NCT04707664

# A randomized Phase 2b trial evaluating clinical outcomes of inhaled sargramostim in high-risk patients with mild-moderate COVID-19

## Sargramostim use in COVID-19 to Recover Patient Health (SCOPE)

**Protocol Number:** PTX-001-003

**Study Drug:** sargramostim

**Version Number:** 4.0

**Version Date:** August 23, 2021

**IND Number:** 149323

| | |
|---|---|
| **Principal Investigator** | MD |
| **Sponsor** | Partner Therapeutics, Inc. |
| **Sponsor address** | 19 Muzzey Street, Lexington, MA 02421 |
| **Medical Monitor** | MD<br>Partner Therapeutics, Inc. |
| **Protocol History** | |
| **Version number** | **Version date** |
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| V3.0 | May 04, 2021 |
| V4.0 | August 23, 2021 |

**TABLE OF CONTENTS**

**LIST OF TABLES**



**LIST OF FIGURES**

**PROTOCOL APPROVAL SIGNATURE PAGE**

## Protocol Number: PTX-001-003

## A randomized Phase 2b trial evaluating clinical outcomes of inhaled sargramostim in high-risk patients with mild-moderate COVID-19

# SCOPE Study

I acknowledge that this study protocol contains all necessary details for my staff and me to conduct the study as described. I will conduct this study in compliance with all applicable regulations and guidelines, as stated in the protocol and other information supplied to me.

| **Partner Therapeutics Chief Medical Officer:** | **Signature:** | **Signature Date:** |
|---|---|---|
| | | |

**INVESTIGATOR SIGNATURE PAGE**

## Protocol Number: PTX-001-003

## A randomized Phase 2b trial evaluating clinical outcomes of inhaled sargramostim in high-risk patients with mild-moderate COVID-19

## SCOPE Study

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| Site Principal Investigator: | Signature: | Signature Date: |
|---|---|---|
| | | |

# 1 STUDY SYNOPSIS

| **Sponsor:** | **Name of Medical Products:** | **Study Phase:** |
|---|---|---|
| Partner Therapeutics, Inc. | sargramostim | Phase 2b |

**Study Title**

A randomized Phase 2b trial evaluating clinical outcomes of inhaled sargramostim in high-risk patients with mild-moderate COVID-19

**Study Center(s)**

Up to approximately 50 sites (US and outside US)

**Study Design**

This Phase 2b, multicenter, placebo-controlled, double-blind study will randomize approximately 500 adult patients who are symptomatic with mild or moderate COVID-19 (as defined in the Food and Drug Administration (FDA) Guidance Document: Covid-19: Developing Drugs and Biological Products for Treatment or Prevention, May 2020) who are at high risk for progression to more severe disease. Patients will be randomized in a 1:1 ratio to inhaled sargramostim plus standard of care (SOC) or placebo plus SOC. Enrollment of patients who have completed a COVID-19 vaccination regimen or participated in a COVID-19 vaccine clinical trial will be capped at approximately 100 patients.

All patients will be randomized to receive either 250 mcg of sargramostim or equivalent volume of placebo diluent. Treatment will be administered once daily for 5 days delivered via a vibrating mesh nebulizer. Additional blood samples will be collected for biomarker assays for approximately 100 randomized patients (approximately 50 from each treatment group).

Patients will be followed for up to 60 days after start of treatment.

An interim safety and benefit/risk review will be performed by a data safety monitoring board (DSMB) after a total of approximately 100 patients (total of both arms) complete through Day 28 (or withdraw from study prior to Day 28).

| Primary Objective | Primary Outcome Measure |
|---|---|
| To evaluate if inhaled sargramostim can prevent progression to more severe disease in an outpatient setting in symptomatic patients with mild or moderate COVID-19 who are at higher risk for progression to more severe disease | Proportion of patients who experience any emergency room visit or hospitalization, or death by Day 28. |

| Secondary Objectives | Secondary Outcome Measures |
|---|---|
| To evaluate the effect of inhaled sargramostim on clinical progression of COVID-19 | Proportion of patients with any progression of disease as determined by a ≥ 2-point increase from baseline in the NIAID ordinal scale up to Day 28, and Day 60 |
| | Time to progression of disease as determined by a ≥ 2-point |

| | |
|---|---|
| | increase in the NIAID ordinal scale up to Day 28, and Day 60 |
| | Change from baseline in overall symptom score, and individual symptom scores, as measured by the Symptom Score Questionnaire up to Day 28. |
| To evaluate the safety of inhaled sargramostim in patients with COVID-19 | Adverse events (AE) up to Day 60. |

| Exploratory Objective | Exploratory Outcome Measures |
|---|---|
| To explore the effect of inhaled sargramostim on biological responses to COVID-19. | Proportion of patients requiring supplemental oxygen up to Day 28 |
| | The effect of sargramostim on SARS-CoV-2 viral load in samples collected from nasopharyngeal swabs up to Day 14 (biomarker cohort only) |
| | Proportion of patients with generation of SARS-CoV-2 antibody up to Day 28 (biomarker cohort only) |
| | Proportion of patients with markers of cellular immunity, via immunophenotyping, up to Day 14 (biomarker cohort only) |
| | Levels of ferritin, c-reactive protein (CRP), d-Dimer up to Day 28 |
| | Immunogenicity to sargramostim up to Day 28 (biomarker cohort only) |
| | Presence or absence of COVID-19 symptoms at Day 60 |

**Inclusion Criteria**

Clinical significance of underlying medical conditions and judgements related to the best interests of the patient are determined by the investigator. Sponsor consultation with the medical monitor is encouraged where there is a concern.

1. Patients with a positive laboratory diagnosis of SARS-CoV-2 infection by an antigen or a molecular test ≤5 days prior to randomization. The test should have been authorized by the relevant regulatory authority.
2. Have one or more of the following mild or moderate COVID-19 symptoms for ≤5 days prior to randomization:
   a) Fever or chills
   b) New onset or worsening cough
   c) Sore throat
   d) Malaise or fatigue
   e) Headache
   f) Muscle pain (myalgias) or body aches
   g) Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)

h) New onset or worsening shortness of breath or difficulty breathing

i) Nasal congestion or runny nose

j) New loss of taste (ageusia) and/or smell (anosmia). Note: any of these symptoms (ageusia, anosmia) alone or in combination cannot be used as the SOLE qualifying symptoms for enrollment.

3. At higher risk for progression to more severe COVID-19

   a) Age ≥ 60 years

   b) Age 18-59 years with a clinically stable medical history of at least 1 or more of the following conditions that could lead to severe COVID-19:

   - Chronic respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis
   - Obesity with BMI ≥ 30 kg/$m^2$
   - Cardiovascular disease
   - Sickle cell disease or thalassemia
   - Diabetes mellitus being managed with concomitant medications
   - Hypertension being managed with concomitant medications
   - Chronic kidney disease

4. Oxygen saturation by pulse oximeter > 93% on room air. Note: at altitudes of >4000 feet above sea level, oxygen saturation by pulse oximeter > 91% on room air is permitted
5. Negative pregnancy test (if woman of childbearing potential)
6. Females of childbearing potential and males with female partners of childbearing potential must agree to use acceptable contraceptive methods (from screening to Day 28)
7. The patient (or legally authorized decision maker) must give informed consent

**Exclusion Criteria**

1. Hospitalized patients
2. Patients who have received or are receiving treatments that are not approved/authorized by the relevant regulatory authority for the treatment of patients with mild or moderate COVID-19 in an outpatient setting
3. Patients enrolled in interventional clinical trials for other experimental therapies
4. Patients on chronic oxygen supplementation due to cardiopulmonary or other conditions
5. Patients with unstable comorbid conditions (e.g., decompensated congestive heart failure, COPD with exacerbation, current angina pectoris, uncontrolled diabetes mellitus, uncontrolled hypertension, uncontrolled asthma)
6. Patients with severe pulmonary comorbid conditions, including systemic steroid-dependent asthma, systemic steroid-dependent COPD, oxygen-dependent COPD, lung transplant, or cystic fibrosis
7. Patients who have received highly immunosuppressive therapy (to include systemic corticosteroids) or anti-cancer combination chemotherapy within 24 hours prior to first dose of study drug
8. Patients with known or suspected intolerance or hypersensitivity to sargramostim, or any component of

the product

9. Patients who have previously experienced severe and unexplained side effects during aerosol delivery of any kind of medical product
10. Pregnant or breastfeeding females
11. Patients who, in the opinion of the Investigator, will not be able to comply with all the study procedures and visits as outlined in the schedule of events, including follow-up

**Patient population:**

Adult non-hospitalized patients with mild-moderate COVID-19 without hypoxemia and at higher risk for progression to severe COVID-19 due to advanced age or comorbidities.

**Rationale:**

COVID-19 is a disease caused by the recently discovered coronavirus designated SARS-CoV-2. COVID- 19 is highly contagious and generally causes fever and respiratory symptoms in symptomatic individuals. Additional symptoms are gastrointestinal, cardiac, taste and smell abnormalities, and neurological. The disease spectrum varies from asymptomatic infection through fatal pneumonia and multiorgan failure. Older adults and individuals with significant comorbidities, including cardiorespiratory diseases, diabetes, obesity, and hypertension, are most severely affected.

Few medications are currently available to treat COVID-19. Remdesivir, dexamethasone, and intravenous antibody treatments have been authorized for critically ill, hospitalized COVID-19 patients, but an easily administered outpatient medication for treatment of COVID-19 is a major unmet medical need.

Sargramostim (Leukine) is a formulation of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), which is a critical cytokine for healthy pulmonary function. Detailed studies have shown that GM-CSF is necessary for alveolar macrophage (AM) maturation and maintenance. Although GM-CSF was discovered as a myelopoietic growth factor, it has diverse additional effects that both promote differentiation of myeloid precursors into neutrophils, monocytes, and dendritic cells and control function of mature myeloid cells. GM-CSF is also known to reverse immunoparalysis seen in sepsis, resulting in beneficial outcomes. In addition, GM-CSF prevents bacteremia in post influenza bacterial pneumonia through locally mediated improved lung antibacterial resistance; and increased reactive oxygen species production by AMs. Pulmonary delivery of this GM-CSF has potential to reduce morbidity and mortality due to viral pneumonias, potentially including COVID-19.

Safety and efficacy of inhaled sargramostim 125 mcg have been evaluated in several clinical studies. In one clinical study of six patients with moderate to severe community-acquired pneumonia or ventilator-associated pneumonia acute respiratory distress syndrome (ARDS), 125 mcg of sargramostim was administered by an Aeroneb Solo nebulizer device (Covidien, Neustadt, Germany) at an interval of 48 hours for 2 doses. At this dose, a significant improvement of oxygenation in response to sargramostim inhalation (p=0.0035), with no drug-related toxicity, was observed. Inhaled sargramostim has been evaluated at doses higher than 125 mcg in patients with autoimmune pulmonary alveolar proteinosis (aPAP).

Patients with aPAP have extremely high titers of anti-GM-CSF antibodies, which sequesters native GM-CSF leading to accumulation of surfactant in alveolar sacs with resultant hypoxia. To overcome high anti-GM-CSF antibody levels in aPAP patients, sargramostim has been administered at doses of up to 500 mcg total daily dose, although daily doses of 125 mcg and 250 mcg have been used and associated with improvement in clinical outcome. Given demonstrated efficacy of 125 and 250 mcg doses, 125 mcg is considered a minimally effective dose when treating viral-related diseases. In PTX-001-002 (NCT04411680), inhaled sargramostim at a dose of 125 mcg twice daily was administered for up to 5 days. In this study, a DSMB has conducted four safety reviews (as of January 2021), and no changes to the study have been required.

**Number of Patients:**

Approximately 500 patients will partake in this study. Approximately 250 patients will receive sargramostim and approximately 250 patients will receive placebo. Enrollment of patients who have completed a COVID-19 vaccination regimen or participated in a COVID-19 vaccine clinical trial will be capped at approximately 100 patients

**Duration of Therapy**

All randomized patients receive sargramostim or placebo for the duration the treatment period (Day 1 - 5), unless the patient has unacceptable toxicity to study treatment; the patient, legally authorized decision maker or Investigator decides to discontinue; or the patient has rapid clinical deterioration not conducive to continued study treatment; pregnancy; or death.

Day 1 is the day the patient receives their first dose of study treatment.

All patients should continue to receive SOC for their underlying comorbidities during the study. All patients may receive supportive care for signs and symptoms of COVID-19, per their study site's institutional standards. The post-treatment period (Days 6-60) will continue until completion of all safety and efficacy assessments on Day 60 (end of study).

Patients who need to start a COVID-19 vaccination regimen, can do so only after Day 21 of the study.

All patients, including those who discontinue treatment early, will be followed for outcome measures until Day 60.

**Duration of Follow-Up**

Patient follow-up will cease upon completion of all safety and efficacy assessments on Day 60.

**Duration of Study**

Study completion is defined as the date when the last patient completes the Day 60 visit or an early termination visit. Alternatively, the study may be stopped earlier for reasons such as poor enrollment, or ethical or safety reasons.

**Test Product/Device, Dose, and Mode of Administration:**

All patients will be randomized to receive either 250 mcg of sargramostim or equivalent volume of placebo diluent. Treatment will be administered once daily for 5 days delivered via a vibrating mesh nebulizer. Patients will be observed in the clinic for approximately 30 minutes after the completion of the drug administration.

**Safety Assessments**

Patients will be followed for clinical and laboratory AEs throughout the course of the study according to the schedule of events. All clinical laboratory assessments will be performed at a central laboratory, except for urine pregnancy test and initial diagnostic SARS-CoV-2 test used for study inclusion.

- Hematology laboratory parameters will include complete blood count with differential, hemoglobin, hematocrit, and absolute counts for white blood cells, platelets, neutrophils, lymphocytes, eosinophils, and monocytes
- Chemistry laboratory parameters will include albumin, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, direct

and total bilirubin, glucose, total protein, sodium, potassium, chloride, bicarbonate, calcium, and uric acid

- Additional laboratory parameters will include serum ferritin, d-Dimer, and CRP
- Vital sign assessments will include body temperature, blood pressure, pulse rate, and respiration rate
- Pulse oximetry
- Physical examination

**Efficacy Assessments**

Efficacy data will include the following:

- Need for emergency room visit or hospitalization
- The NIAID ordinal scale
- Evaluation of symptoms using a symptom score, patient global impression, and Day 60 COVID-19 symptom evaluation questionnaires

**Exploratory Assessments**

In approximately 100 patients (approximately 50 from each treatment group), the following will be performed:

- Nasal swab for SARS-CoV-2 viral RNA level and viral clearance
- Blood sample collection for biomarker assays including
    - Antibody production against SARS-CoV-2
    - Immunophenotyping for cellular immunity,
    - Sargramostim anti-drug antibodies

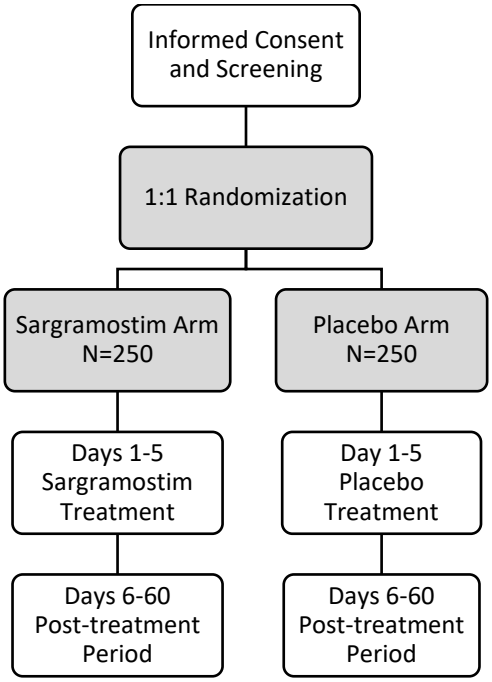
**Statistical Plan**

The primary efficacy endpoint, proportion of patients who experience any emergency room visit or hospitalization, or death will be compared using logistic regression stratified by the factors used to randomize patients (full analysis set). Additionally, the primary analysis will be repeated in the modified intention to treat population.

Key secondary endpoints summarized using proportions will be tested using a logistic regression model. Time to event endpoints will be analyzed using the stratified log-rank test with Kaplan-Meier curves used to descriptively summarize the data (hazard ratio estimate from Cox Regression). Change from baseline in the overall symptom questionnaire score, and individual symptom scores from baseline to Day 28 and Day 60 will be analyzed using a mixed model repeated measures analysis with the missing at random assumption for handling missing data. All randomized patients will be included in the analysis of the key secondary endpoints.

As this is a Phase 2b study; no adjustments for multiple comparisons will be made.

## 2 SCHEMATIC OF STUDY DESIGN



# 3 ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of Daily Living |
| AE | Adverse Event |
| AEC | Alveolar Epithelial Cell |
| AM | Alveolar Macrophage |
| aPAP | Autoimmune Pulmonary Alveolar Proteinosis |
| ARDS | Acute Respiratory Distress Syndrome |
| CD | Cluster of Differentiation |
| CFR | Code of Federal Regulations |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF/eCRF | Case Report Form/electronic Case Report Form |
| CRP | c-reactive Protein |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GM-CSF | Granulocyte-Macrophage Colony-Stimulating Factor |
| HHC | Home Health Care |
| HLA-DR | Human Leukocyte Antigen – DR Isotype |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IFN | Interferons |
| IL | Interleukin-1 |

| | |
|---|---|
| IRB | Institutional Review Boards |
| IV | Intravenous |
| mITT | Modified Intention to Treat |
| NK | Natural Killer (cells) |
| PI | Principal Investigator |
| SAE | Serious Adverse Event |
| SARS-CoV | Severe Acute Respiratory Syndrome (SARS)-associated Coronavirus |
| SOC | Standard of Care |
| TM | Telemedicine |
| TNF-α | Tumor Necrosis Factor alpha |
| US | United States |
| WOCBP | Women of Childbearing Potential |

# 4 BACKGROUND

## 4.1 Sargramostim

Sargramostim (Leukine®), a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), was approved in 1991 **(29)**. In addition to hematopoietic growth factor activity, GM-CSF has diverse effects on differentiation and function of myeloid cells, including capacities for phagocytosis and antigen presentation **(70)**. Importantly, the Leukine® systemic safety profile is well characterized. Over 500,000 recipient patients provide extensive clinical and post-marketing data across disease states in diverse groups, including neonates and the elderly.

## 4.2 Role of GM-CSF in Lung Function and Disease

GM-CSF plays a vital role in healthy pulmonary function. Alveolar macrophage (AM) maturation from fetal monocytes and maintenance in adulthood both rely on GM-CSF **(15, 20)**. GM-CSF released from alveolar epithelial cells (AECs) ensures effective viral and surfactant clearance by AMs fostering maintenance of optimal gas exchange. GM-CSF neutralization by specific antibodies leads to the rare lung disease pulmonary alveolar proteinosis in which alveolar surfactant accumulation results in hypoxia.

AEC-expressed GM-CSF stimulates macrophages to generate healing effects on injured epithelium by orchestrating epithelial proliferation and barrier repair **(54, 55)**. Additionally, GM-CSF signals B1a B cells to secrete polyreactive emergency immunoglobulin M and ensures effective early frontline defense against bacterial lung invasion **(65)**. GM-CSF has been shown to be protective in models of acute lung injury **(52)**. During oxidative stress, GM-CSF protects AECs against apoptosis resulting from mitochondrial injury via induction of anti-apoptotic Mcl-1 and activation of the Akt pathway. Finally, inhaled GM-CSF prevents systemic bacteremia in post influenza bacterial pneumonia, primarily via locally mediated lung infection resistance **(51, 60)**, as well as by increased production of reactive oxygen species by AMs **(54)**. GM-CSF has been shown to reverse immunoparalysis seen in sepsis by immune activation **(32, 34)**.

Animal model studies demonstrate GM-CSF activity against acute respiratory distress syndrome (ARDS) and infections. *In vivo* airway GM-CSF rescues mice from lethal influenza pneumonia and reduces inflammation-induced damage from influenza A **(22)**. Similarly, GM-CSF–dependent crosstalk between influenza virus infected AECs and cluster of differentiation (CD)103+ dendritic cells promote viral clearance and recovery, suggesting GM-CSF utility for severe influenza virus pneumonia **(61)**. GM-CSF conferred resistance to influenza in mice via AMs that became more resistant to influenza- induced apoptosis. Delivery of intranasal GM-CSF to wild-type mice also conferred resistance to influenza **(27)**.

In conclusion, GM-CSF confers resistance to influenza by enhancing innate immune mechanisms that depend on AMs for health and normal function. Pulmonary sargramostim delivery has potential to reduce morbidity and mortality due to viral pneumonia, as displayed in **Figure 1**.

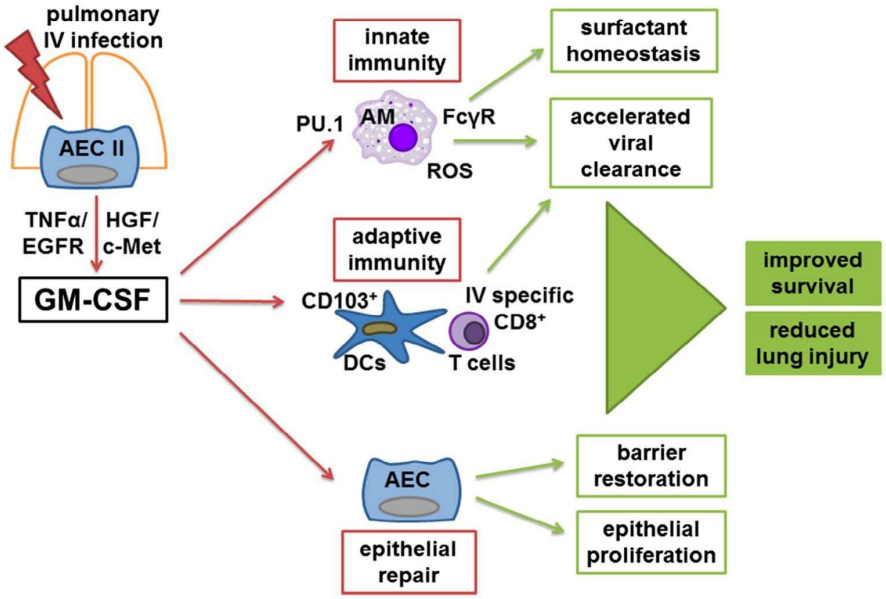



**Figure 1:** *GM-CSF modulates immune response to influenza virus infection (45).*

*After pulmonary influenza virus infection GM-CSF is released from AEC II, mediated through HGF/c-Met and TGF-α/EGFR signaling. In an autocrine manner, it stimulates epithelial repair, including epithelial proliferation and barrier restoration. Via PU.1, GM-CSF improves AM resistance, maturation, ROS production, and phagocytosis capacity, e.g., by the FcγR-mediated opsonophagocytosis. GM-CSF stimulates activation and proliferation of DC, especially CD103⁺ DC, and T cells and enhances antigen priming and influenza virus-specific CD8⁺ T cell recruitment. Innate and adaptive immunity are activated, resulting in accelerated viral clearance. Altogether AECs GM-CSF leads to increased survival and reduced lung injury.*

*[AEC alveolar epithelial cells, AM alveolar macrophage, c-Met hepatocyte growth factor receptor, DC dendritic cells, EGFR epithelial growth factor receptor, FcγR Fcɣ receptor, GM-CSF granulocyte-macrophage colony-stimulating factor, HGF hepatocyte growth factor, PU.1 transcription factor PU.1, ROS reactive oxygen species, TGF-α transforming growth factor α].*

### 4.3 Use of sargramostim in conditions that are similar to COVID-19 ARDS

A double-blind randomized placebo-controlled trial (N=18) of low-dose (3 mcg/kg daily for 5 days) intravenous (IV) GM-CSF in adults with sepsis and respiratory dysfunction showed that GM-CSF treatment led to improved gas exchange **(40)**. A Phase II randomized placebo-controlled trial (N=130) in patients with sepsis and respiratory dysfunction studied IV sargramostim (250 mcg/m$^2$ daily for 14 days). Improved 28-day mortality on sargramostim was observed but did not reach statistical significance **(36)**. In a clinical study of six patients with moderate to severe community- acquired pneumonia or ventilator-associated pneumonia ARDS, 125 mcg of sargramostim was administered by an Aeroneb Solo nebulizer device (Covidien, Neustadt, Germany) at an interval of 48 hours for 2 doses **(25)**. At this dose, a significant improvement of oxygenation in response to sargramostim inhalation (p=0.0035), with no drug-related toxicity, was observed. There was improvement in morbidity using standard scoring systems, and four of six patients recovered and were discharged from the hospital.

Six additional trials evaluated sargramostim given by IV, subcutaneous, or inhaled routes in critically ill patients. These trials monitored systemic cytokines, markers of inflammation, and safety **(21, 25, 34, 36,**

**38, 44).** None of these studies showed an increase in systemic cytokines, including interleukin (IL)-6, IL-8, IL-1β, IL-10, tumor necrosis factor (TNF)α, GM-CSF, and IL-12-p70, treatment-related organ toxicity, or increased rates of treatment-related serious adverse events (SAE). In studies monitoring IL-6, a key driver of cytokine storm, no changes in systemic IL-6 levels were observed. These data support that sargramostim does not increase the risk of cytokine storm in critically ill patients. Evidence of sargramostim clinical activity was observed.

### 4.4 Recent Translational Data in COVID-19

Severe acute respiratory syndrome (SARS)-associated Coronavirus (SARS-CoV)-2 replication generated limited antiviral responses in both a human lung alveolar carcinoma cell line and in vivo in ferrets (4). Also, human ex vivo lung tissue explants challenged by SARS-CoV-2 or SARS-CoV revealed higher amounts of virus with lower interferons (IFNs) and pro- inflammatory cytokines/chemokines on SARS-CoV-2 challenge, suggesting avoidance of innate immune detection (13). Early phase immune evasion may allow unchecked SARS-CoV-2 replication in the respiratory tract, leading to high viral load and asymptomatic person-to-person transmission (66). Most, but not all hospitalized patients seem to mount both CD8+ and CD4+ T cell responses. However, suboptimal, excessive, or otherwise inappropriate T cell responses have been associated with severe disease (8). Along with increased systemic cytokines, a decrease in blood immune cell populations such as CD4, CD8 and natural killer (NK) cells were identified as risk factors for cytokine storm in COVID-19-infected pneumonia patients (9, 46, 64). Additionally, NK cells and cytotoxic lymphocytes appeared to be exhausted with reduced ability to produce CD107a, IFN-γ, IL-2, granzyme B, and TNF-α (71). T cells from COVID-19 patients also demonstrate higher exhaustion marker PD-1 expression, relative to healthy controls (71). T cell PD-1 and Tim-3 expression increased as COVID-19 infections progressed from mildly symptomatic to severe, also suggestive of T cell exhaustion (12, 14, 49, 62).

Lung damage due to unchecked viral replication leads to epithelial barrier breakdown with diffuse alveolar damage and increased microvascular permeability. Leakage of inflammatory cytokines IL-6 and IL-1 into systemic circulation recruits neutrophils and pro-inflammatory monocytes into the lung. This 'cytokine storm' can overwhelm homeostatic pulmonary tissue repair, leading to AM depletion and irreversible tissue damage (26, 68). During this process activated fibroblasts deposit excess collagen, impairing gas exchange (33). Epithelial cell death may also expose the basement membrane to secondary microbial pathogens, offering them access to the systemic circulation (39). AMs are innate immune sentinels against respiratory pathogens that release oxygen metabolites and anti-microbial proteases, as well as recruit neutrophils into alveolar spaces. They also aid in resolving inflammation by phagocytosing apoptotic neutrophils and producing anti-inflammatory cytokines, such as transforming growth factor-□ and IL-10 (23, 28). Thus, AM loss may contribute to failed lung function in COVID-19 patients. Importantly, while AMs are the principal lung macrophages in heathy controls and mildly infected COVID-19 patients, they were almost completely lost in severely infected lungs (30).

Viral, bacterial, and fungal pulmonary infections can all cause a cytokine storm syndrome. A complex cytokine response that builds in infection is characterized by a series of overlapping networks that may show similarities across indications pathogens and are challenging to differentiate clinically. Cytokine release syndrome is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction that is associated with chimeric antigen receptor T cell therapy, therapeutic antibodies, and haploidentical allogeneic transplantation. Levels of inflammatory markers and cytokines may differ dramatically among cytokine storm variants (63). The COVID-19 hyperinflammatory response has been

likened to conditions including classical ARDS, macrophage activation syndrome, or hemophagocytic lymphohistiocytosis, or simply "cytokine storm." COVID-19 patients display diverse inflammatory effects and pathophysiology with some biomarkers showing a strong correlation to worse disease or mortality (9, 11, 43). The COVID-19 hyperinflammatory response is accompanied by a simultaneous anti-inflammatory response that associates with poor outcomes and may increase risk of secondary bacterial infections. Peripheral immune responses in severe COVID-19 patients demonstrate reconfiguration of immune cell composition and phenotype (67). SARS-CoV-2 infection also induces profound alterations of the myeloid compartment (47). While mild COVID-19 was marked by presence of inflammatory Human Leukocyte Antigen – DR Isotype (HLA-DR)hiCD11chi CD14+ monocytes, an increase in dysfunctional HLA-DRloCD163hi and HLA- DRloS100Ahi CD14+ monocytes was observed as patients transitioned to moderate/severe disease (47).

Functional immunoparalysis and disruption of immune homeostasis in moderate/severe cases has been further confirmed in translational data reported in COVID-19 patients, warranting exploration of precision based immunomodulatory therapy against SARS CoV-2 (24, 50, 53).

A long-term strategy to ameliorate the COVID-19 pandemic has been to develop an effective vaccine that can prevent new infections and stop disease transmission. While vaccines targeting SARS-CoV-2 are now authorized for emergency use, limited quantities will be available. Also, geographic differences affecting availability are likely. Although data supporting preventive vaccines is encouraging, longer- term efficacy and safety remain to be seen. Additionally, certain patient populations may not respond adequately to a vaccine. Other therapeutic options, such as pathogen-targeted antibodies and antivirals, are also being explored. Yet their efficacy and safety in patients with mild or moderate COVID- 19 at risk for progression to severe disease is not well elucidated. Therefore, it is important to investigate treatment options that may relieve disease immunopathology, such as inhaled sargramostim in patients with mild or moderate COVID-19. In addition, evaluation of inhaled sargramostim in patients with COVID-19 may extend its applicability for therapeutic use in patients with other viral respiratory infections.

### 4.5 Clinical Experience of Inhaled Sargramostim

Safety of inhaled sargramostim follows from studies in autoimmune pulmonary alveolar proteinosis (aPAP). In this disease, surfactant accumulates in alveolar sacs, resulting in hypoxia. Tazawa and colleagues conducted a Phase II study of inhaled sargramostim in patients with unremitting or progressive aPAP with hypoxia and symptoms (57). Patients received 250 mcg daily by inhalation for 7 days, repeated every other week for six cycles (total 12 weeks). Treatment was well tolerated with no serious adverse events. Adverse events (AE) were reported in 7 of 39 patients receiving sargramostim; all these events were transient. Treatment led to improved oxygenation, radiological changes, and symptoms. Thirty-five such patients were followed for a 30-month observation period, and sargramostim was shown to sustain remission in over half (56). A study in 6 aPAP patients evaluated inhaled sargramostim 250 mcg once daily in a 4 days-on, 4 days-off schedule, as long as needed (37). Upon remission, sargramostim dose was reduced. All patients achieved remission, and 3 patients maintained remission when dose was reduced. No significant AEs were noted (37).

A larger randomized Phase 3 study was conducted by Japanese investigators in 12 centers. Sixty-four patients with mild to moderate aPAP and hypoxia were randomized to receive placebo or sargramostim (33 patients) at a dose of 125 mcg twice a day for 7 days, followed by a week of no treatment. This two-week cycle was repeated 12 times over a period of 24 weeks. Treatment was well tolerated with no significant differences in AEs between groups. Sargramostim treated patients had a significantly improved

alveolar-arterial oxygen gradient, as well as lung field density by computed tomography (58). Additionally, interim results from a study (6) in 18 patients with aPAP suggested that inhaled sargramostim could increase relapse-free time after whole lung lavage.

Inhaled sargramostim has been studied in other diseases, including cancers, ARDS, cystic fibrosis, and Sezary syndrome (1-3, 5, 25, 31, 35, 37, 41, 42, 48, 59, 69). In total, 259 patients received inhaled sargramostim at doses of up to 2000 mcg BID and durations up to about 1.5 years. In these studies, inhaled sargramostim was well-tolerated. Clinical experience with sargramostim in viral pneumonia and aPAP suggests salutary effects. In addition, these studies establish safety of inhaled sargramostim and provide evidence for activity of inhaled sargramostim.

### 4.6 Use of Sargramostim Inhalation in COVID-19

An investigator-sponsored study in Belgium [NCT04326920], "Prospective, Randomized, Open-label, Interventional Study to Investigate the Efficacy of Sargramostim (Leukine®) in Improving Oxygenation and Short- and Long-term Outcome of COVID-19 (Corona Virus Disease) Patients Acute Hypoxic Respiratory Failure" was initiated on March 26, 2020. Approximately 80 patients were randomized to receive either inhaled sargramostim 125 mcg twice daily via a vibrating mesh nebulizer for 5 days (active group) together with institutional standard of care (SOC), or SOC alone (control group). SOC included: administration of antibiotics, anti-viral therapy, other COVID-19 therapy, and use of supplemental oxygen and noninvasive or invasive ventilation. A data and safety monitoring board (DSMB) oversaw the study. After the first 20 and 40 patients were enrolled and treated with 5 days of sargramostim, the DSMB reviewed safety data. The study continued as planned with no changes needed due to safety findings. At these interim assessments, levels of c-reactive protein (CRP) and ferritin were lower and declining during sargramostim treatment, compared to control patients whose CRP levels remained higher and ferritin levels increased during the same time period. Furthermore, during treatment, patients who received sargramostim had greater improvements in eosinophils and lymphocyte counts than control patients, showing improvement in immune function (personal communication by Prof Bart Lambrecht, Principal Investigator [PI]). Preliminary results from this study in patients with COVID-19 indicate that cytokine storm is not occurring with sargramostim use in this patient population.

An additional investigator-sponsored study in Singapore (NCT04400929), "Using GM-CSF as a Host Directed Therapeutic Against COVID-19" was initiated in June 2020. This randomized placebo-controlled trial is actively recruiting and is evaluating sargramostim by IV administration in approximately 30 patients with COVID-19.

The ongoing Partner Therapeutics study, iLeukPulm (PTX-001-002, NCT04411680) is a Phase 2 trial evaluating sargramostim in hospitalized patients with COVID-19 associated acute hypoxemia. This study will randomize approximately 120 patients with COVID-19; 80 will receive sargramostim plus the SOC, and 40 patients will receive SOC alone. All patients on the sargramostim arm will be treated with 125 mcg inhaled sargramostim twice for 5 days delivered via a vibrating mesh nebulizer, in addition to institutional SOC. A DSMB is overseeing this study. After the first 9 and 22 patients were enrolled and treated with 5 days of sargramostim, the DSMB reviewed safety data. Additional safety reviews were performed after approximately 60 and 80 patients (total across both arms) were randomized. The study continued as planned with no changes needed based on safety findings.

In COVID-19 studies described above, about 120 patients have received inhaled sargramostim for treatment of COVID-19. However, these studies are in patients who were hospitalized with more severe

disease. Observed safety in these studies informs potential benefits and risks for evaluating inhaled sargramostim in patients with mild to moderate COVID-19 who are at high-risk for progression to more severe disease.

GM-CSF is vital to maintain and restore lung function and immune homeostasis, clinical data in critically ill patients and patients with COVID-19 support safety of inhalational sargramostim. Hence, this randomized double-blind placebo-controlled study will evaluate whether once-daily inhaled sargramostim for 5-days can prevent progression to more severe disease in an outpatient setting in symptomatic patients with mild or moderate COVID-19 who are at high risk for progression to more severe disease.

Furthermore, available pharmacokinetic data in healthy volunteers, suggests that a single inhaled sargramostim dose (125 mcg, 250 mcg or 500 mcg) supports dose proportional exposure (35). Based on the totality of available data, including with approximately 120 hospitalized patients treated with inhaled sargramostim 125 mcg twice daily for COVID-19, a once daily dose of 250 mcg of inhaled sargramostim has been chosen for this outpatient study. Also, the study drug will be prepared and administered at the investigational site, therefore, a single daily dose enables both patient convenience and treatment compliance. A single daily dose also minimizes exposure to an infectious agent for the health care staff.

Since early 2021, the number of individuals in the US vaccinated against COVID-19 continues to increase. As of August 9, 2021, more than 166 million people in USA have been fully vaccinated. While many vaccinated individuals who get COVID-19 may be asymptomatic or have mild symptoms, over 8000 fully vaccinated patients have been reported to have a breakthrough COVID-19 infection and been hospitalized or died (7). While these numbers are likely undercounted, hospitalizations and deaths are much less likely to occur among fully vaccinated individuals compared to unvaccinated or partially vaccinated individuals. Although the great majority of SARS-CoV-2 infected individuals presenting for health care are unvaccinated, the large number of vaccinated individuals raises the possibility that a significant number of screened subjects might have been vaccinated. Therefore, the number of subjects who have been vaccinated will be capped at approximately 100 in order to ensure adequate power to determine the efficacy of sargramostim.

# 5 OBJECTIVES

## 5.1 Primary Objective

| Primary Objective | Primary Outcome Measure |
|---|---|
| To evaluate if inhaled sargramostim can prevent progression to more severe disease in an outpatient setting in symptomatic patients with mild or moderate COVID-19 who are at higher risk for progression to more severe disease | Proportion of patients who experience any emergency room visit or hospitalization, or death by Day 28. |

## 5.2 Secondary Objectives

| Secondary Objectives | Secondary Outcome Measures |
|---|---|
| To evaluate the effect of inhaled sargramostim on clinical progression of COVID-19 | Proportion of patients with any progression of disease as determined by a ≥ 2-point increase from baseline in the NIAID ordinal scale up to Day 28, and Day 60. |
| | Time to progression of disease as determined by a ≥ 2-point increase in the NIAID ordinal scale up to Day 28, and Day 60 |
| | Change from baseline in overall symptom score, and individual symptom scores, as measured by the symptom questionnaire up to Day 28. |
| To evaluate the safety of inhaled sargramostim in patients with COVID-19 | AEs up to Day 60. |

## 5.3 Exploratory Objective

| Exploratory Objective | Exploratory Outcome Measures |
|---|---|
| To explore the effect of inhaled sargramostim on biological responses to COVID-19. | Proportion of patients requiring supplemental oxygen up to Day 28 |
| | The effect of sargramostim on SARS-CoV-2 viral load in samples collected from nasopharyngeal swabs up to Day 14 (biomarker cohort only) |
| | Proportion of patients with generation of SARS-CoV-2 antibody up to Day 28 (biomarker cohort only) |
| | Proportion of patients with markers of cellular immunity, via immunophenotyping, up to Day 14 (biomarker cohort only) |
| | Levels of ferritin, CRP, d-Dimer up to Day 28 |
| | Immunogenicity to sargramostim up to Day 28 (biomarker cohort only) |
| | Presence or absence of COVID-19 symptoms at Day 60 |

# 6 STUDY DESIGN

This study is a randomized placebo-controlled double-blind study.

Neither patients, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base lock at the conclusion of the study.

## 6.1 Study Description

This Phase 2b study will randomize approximately 500 patients who are symptomatic with mild or moderate COVID-19 (as defined in the Food and Drug Administration (FDA) Guidance Document: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention, May 2020) who are at high risk for progression to more severe disease. Patients will be randomized in a 1:1 ratio to inhaled sargramostim plus SOC or placebo plus SOC. Enrollment of patients who have completed a COVID-19 vaccination regimen or participated in a COVID-19 vaccine clinical trial will be capped at approximately 100 patients.

All patients will be randomized to receive either 250 mcg of sargramostim or equivalent volume of placebo diluent. Treatment will be administered once daily for 5 days delivered via a vibrating mesh nebulizer. Additional blood samples will be collected for biomarker assays for approximately 100 randomized patients (approximately 50 from each treatment group).

Patients will be followed for up to 60 days after start of treatment.

## 6.2 Randomization

Each eligible patient will be randomized to either the treatment (inhaled sargramostim) or placebo groups using a 1:1 randomization ratio with stratification based on

- geographic region (US, outside the US), and
- completion of a COVID-19 vaccination regimen or participation in a COVID-19 vaccine clinical trial (yes, no).

Patients will be randomized using a centralized, automated randomization system, which will be used to assign a blinded treatment assignment to each patient.

### 6.2.1 Emergency Unblinding

Emergency unblinding may be required for medical management of patients:

- Patient safety must always be the first consideration in making such a determination.
- In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted.
- The investigator should make all attempts to contact the Medical Monitor in advance of unblinding.
- If a patient's treatment assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance.

### 6.2.2 Replacement of Ineligible Patients

Ineligible patients will not be replaced after enrollment.

## 7 ELIGIBILITY CRITERIA

Clinical significance of underlying medical conditions and judgements related to the best interests of the patient are determined by the investigator. Sponsor consultation with the medical monitor is encouraged where there is a concern.

### 7.1 Inclusion Criteria

1) Patients with a positive laboratory diagnosis of SAR-CoV-2 infection by an antigen or a molecular test ≤5 days prior to randomization. The test should have been authorized by the relevant regulatory authority.
2) Have one or more of the following mild or moderate COVID-19 symptoms for ≤5 days prior to randomization:
    a. Fever or chills
    b. New onset or worsening cough
    c. Sore throat
    d. Malaise or fatigue
    e. Headache
    f. Muscle pain (myalgias) or body aches
    g. Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)
    h. New onset or worsening shortness of breath or difficulty breathing
    i. Nasal congestion or runny nose
    j. New loss of taste (ageusia) and/or smell (anosmia). Note: any of these symptoms (ageusia, anosmia) alone or in combination cannot be used as the SOLE qualifying symptoms for enrollment.
3) At higher risk for progression to more severe COVID-19
    a. Age ≥ 60 years
    b. Age 18-59 years with a clinically stable medical history of at least 1or more of the following conditions that could lead to severe COVID-19
        i. Chronic respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis
        ii. Obesity with BMI ≥ 30 kg/m2
        iii. Cardiovascular disease
        iv. Sickle cell disease or thalassemia
        v. Diabetes mellitus being managed with concomitant medications

vi. Hypertension being managed by concomitant medications

vii. Chronic kidney disease

4) Oxygen saturation by pulse oximeter > 93% on room air. Note: at altitudes of >4000 feet above sea level, oxygen saturation by pulse oximeter > 91% on room air is permitted
5) Negative pregnancy test (if woman of childbearing potential)
6) Females of childbearing potential and males with female partners of childbearing potential must agree to use acceptable contraceptive methods from screening to Day 28 (see Section **12.4** for Contraceptive Guidance)
7) The patient (or legally authorized decision maker) must give informed consent

### 7.2 Exclusion Criteria

1) Hospitalized patients
2) Patients who have received or are receiving treatments that are not approved/authorized by the relevant regulatory authority for the treatment of patients with mild or moderate COVID-19 in an outpatient setting
3) Patients enrolled in interventional clinical trials for other experimental therapies
4) Patients on chronic oxygen supplementation due to cardiopulmonary or other conditions
5) Patients with unstable comorbid conditions (e.g., decompensated congested heart failure, COPD with exacerbation, current angina pectoris, uncontrolled diabetes mellitus, uncontrolled hypertension, uncontrolled asthma)
6) Patients with severe pulmonary comorbid conditions, including systemic steroid- dependent asthma, systemic steroid-dependent COPD, oxygen-dependent COPD, lung transplant, or cystic fibrosis
7) Patients who have received highly immunosuppressive therapy (to include systemic corticosteroids) or anti-cancer combination chemotherapy within 24 hours prior to first dose of study drug
8) Patients with known or suspected intolerance or hypersensitivity to sargramostim, or any component of the product
9) Patients who have previously experienced severe and unexplained side effects during aerosol delivery of any kind of medical product
10) Pregnant or breastfeeding females
11) Patients who, in the opinion of the Investigator, will not be able to comply with all the study procedures and visits as outlined in the schedule of events, including follow-up

## 8 DRUG INFORMATION

### 8.1 Treatment Regimen

All patients will be randomized to receive either 250 mcg of sargramostim or equivalent volume of placebo diluent. Treatment will be administered once daily for 5 days delivered via a vibrating mesh nebulizer.

Patients will be observed in the clinic for approximately 30 minutes after the completion of the drug administration.

Refer to the Pharmacy Manual for full details on study drug supply, preparation, and accountability.

#### 8.1.1 Dose Modifications

Patients with documented white blood cell count > 50,000/mm3 should stop study treatment.

### 8.2 Concomitant Medications and Medical Procedures

All concomitant medications administered during the patient's participation in the study until Day 60 must be recorded in the source documents and eCRF.

#### 8.2.1 Permitted therapies

##### 8.2.1.1 Outpatient setting

- Medications such as antipyretics, antiemetics, antidiarrheals, analgesics, and other medications intended to treat signs and symptoms of COVID-19.
- Antibiotics can be used to treat suspected bacterial respiratory infections secondary to COVID-19.
- Oxygen supplementation, as needed, including low-flow oxygen, high-flow oxygen, or any other form of respiratory support per the Investigator discretion
- Medications to treat underlying or newly diagnosed medical conditions
- Approved/authorized (by the relevant regulatory authority) treatments (including monoclonal antibodies) for patients with mild or moderate COVID-19 in an outpatient setting.

##### 8.2.1.2 Inpatient setting

If a patient is hospitalized, patients should receive SOC for COVID-19 per the institutional standards without any exceptions. If a patient is hospitalized, prior to completing the 5 days of study treatment, the study treatment should be discontinued. Patients who discontinue study treatment will continue to be evaluated for efficacy and safety endpoints.

#### 8.2.2 Prohibited therapies in the outpatient setting

- Use of GM-CSF for any purpose other than study treatment.
- Any investigational drugs or non-approved/authorized (by the relevant regulatory authority) treatments for patients with mild or moderate COVID-19 in an outpatient setting during the period of study participation.

#### 8.2.3 COVID-19 Vaccination

Patients who are at least 2 weeks post completion of a COVID-19 vaccination regimen (either 2 dose or 1

dose regimen as applicable) can be included in the study.

Patients who need to start a COVID-19 vaccination regimen, can do so only after Day 21 of the study.

Patients who participated in and completed a COVID-19 vaccine clinical study can be included.

# 9 STUDY EFFICACY AND SAFETY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Events (**Table 1**). Adherence to the study procedures and their timing is essential for study conduct. All screening evaluations should be done after signing of the informed consent document. They must be completed and reviewed to confirm that potential patients meet all eligibility criteria.

## 9.1 Study Visits

The screening visit, Day 1 through Day 5, Day 14, and Day 28 visits should take place at the investigational site. If the patient is unable to come to the investigational site, the procedures may be done via home health care (HHC) visit.

Telemedicine (TM) or HHC visits will be conducted daily during Days 6-13 and every other day during Days 15-27, and at Day 60. A TM visit is defined as a member of the study staff contacting the patient via a video or telephone call to check on the patient's well-being. If the study site research staff detects a decline in a patient's condition (e.g., pulse ox ≤ 93%), in consultation with the site clinical staff the patient should get a HHC visit or be directed to return to the clinic or go to the Emergency Room or hospital affiliated with the investigational site.

HHC visits are defined as a health care provider visiting the patient at their home setting to facilitate vital signs collection (body temperature, blood pressure, pulse rate) and pulse oximetry and/or to assess the patient's condition.

Baseline is considered to be either the screening or Day 1 assessment that occurs closest to and prior to the first dose of study treatment.

## 9.2 Ordinal Scale

A patient's status will be assessed by study staff per the Schedule of Events using the NIAID Ordinal Scale (**Appendix A**).

## 9.3 Symptom Questionnaire, Patient Global Impression, and Day 60 Symptom Evaluation

Patients in the outpatient setting, will rate their severity of symptoms associated with COVID-19 by a daily questionnaire (Appendix B).

The questionnaire contains assessment of these symptoms:

- Nasal congestion/rhinorrhea
- Sore throat
- Shortness of breath

- Cough
- Fatigue
- Body aches and pain
- Headache
- Chills
- Feeling feverish
- Nausea
- Vomiting
- Diarrhea
- Sense of smell
- Sense of taste

Patient-reported global impression will be assessed daily by the patient reflecting their impression on their return to usual health, ability to perform usual activities in the past 24 hours, rated as Yes or No. In addition, patients will rate the severity of their overall COVID-19 symptoms, as none, mild, moderate, or severe. Patient global impression is shown in Appendix C.

The symptom questionnaire and patient global impression will be completed electronically, by the patient, at approximately the same time every day. An alternative format will be available for patients who cannot complete these questionnaires electronically. The symptom questionnaire should be completed first, then followed by the patient global impression. On the study drug dosing days this will be done prior to administration of the study drug. On other days, this will be done before any other study related procedure or assessment is performed.

Translations of these questionnaires will be available for patients. If a patient cannot read or does not have access to any translations in his/her language, a close contact of the patient can help the patient complete the assessments. Investigator or clinic staff should not help the patients complete these assessments.

At Day 60, patients will be asked for presence or absence of COVID-19 symptoms in the 7 days prior to the visit (see Appendix D).

### 9.4 Physical Examinations

A complete physical examination will be performed at screening. This examination will not include pelvic, rectal, and breast examinations unless clinically indicated. A targeted (symptom- directed) physical examination will be performed at other visits, as specified in the Schedule of Events, and as clinically indicated. A targeted physical examination can occur at the HHC visit or the clinic visit.

### 9.5 Vital Signs and Pulse Oximetry

Vital signs and pulse oximetry will be measured as specified in the Schedule of Events and as clinically indicated. Vital signs include body temperature, blood pressure, pulse rate, and respiration rate.

Vital signs and pulse oximetry at additional times may be measured during the study if warranted, as determined by the Investigator.

Vital signs and pulse oximetry in the home setting will be obtained by the patient using devices provided by the sponsor. In home vital signs and pulse oximetry will be performed at approximately the same time of day. The site staff will obtain the vital sign and pulse oximetry data from the patient for recording on the eCRF.

### 9.6 Clinical Laboratory Assessments

All clinical laboratory assessments will be performed at a central laboratory, except for urine pregnancy test and initial diagnostic SARS-CoV-2 test used for study inclusion. See Schedule of Events for the timing and frequency. See laboratory manual for sample collection details.

Hematology laboratory parameters will include complete blood count with differential, hemoglobin, hematocrit, and absolute counts for white blood cells, platelets, neutrophils, lymphocytes, eosinophils, and monocytes.

Chemistry laboratory parameters will include albumin, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, bicarbonate, calcium, and uric acid.

Additional laboratory parameters will include serum ferritin, d-Dimer, and CRP.

Clinically significant abnormal laboratory findings are those which are not associated with COVID-19, unless judged by the Investigator to be more severe than expected for the patient's condition. These laboratory findings will be deemed clinically significant if needing intervention (e.g., discontinuation of study drug, need for additional procedures, need for concomitant medications) and/or associated with an SAE or an AE.

The Investigator must review the laboratory report, document this review, and record any clinically significant abnormal findings occurring during the study in the AE section of the Case Report Form (CRF).

If a clinical laboratory assessment performed at the Investigators local laboratory leads to a change in patient management or is considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), it will be reported in the AE section of the CRF.

### 9.7 Pregnancy Testing

Women of childbearing potential (WOCBP) must undergo urine pregnancy testing at the investigative site according to the Schedule of Events.

### 9.8 Emergency Room Visit, Hospitalizations and Deaths

Hospitalization will be defined as ≥24 hours of acute care.

If a patient treated in the outpatient setting is subsequently hospitalized, study treatment should be discontinued. Patients should continue on study for the efficacy and safety evaluations.

Every effort should be made to collect the following data from the emergency room visit or hospitalization

- NIAID ordinal scale information
- Whether the visit was related to COVID-19
- Death

Record on the CRF if the following events occur:

- Emergency room visits
- Hospitalization and discharge
- ICU admittance and discharge
- Extended care facility admittance and discharge

### 9.9 SARS-CoV-2 Variant Assessment

The presence of SARS-CoV-2 variants on Day 1 will be evaluated by nasopharyngeal swabs collected in all patients per the Schedule of Events (Table 1). See laboratory manual for sample collection details.

### 9.10 Exploratory Biomarker Assessments

Approximately 100 patients (approximately 50 from each treatment group) enrolled into the study at selected sites, will have the samples collected for biomarker assessments as detailed below. These samples may also be used for additional exploratory analysis of biomarkers to further understand pathways associated with COVID-19 disease, and sargramostim pharmacokinetics and pharmacodynamics.

#### 9.10.1 SARS-CoV-2 Viral Load Assessment

The SARS-CoV-2 viral RNA level and viral clearance will be evaluated by nasopharyngeal swabs collected per the Schedule of Events (Table 1). See laboratory manual for sample collection details.

#### 9.10.2 Anti-SARS-CoV-2 Antibody Assessments

Blood samples will be collected per the Schedule of Events to assess the generation and level of antibody production against SARS-CoV-2. See laboratory manual for sample collection details.

#### 9.10.3 Immunophenotyping for Cellular Immunity

Blood samples will be collected per the Schedule of Events for immunophenotyping to assess changes in cellular immunity. See laboratory manual for sample collection details.

#### 9.10.4 Sargramostim Immunogenicity Assessment

Blood samples will be collected per the Schedule of Events to assess sargramostim anti-drug antibodies. See laboratory manual for sample collection details.

# 10 SAFETY MONITORING

All AEs will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

## 10.1 Definitions

### 10.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient administered study treatment and which does not necessarily have to have a causal relationship with this treatment.

This includes the following:

- AEs not previously observed in the patient that emerge during the reporting period, that were not present prior to the AE reporting period
- Preexisting medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the reporting period

The following clinical events associated with COVID-19 are exempt from AE reporting unless deemed by the Investigator to be related to the administration of study drug:

- Hypoxemia/respiratory failure due to COVID-19 requiring supplemental oxygen, high flow oxygen devices, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation.

The following clinical events associated with COVID-19 are exempt from AE reporting unless deemed by the Investigator to be related to the administration of study drug and/or judged by the Investigator to be more severe than expected for the patient's condition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments
- Expected progression, signs, or symptoms of COVID-19

All hospitalizations, emergency room visits, and deaths are part of the efficacy evaluation of this study, whether they are considered AEs/SAEs or not. Hence, they are required to be reported on the appropriate pages of the Case Report Form. See Section 9.8.

### 10.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence regardless of causality that results in any of the following:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

- An important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

If an event is not an AE as defined above (Section **10.1.1**), then it cannot be an SAE even if conditions for seriousness are met (e.g., hospitalization for signs/symptoms of COVID-19, death due to progression of COVID-19).

## 10.2 Safety Reporting

### 10.2.1 Adverse Event Reporting

All AEs (as defined in section 10.1.1) regardless of seriousness, starting from informed consent (i.e., occurring during the baseline period even in the absence of any administration of study treatment), until participation in the study has ended (Day 60) are to be recorded on the CRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, severity, action taken with respect to study drug, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

AE should be followed until the event has resolved, stabilized, has decreased in severity to the same or less than baseline (pre-treatment), or patient has completed the follow-up period.

Vital signs abnormalities are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or modification of dosing and/or fulfilling a seriousness criterion.

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation, modification of dosing, fulfill a seriousness criterion, additional concomitant therapy, and/ or additional medical procedures.

Treatment-emergent AEs are AE that begin or worsen after the start of treatment.

### 10.2.2 Attribution of the AE

The relationship or attribution of an AE to study treatment is defined as follows:

- *Definite* - The AE is clearly related to the study treatment
- *Probable* - The AE is likely related to the study treatment
- *Possible* - The AE may be related to the study treatment
- *Unlikely* - The AE is doubtfully related to the study treatment
- *Unrelated* - The AE is clearly NOT related to the study treatment

### 10.2.3 Grading of Adverse Events

All AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 or later. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

**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), i.e., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, i.e., bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

**Grade 4**: Life-threatening consequences; urgent intervention indicated

**Grade 5:** Death related to AE

CTCAE resources:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Quick reference guide:

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

### 10.2.4 Serious Adverse Event Reporting

In the case of a SAE, a pregnancy report, or an overdose, the Investigator must immediately:

- REPORT (**within 24 hours of becoming aware of an SAE** by fax or e-mail) information related to the SAE, pregnancy, or overdose to Partner Therapeutics as noted below:

e-mail: projects.partnertx@symogen.com and ScopeSAEs@partnertx.com,
or
fax number: +44 (0) 1628 460018

ENTER SAE information on SAE Report Form and complete the AE CRF. Include a photocopy of all examinations done and dates on which these examinations were performed. Care should be taken to ensure that patient identity is protected (and redacted), and patient trial identifiers are present on copies of source documents provided to the Partner Therapeutics. For laboratory results, include laboratory normal ranges.

- All further data updates should be recorded in the SAE reporting form and AE CRF, as appropriate. Further documentation with additional laboratory data, concomitant medication, and patient status should be reported to Partner Therapeutics as above within 24 hours of knowledge. Fatal or life-threatening SAEs should be updated within the week (7 days) following initial notification.

- An SAE occurring at a different time interval or otherwise considered unrelated to a previously reported one should be reported separately as a new event.

### 10.2.5 Pregnancy

Patients who become pregnant will be discontinued from the study treatment and should continue to be followed for efficacy and safety evaluations. If a pregnancy is reported, the Investigator should inform Partner Therapeutics within 24 hours of learning of the pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the newborn, and the information will be forwarded to Partner Therapeutics. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Additionally, congenital anomalies in the neonate and ectopic pregnancy are considered SAEs.

## 10.3 Expected and Unexpected Toxicities

Refer to the Investigator Brochure for any expected or unexpected toxicities. These will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

# 11 SCHEDULE OF EVENTS AND STUDY PARAMETERS

**Table 1: Schedule of Events**

| | Screen | Treatment Period | | | | | Post-treatment Period | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **(-5)-0 [a]** | **1** | **2** | **3** | **4** | **5** | **6-13 [b]** | **14 ± 2** | **15-27 [c]** | **28 ± 2** | **60 ± 7** |
| **Visit Location** | **C** | **C** | **C** | **C** | **C** | **C** | **TM or HHC** | **C** | **TM or HHC** | **C** | **TM or HHC** |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria Review | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| SARS-CoV-2 Test | X | | | | | | | | | | |
| Pregnancy Test [d] | X | | | | | | | | | | |
| Randomization | | X | | | | | | | | | |
| Patient Reported Outcomes: | | | | | | | | | | | |
| Symptom Score Questionnaire | | X [f] | X [f] | X [f] | X [f] | X [f] | X | X | daily | X | |
| Patient Global Impression | | X [f] | X [f] | X [f] | X [f] | X [f] | X | X | daily | X | |
| Day 60 COVID-19 Symptom Evaluation | | | | | | | | | | | X |
| NIAID Ordinal Scale | | X [f] | X | X | X | X | X | X | X | X | X |
| ER/Hospitalization and associated Events [i] | | X | X | X | X | X | X | X | X | X | X |
| Physical examination [e] | X | X [f] | X [f] | X [f] | X f | X [f] | | X | | X | |
| Vital Signs and Pulse oximetry [g] | X | X [f] | X [f] | X [f] | X [f] | X [f] | X | X | X | X | |
| Hematology with Differential | | X [f] | | | | | | X | | X | |
| Blood Chemistry | | X [f] | | | | | | X | | X | |
| CRP/Ferritin/d-Dimer | | X [f] | | | | X | | X | | X | |
| Nasopharyngeal Swab | | X [f] | | | | | | | | | |
| Blood samples for biomarker cohort<br>Anti-SARS-CoV-2 antibody [h] | | X [f] | | | | X [f] | | X | | X | |
| Immunogenicity [h] | | X [f] | | | | X [f] | | X | | X | |
| Immunophenotyping [h] | | X [f] | | | | X [f] | | X | | | |
| Nasopharyngeal Swab (biomarker cohort only) [h] | | | | | | X [f] | | X | | | |
| Study Drug Administration | | X | X | X | X | X | | | | | |
| AE Monitoring | | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X |
| Oxygen supplementation | X | X | X | X | X | X | X | X | X | X | X |
| Survival status | | X | X | X | X | X | X | X | X | X | X |

Abbreviations: C = Clinic; TM = Telemedicine; HHC = Home Health Care

a. Day 0 and Day 1 procedures can be done on the same day.
b. Telemedicine/HHC visits will be conducted **daily** by video call or telephone call
c. Telemedicine/HHC visits will be conducted **every other day** by video or telephone call
d. Urine pregnancy test for women of child-bearing potential
e. A complete physical examination will be conducted at screening. A targeted (symptom-directed) physical examination may be conducted at other clinic visits.
f. Must be collected/done prior to study treatment administration
g. Vital signs include body temperature, blood pressure, pulse rate, respiration rate (clinic/HHC visits only)
h. After Day 1, no sample collection needed if patient is hospitalized.
i. Record if the following events occur: Emergency room visits, hospitalized, ICU admittance, Extended care facility admittance, and discharge

# 12 RISKS AND TOXICITIES

## 12.1 Overdose

There is no clinical experience with overdose of sargramostim, and no specific antidote or detoxification measures can be recommended to date. If accidental overdose is suspected, the patient should be treated symptomatically.

## 12.2 Pregnancy

There are limited data in pregnant and breastfeeding women. There is potential for increased risk of spontaneous abortion based on rabbit studies. Investigators should counsel patients of the risk to the fetus.

Note: this information is based on systemic administration of sargramostim. There are no data available for inhaled sargramostim.

## 12.3 Pregnancy Risk Summary

Limited available data on sargramostim use in pregnant women are insufficient to inform drug- associated risk of adverse developmental outcomes. Based on animal studies sargramostim may cause embryofetal harm. In animal reproduction studies, administration of sargramostim to pregnant rabbits during organogenesis resulted in adverse developmental outcomes including increased spontaneous abortion at systemic exposures ≥1.3 times the human exposure expected at the recommended human dose. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the

U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2%-4% and 15%-20%, respectively.

## 12.4 Contraceptive Guidance

A woman is of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 consecutive months without an alternative medical cause.

A man is considered fertile after puberty unless sterile by bilateral orchidectomy or vasectomy.

Acceptable effective methods of contraception for WOCBP to be used from time of screening through Day 28 include:

- combined (estrogen and progestogen containing) hormonal contraception associated with

inhibition of ovulation: oral, intravaginal, transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm, or sponge with spermicide
- combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence – continuous abstinence during the study period

Male patients with pregnant or non-pregnant WOCBP partner should use condoms from time of screening through Day 28. Additionally, they should not donate sperm during this period.

# 13 STUDY DURATION AND EARLY TERMINATION

## 13.1 Treatment Discontinuation Criteria

Patients will receive sargramostim or placebo, in addition to the SOC, unless:

- patient withdraws consent or decision by the patient (or his/her legally authorized decision maker), or Investigator/attending physician decides to stop treatment
- unacceptable toxicity to study drug
- rapid deterioration requiring other advanced treatments or medical care not conducive to continued treatment with study drug
- pregnancy
- death

Patients who discontinue treatment early, should remain on study and continue follow-up per the schedule of events (unless consent is withdrawn from study participation).

Only patients that have withdrawn their consent to participate in the trial are excluded from further follow-up after their consent has been withdrawn. Any available data up to the date of withdrawal of consent will be used for the purpose of this study.

All efforts should be made to follow a patient for survival through Day 60. For patients who are lost to follow-up, or contact cannot be made (despite repeated attempts), Investigators are strongly encouraged to contact the patient's next of kin or legally authorized representative, and/or to search publicly available records (as permitted by local laws) to determine patient survival status.

If a patient is discontinuing study prior to Day 60, all Day 60 evaluations should be completed at discontinuation.

### 13.2 Treatment Period (Days 1-5)

All randomized patients will receive study drug for 5 days (unless hospitalized on/before Day 5 when study drug should be discontinued). Patients who are hospitalized should continue on study for the efficacy and safety evaluations. Day 1 is the day the patient receives the first dose of the study treatment.

If at any time the constraints of this protocol are detrimental to the patient's health, the study drug should be discontinued. This includes any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy is not in the best interest of the patient.

### 13.3 Post-Treatment Period (Days 6-60)

Following the treatment period (Days 1-5), patients should continue to receive SOC (see Section 8.2) as appropriate per the Investigator. The patients will undergo study assessments per the Schedule of Events.

All patients, including those who discontinue treatment early, should be followed for the duration of the study.

### 13.4 Study Completion

Study completion will be defined as the date when the last patient completes the Day 60 visit or an early termination visit. The study may be stopped earlier for reasons such as poor enrollment, ethical or safety reasons.

## 14 STATISTICAL PLAN

### 14.1 Sample Size

A total of approximately 500 patients will be randomized using a 1:1 assignment ratio. The sample size is selected to achieve at least 80% power to detect a difference at the 0.05 level of significance (2-sided) in the proportion of patients who experience any emergency room visit or hospitalization, or death over 28 days.

This sample size is based upon an assumed 3% rate for the sargramostim arm and a 10% rate for the placebo arm (risk ratio of 0.30) in unvaccinated patients (similar to that observed for bamlanivimab BLAZE-1 study (10, 18, 19). As discussed in Section 4.6, the rate of any emergency room visit or hospitalization, or death over 28 days is expected to be very low, or near zero for vaccinated patients.

It is also assumed that the proportion of vaccinated patients will be approximately 20-25% of the study population, with enrollment of patients who have completed a COVID-19 vaccination regimen or participated in a COVID-19 vaccine clinical trial capped at approximately 100 patients; no events are expected to occur in these patients for either treatment arm. Therefore, the overall event rate (for

unvaccinated and vaccinated patients combined) for the primary endpoint is expected to be 2.4% for sargramostim and 8.0% for placebo (risk ratio of 0.30) and maintains at least 80% power. As discussed in Section 6.2, one of the randomization stratification factors is completion of a COVID-19 vaccination regimen or participation in a COVID-19 vaccine clinical trial (yes, no).

The Sponsor (or designee) will monitor (in a blinded manner and pooled across both treatment arms) the usage rate of authorized/approved therapies (such as monoclonal antibodies) for patients with mild or moderate COVID-19 in an outpatient setting. If there is a notable rate of these therapies, which could further impact the assumed event rates for the primary endpoint, a re-evaluation of sample size and power may be required. In this scenario, no adjustment to Type 1 error is required. Further details will be provided in the Statistical Analysis Plan.

### 14.2 General Statistical Methods

As this is a Phase 2b study; no adjustments for multiple comparisons will be made. Derivation of two-sided 95% confidence intervals and p-values will be generated where applicable.

Continuous endpoints will be summarized by n, means, medians, minimum, maximum, and 25th and 75th percentiles.

Alternative statistical methods will be employed if underlying assumptions and/or distributions for a given statistical method are not satisfied. If there are insufficient numbers of patients or events for any randomization stratification factor (such as COVID-19 vaccination) to permit valid stratified analyses, then factor(s) may be dropped from analyses.

Missing data may be imputed using last-observation-carried forward, or other advanced statistical imputation methods (such as linear interpolation or multiple imputations), depending on the endpoint. Methods for handling missing data will be specified in the Statistical Analysis Plan.

Additional exploratory analyses may be performed to evaluate the robustness and sensitivity of the study results, including but not limited to the analysis populations, subgroup analyses, treatment interactions, adjusted or stratified analyses, and/or alternative statistical methods.

A Statistical Analysis Plan will contain further details of the planned statistical analyses for efficacy and safety endpoints. Unblinding details will be specified in the unblinding plan section of the Statistical Analysis Plan or in a separate unblinding plan document.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the Statistical Analysis Plan prior to unblinding.

### 14.3 Analysis Sets

Full Analysis Set: All randomized patients and analyzed according to the treatment as randomized. This population is analogous to an intent-to-treat population.

Modified Intent-To-Treat (mITT): All randomized patients who meet eligibility criteria and receive at least 1 dose of any study treatment. Patients will be excluded from the mITT Population, if they fail to meet eligibility criteria or if they do not receive any study treatment. This population will be used for the purposes of sensitivity analyses, and analyses will be performed according to the treatment as randomized.

Safety Set: All randomized patients receiving 1 or more doses of either study treatment, analyzed according to the treatment as received on Day 1.

### 14.4 Efficacy Analysis

Unless otherwise specified, the efficacy analysis will be performed on the full analysis set.

The efficacy analyses will consider all data, regardless of any intercurrent events, such as early discontinuation of therapy, any protocol deviations, or any additional treatments for COVID-19; i.e., the treatment policy strategy.

#### 14.4.1 Description of Patient Population

Patient disposition, demographics, baseline SARS-CoV-2 test, SARS-CoV-2 variant, and any concomitant procedures/surgeries, will be summarized. A summary of each analysis population will be tabulated, including any reasons for exclusion from a given analysis population.

Baseline medical history (including preexisting conditions) will be coded using the latest version of the Medical Dictionary for Regulatory Activities. Medical history will be summarized by system organ class and preferred term; a patient will only be counted once per system organ class and once per preferred term within a treatment group.

Concomitant medications will be coded using the most current WHO Drug Dictionary and summarized by drug class and medication term with results presented by treatment group.

Intercurrent events such as early discontinuation of treatment, any treatment crossover, any major protocol deviations, and any other approved or authorized treatments to prevent progression of COVID-19 disease severity or to treat COVID-19 (such as monoclonal antibodies, antivirals such as remdesivir, etc.) will be tabulated.

#### 14.4.2 Primary Endpoint

The primary endpoint is the proportion of patients who experience any emergency room visit or hospitalization, or death by Day 28. Any occurrence of any of the 3 types of events will be considered as an event.

Statistical hypothesis testing for the primary endpoint will be conducted using a logistic regression model with a Firth penalized likelihood (16) at the two-sided 0.05 significance level. The model will include treatment as the independent variable. Event rates within strata will be evaluated to determine whether it is appropriate to conduct a sensitivity analysis that which includes, stratification by the randomization stratification factors for geographic region (US vs outside US) and completion of a COVID-19 vaccination regimen or participation in a COVID-19 vaccine clinical trial (yes, no).

The primary estimand of treatment effect will be the treatment risk difference between arms, the corresponding 95% confidence interval (CI), and p-value. Additionally, the odds ratio, corresponding 95% CI, and p-value will be generated.

The proportion of patients who have any emergency room visit or hospitalization, or death by Days 7, 14 and Day 28 will be tabulated. A Chi-square or Fisher's exact test will compare treatment arms at each timepoint of interest.

A sensitivity analyses of the primary endpoint will be the analysis of COVID-19-related emergency room visits, COVID-19-related hospitalizations, or deaths (any cause). The analysis methods will mirror the primary endpoint as specified above.

A sensitivity analysis of the primary analysis will use the modified Intent-to-Treat population. The analysis methods will mirror the primary endpoint as specified above.

### 14.4.3 Secondary Endpoints

#### 14.4.3.1 Proportion of patients with any progression of disease as determined by a ≥ 2-point increase in the NIAID ordinal scale up to Day 28 and Day 60

The proportion of patients with any progression of disease as determined by a ≥ 2-point increase in the NIAID ordinal scale up to Day 28 and Day 60 (e.g., a change from 2 to 4, or a change from 2 to 5). The analysis will be performed using a logistic regression model as specified above for the primary endpoint and will have the same estimands.

The proportion of patients with any progression of disease as determined by a ≥ 2-point increase in the NIAID ordinal scale by Days 7, 14, 28 and 60 will be tabulated. A Chi-square or Fisher's exact test will compare treatment arms at each timepoint of interest.

In the event of missing NIAID assessments, hospitalization records, supplemental oxygen use, or death, provided the data are known, can be used to impute the NIAID ordinal score.

#### 14.4.3.2 Time to progression of disease as determined by a ≥ 2-point increase in the NIAID ordinal scale up to Day 28 and Day 60

The time to progression is defined as the time from randomization to the first occurrence of a ≥ 2-point increase in the NIAID ordinal scale up to Day 60. Patients who do not have a ≥ 2-point increase in the NIAID ordinal scale up to Day 60 will be censored at the date of last non-missing NIAID assessment up to Day 60. If the event of missing NIAID assessments, hospitalization records, supplemental oxygen use, or death, provided the data are known, can be used to impute the NIAID ordinal score.

Kaplan Meier methods will be used for time to event endpoint analyses. A stratified logrank test (stratified by the 2 randomization factors) will compare the two treatment arms. Timepoints estimates (7, 14, 28 and 60 days) and median point estimates will be derived from the Kaplan Meier analysis. The primary estimands of treatment effect will be the hazard ratio and 95% CI, derived from a Cox proportional hazards, stratified by the 2 randomization factors, along with comparisons of the timepoint estimates at Day 28 and Day 60.

#### 14.4.3.3 Change from baseline in overall symptom score, and individual symptom scores, as measured by the symptom questionnaire up to Day 28

The overall symptom score will be calculated as a sum of the individual scores from the 14 questions on the symptom score questionnaire (Appendix B). Each response will be scored according to the FDA's Guidance on "Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment" (17). The scores correspond to the responses:

Questions 1-10: None = 0, Mild = 1, Moderate = 2, Severe = 3;
Questions 11-12: Not at all = 0, 1-2 times = 1, 3-4 times = 2, 5 or more times = 3;
Questions 13-14: Same as usual = 0, Less than usual = 1, No sense = 2.

Change from baseline in the overall symptom questionnaire score, and individual symptom scores from baseline to 28 will be analyzed using a mixed model repeated measures analysis with the missing at random assumption for handling missing data. The model will contain baseline as a covariate, treatment, day, and treatment-by-day interaction as fixed effects, along with strata for the 2 randomization factors. The primary estimand of treatment effect will be the treatment differences and corresponding 95% CIs, with p-values. Estimates at days 7 and 14 will also be generated. All available data will be used in the analysis.

A graphical approach for the overall symptom questionnaire score and each individual symptom will plot the means (and 95% confidence intervals) of the patient's daily symptom scores from baseline through Day 28, by treatment arm (e.g., linear plot over time).

### 14.4.4 Subgroup Analysis and Adjustment for Covariates

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory. Subgroup analyses will be conducted for the primary endpoint, and if warranted, on other efficacy endpoints. Subgroup by treatment interactions will be included to assess differential treatment effects.

Prior to performing the analyses, a blinded review of the baseline characteristics will be performed, to evaluate whether there are enough patients in each category. If there are insufficient numbers of patients in each category, some categories may be combined. Conversely, if there are more patients than expected in each category, additional categories may be considered.

Baseline characteristics will be considered for subgroup analyses and covariate adjustment in statistical models. As the science evolves, additional baseline factors may be considered for these analyses.

- Region (US, outside US)
- Completion of a COVID-19 vaccination regimen or participation in a COVID-19 vaccine clinical trial (yes, no).
- Age group (18-59, ≥ 60 years). For regulatory purposes, an additional analysis may be performed using age groups defined as 18-64, and ≥ 65 years. If there are enough patients ≥ 75 years or ≥ 85 years, these categories may be included.

- Number of pre-existing medical conditions which put patients at higher risk of progression to severe COVID-19 (0-1, 2 or more), based on inclusion criteria 3b. Note: age will be considered separately as denoted above. If there are enough patients for any pre-existing condition in Inclusion Criteria 3b, a subgroup analysis may be performed.
- Duration of any COVID-19 symptoms (0-2, 3-5 days)
- Baseline NIAID ordinal score (1, 2)
- Gender (male, female)
- Race (White, Black, or African American, Asian, all others)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body mass index (<18.5 kg/$m^2$, 18.5 to <25 kg/$m^2$, ≥25 to <30 kg/$m^2$, ≥30 kg/$m^2$)
- Baseline SARS-CoV-2 variant (groupings to be determined based on prevalence)
- Use of approved/authorized COVID-19 therapies (including monoclonal antibodies) prior to randomization (if there are enough patients)

To evaluate the precision of the estimates of the primary endpoint, covariate adjustment using baseline factors will be performed, in an exploratory manner. Covariate adjustment may be performed on the secondary efficacy endpoints.

- First, each baseline factor will be assessed for potential impact on the outcome of interest in a model containing treatment arm (and randomization stratification factors as appropriate). Baseline factors will be assessed based on a p-value < 0.05.

- Baseline factors with a p-value < 0.05, will be added to a multivariate model containing treatment arm (and randomization stratification factors as appropriate). A stepwise approach will be used to determine the final covariate-adjusted model for each outcome of interest.

### 14.5 Safety Analyses

The Safety Set will be used in the safety analysis.

Treatment administration and compliance will be summarized.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs and SAEs will be summarized by system organ class and preferred term; a patient will only be counted once per system organ class and once per preferred term within a treatment.

Clinical laboratory and other continuous parameter results (such as vital signs) at each time point and change from baseline will be displayed using summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values) by treatment group.

## 15 DATA AND SAFETY MONITORING BOARD

The DSMB will comprise of independent external experts to review the safety data and benefit/risk

evaluation from Day 1 - 28 (or study discontinuation) in approximately 100 randomized patients (total across both arms). Enrollment will not be paused during the DSMB process.

This safety and risk/benefit review will use the available safety and efficacy data to formulate a benefit/risk evaluation. The available data will be accepted as is, and the data may not have gone through data cleaning processes.

No formal interim efficacy analysis will be performed for the purpose of stopping the study. Based on the totality of data, if the DSMB perceives an unfavorable benefit/risk or overall lack of efficacy, the DSMB may recommend Partner Therapeutics take appropriate actions, including an enrollment pause, modifying or stopping the study, and/or requesting an additional DSMB data review and meeting.

Additional details will be provided in the DSMB charter.

## 16 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The PI and/or designee, will prepare and maintain adequate and accurate patient case histories with observations and data pertinent to the study. Study specific CRFs will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into standardized CRFs in accordance with the overall study schedule.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by study site personnel. All original source documentation must be maintained at the study site.

In accordance with Good Clinical Practices (GCP) and all applicable regulatory requirements, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

In signing this protocol, the Investigator understands and agrees to give access to the necessary source documentation and files to enable study monitoring by employees or representatives of Partner Therapeutics.

Monitoring of the study will be performed in compliance with GCP and all applicable regulatory requirements. Alternative methods of monitoring may need to be employed in light of the COVID-19 pandemic, and in accordance with FDA guidance: Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, and/or applicable guidance from other regulatory authorities.

## 17 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and applicable regulatory requirements, a quality assurance audit may be conducted. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after study completion. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. In the case of an audit or inspection, the Investigator or a designee will alert Partner Therapeutics as soon as he/she becomes aware of the audit or inspection.

The Investigator is responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by Partner Therapeutics and its designees, and/or regulatory agencies.

## 18 ETHICS

This study will be conducted in compliance with Institutional Review Board (IRB)/Ethics Committee (EC) and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP Guidelines; United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR § 50, 56, 312); the Declaration of Helsinki, and with applicable ICH guidelines regarding scientific integrity. This study will also adhere to all FDA and local regulatory requirements, and requirements for data protection.

### 18.1 Informed consent

Investigators must follow local IRB/EC approved institutional practice for obtaining either written or verbal informed consent which should be obtained after adequate, thorough, and clear explanation of the study objectives, procedures, as well as the potential hazards of the study. The Investigator must use the most current IRB/EC-approved consent form. In cases where the patient is incapable of providing consent and the patients legally authorized decision maker is providing consent, the patient should be informed about the study to the extent possible given his/her understanding.

## 19 DATA HANDLING AND RECORD KEEPING

Data collection is the responsibility of investigational site study staff under the oversight of the PI. The PI must maintain complete and accurate source documentation.

Clinical research data from source documentation will be entered by the site into CRFs via a 21CRF Part 11 compliant electronic data collection system (EDC). The EDC system includes password protection and internal quality checks, such as automatic range checks, to identify data that appears inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of WHODrug and MedDRA dictionaries.

Collection and processing of personal data from patients enrolled in this study will be limited to data necessary to fulfill study objectives. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Records related to the study will be retained for a period of fifteen (15) years after study completion or discontinuation, unless otherwise notified by the Sponsor.

Appropriate technical and organizational measures to protect personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep patient identity confidential.

Patient informed consent includes explicit consent for processing personal data and for Investigator/institution access to original medical records (source data/documents) for study-related monitoring, audit, Ethics Committee review and regulatory inspection, as well as for research purposes unrelated to this study. This consent also addresses data transfer to other entities, if applicable.

## 20 FINANCING AND INSURANCE

Before study initiation, each Investigator must provide a protocol signature page and a fully executed and signed Form FDA 1572 (for US sites) to Partner Therapeutics. For sites in countries other than US, Investigators will provide a Statement of Investigator Form which includes commitment to compliance to GCP (21 CFR 312.120).

Financial Disclosure Forms must be completed by all Investigators and Sub Investigators who will be directly involved in the treatment or evaluation of research patients in this study. The Investigator(s) are required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study following information; any significant payments of other sorts from Partner Therapeutics, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in sargramostim; any significant equity interest in Partner Therapeutics as defined in the US Code of Federal Regulations (21 CFR 54 2(b)).

## 21 PUBLICATION POLICY

In accordance with Partner Therapeutics' publication policy, this study's results will be submitted for publication by a peer-reviewed journal if results are of significant medical importance.

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## APPENDIX A: NIAID ORDINAL SCALE

| Measure | Ordinal Score |
|---|---|
| Death | 8 |
| Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) | 7 |
| Hospitalized, requiring non-invasive ventilation or use of high flow oxygen devices | 6 |
| Hospitalized, requiring supplemental oxygen | 5 |
| Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (related to COVID-19 or to other medical conditions) | 4 |
| Hospitalized, not requiring supplemental oxygen and no longer requires ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons) | 3 |
| Not hospitalized, with limitation of activities, home oxygen requirement, or both | 2 |
| Not hospitalized, no limitations on activities | 1 |

## APPENDIX B: SYMPTOM SCORE QUESTIONNAIRE

This Symptom Score Questionnaire is based on the FDA Guidance document Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment (17).

**Instructions**

As a participant taking part in our research study, you are being asked to complete this questionnaire. This questionnaire asks about the impact of COVID-19 on your health.

Your answers should reflect the severity of the symptoms at their **worst** over the last 24 hours**.** Please respond to the questions below to the best of your ability and ask the research study staff if you have any questions.

1) What was the severity of your **STUFFY OR RUNNY NOSE** 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 the was the severity of your **SHORTNESS OF BREATH** (difficulty breathing) at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

4) What was the severity of your **COUGH** at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

5) What was the severity of your **LOW ENERGY OR TIREDNESS** at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

6) What was the severity of your **MUSCLE OR BODY ACHES** at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

7) What was the severity of your **HEADACHES** at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

8) What was the severity of your **CHILLS OR SHIVERING** at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

9) What was the severity of **FEELING HOT OR FEVERISH** at its worst over the last 24 hours?
   - ◯ None
   - ◯ Mild
   - ◯ Moderate
   - ◯ Severe

10) 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

11) How many times did you **VOMIT** (throw up) in the last 24 hours?
   - ◯ I did not vomit at all
   - ◯ 1-2 times
   - ◯ 3-4 times
   - ◯ 5 or more times

12) How many times did you have **DIARRHEA** (loose or watery stools) in the last 24 hours?
   - ◯ I did not have diarrhea at all
   - ◯ 1-2 times
   - ◯ 3-4 times
   - ◯ 5 or more times

13) 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

14) 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

## APPENDIX C: PATIENT GLOBAL IMPRESSION

**Instructions**

As a participant taking part in our research study, you are being asked to complete this questionnaire. This questionnaire asks about the impact of COVID-19 on your health.

Complete this questionnaire after completing the symptom questionnaire.

1. In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?

   ◯ Yes

   ◯ No

2. In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?

   ◯ Yes

   ◯ No

3. In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst?

   ◯ None

   ◯ Mild

   ◯ Moderate

   ◯ Severe

## APPENDIX D: DAY 60 COVID-19 SYMPTOM EVALUATION

This Symptom Evaluation includes the same symptoms as in the FDA Guidance document *Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment* (FDA, 2020). The purpose of this Day 60 symptom evaluation is to evaluate whether patients have COVID-19 symptoms.

**Instructions**

On Day 60, as the patient completes the study, the investigator site staff should ask the patient whether they have had any symptoms of COVID-19 over the last 7 days.

1) Have you had any **STUFFY OR RUNNY NOSE** over the last 7 days?
   - ◯ Yes
   - ◯ No

2) Have you had a **SORE THROAT** over the last 7 days?
   - ◯ Yes
   - ◯ No

3) Have you had any **SHORTNESS OF BREATH (difficulty breathing)** over the last 7 days?
   - ◯ Yes
   - ◯ No

4) Have you had any **COUGH** over the last 7 days?
   - ◯ Yes
   - ◯ No

5) Have you had any **LOW ENERGY OR TIREDNESS** over the last 7 days?
   - ◯ Yes
   - ◯ No

6) Have you had any **MUSCLE OR BODY ACHES** over the last 7 days?
   - ◯ Yes
   - ◯ No

7) Have you had any **HEADACHES** over the last 7 days?

◯ Yes

◯ No

8) Have you had any **CHILLS OR SHIVERING** over the last 7 days?

◯ Yes

◯ No

9) Have you had any **FEELING HOT OR FEVERISH** the last 7 days?

◯ Yes

◯ No

10) Have you had any **NAUSEA** (feeling like you wanted to throw up) over the last 7 days?

◯ Yes

◯ No

11) Have you **VOMITED** (thrown up) over the last 7 days?

◯ Yes

◯ No

12) Have you had **DIARRHEA** (loose or watery stools) over the last 7 days?

◯ Yes

◯ No

13) Has your **SENSE OF SMELL** been the same as usual over the last 7 days?

◯ Yes

◯ No

14) Has your **SENSE OF TASTE** been the same as usual over the last 7 days?

◯ Yes

◯ No