*

_____
Name of Person Conducting Informed Consent Discussion

---------- Use this witness section only if applicable ----------

If this consent form is read to the subject because he/she is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. He/she freely consented to be in the research study.

_____

Printed Name of Impartial Witness

_____ _____

Signature of Impartial Witness *Date*

An impartial witness is:

- a person who is independent of the trial,
- who cannot be unfairly influenced by people involved with the trial,
- who attends the informed consent process, and
- who reads the informed consent form and any other written information supplied to the subject.

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

While you are participating in this research study, the study doctor and his study staff will collect and create personal health information about you and record it on study forms. This information may include health histories, examinations and results of tests. The study doctor will keep this information in study records. He may also gather information regarding your past, present, and/or future medical conditions from your primary medical doctor. These records may also include personal information such as your birth date, social security number, or medical record numbers which could be used to identify you. This type of information is called "Protected Health Information" (PHI).

The terms "you" and "your" in this Authorization refer to the research subject.

Under a United States federal law called the "Privacy Rule" or Health Insurance Portability and Accountability Act of 1996 (HIPAA), your PHI that is gathered and obtained during research cannot be used to conduct the research or be given to anyone for research purposes without your permission. Because of this rule, you may not participate in this study unless you give your permission to use and disclose your PHI. You do not have to sign this form, but if you do not, you cannot participate in this study.

By signing this consent form, you are giving permission for the study doctor and his study staff to use your PHI to conduct this study, to monitor your health status, and possibly to develop new tests, procedures and commercial products.

You are also agreeing to allow your PHI to be disclosed to the study sponsor and any representatives working with them. The sponsor may also give your PHI to the FDA or other regulatory agencies which are responsible for ensuring that the research is being done correctly.

Study staff will assign a code number to you for this study. This will help to protect your identity; however, the sponsor may look at your complete study records which will identify you. The sponsor will also send representatives to your study doctor's office to oversee how the study is being conducted. These

representatives will review your PHI to make sure the information is correct. The Institutional Review Board (IRB) may also have access to your PHI. These disclosures help to make sure that all information related to the research is available to those who need it.

Your identity will remain confidential and except for the disclosures described above and detailed specifically in the consent page, will not be shared with others, unless it is required by law. If your PHI is given to the parties listed above or to anyone who is not required to follow federal law, your PHI will no longer be protected by the "Privacy Rule" and could possibly be used or disclosed in ways other than are listed here.

You have the right to see and make copies of your PHI. You are agreeing, however, not to see or make copies of your PHI until all of the sponsor work has been completed. At that time, you may ask to see your records.

Your HIPAA Authorization will expire 50 years from the date you sign and date it unless you revoke (cancel or withdraw) it sooner. You have the right to cancel or withdraw this authorization at any time. If you cancel this authorization, your PHI will no longer be used for this study, unless it is necessary (based on your earlier authorization) to complete analysis (test) and reports for this research. If you withdraw your permission, no new health information will be gathered unless you have a side effect related to the study.

If you withdraw from the study but do not withdraw your Authorization, new health information may be collected until this study ends.

In the event of an adverse drug reaction/serious side effect following revocation of Authorization, your information may still be used and disclosed as necessary for study purposes.

To cancel your permission to use PHI, you must send a written notice to your study doctor's office stating that you are canceling your authorization to use or disclose your protected health information. If you cancel this authorization, you will not be allowed to continue in this study.

Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are otherwise entitled.

AUTHORIZATION
I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above. I will receive a signed and dated copy of this Authorization.

_____
Printed Name of Participant
(Study Subject)

_____ _____ _____
Participant's Signature *Date* *Time*

Statement of the Witness (when applicable*)
The information in the authorization was accurately explained to, and appeared to be understood by the subject. Authorization was freely given.

_____
Printed Name of Impartial Witness

_____
Signature of Impartial Witness *Date*

*Impartial Witness: If the subject cannot read, the signature of an Impartial Witness is needed.

An impartial witness is:

- a person who is independent of the trial,

- who cannot be unfairly influenced by people involved with the trial,
- who attends the informed consent process, and
- who reads the informed consent form and any other written information supplied to the subject.

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
Apr 30, 2021

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	A Phase 2, Two-Part Study (8-Week, Randomized, Double Blind, Placebo Controlled Period Followed by a 4-Week, Open-Label Extension Period) to Evaluate the Efficacy and Safety of Leronlimab in Patients Experiencing Prolonged Coronavirus Disease 2019 (COVID-19) Symptoms [Long-Haulers]
PROTOCOL NO.:	CD15_COVID-19 IRB Protocol #20210354
SPONSOR:	CytoDyn, Inc.
INVESTIGATOR:	Name Address City, State Zip Country
STUDY-RELATED PHONE NUMBER(S):	Phone Number Phone Number (24 hours) **[24-hour number is required]**

You have already agreed to participate in the above mentioned research study. We are asking for your consent to collect additional data using Global Health Assessment Questionnaire.

- You will be asked to complete a series of questions related to your general health (physical and mental health) and quality of life at V17 (EOT/Day 56).

Note: This addendum to the consent form is applicable for all patients completing 8-week, double blind, placebo controlled period and is regardless of whether you decide to (or eligible for) participation in the 4-week, open-label extension period.

REIMBURSEMENT FOR PARTICIPATION

There is no change in the reimbursement for qualifying study-related travel costs and/or expenses. You will not receive any additional payment for completing this questionnaire.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation for completing this questionnaire is voluntary.

WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions, concerns, or complaints about the study or problems relating to your participation in this study, please contact:

[Name] at [Number]

If, at any time, you feel you have experienced a research-related injury or reaction to the study drug, contact your study doctor:

[Name] at [Number] (24 hours)

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or researchquestions@wcgirb.com if

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

The IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to complete this additional Questionnaire in this study, you will receive a signed and dated copy of this consent form addendum for your records.

If you choose to participate in this study, please read the following and sign where indicated.

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
Apr 30, 2021

PARTICIPANT STATEMENT OF CONSENT

I confirm that I have read this consent form (or it has been read to me) and have had the opportunity to ask questions. I agree to participate in this study and comply with the requirements to the best of my ability.

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time.

By signing this consent form, I have not given up any of my legal rights. I will receive a signed and dated copy of this consent form.

_____
Printed Name of Participant

_____ _____ _____
Participant's Signature *Date* *Time*

STATEMENT OF PERSON CONDUCTING INFORMED CONSENT DISCUSSION

I, the undersigned, certify that to the best of my knowledge that subject named above had the study fully and carefully explained, including the nature, risks, and benefits of his/her participation in the research study; and all questions were answered to his/her satisfaction. I confirm that he/she freely and voluntarily gave consent to participate in this research study. A medical problem or language or educational barrier has not precluded this understanding.

I reviewed the consent form with the subject and answered his/her questions. The subject appeared to have understood the information.

_____ _____ _____
Signature of Person Conducting Informed Consent Discussion *Date* *Time*

_____
Name of Person Conducting Informed Consent Discussion

---------- Use this witness section only if applicable ----------

If this consent form is read to the subject because he/she is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. He/she freely consented to be in the research study.

_____

Printed Name of Impartial Witness

_____ _____

Signature of Impartial Witness *Date*

An impartial witness is:

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