Statistical Analysis Plan

Study Protocol Number: PTX-001-002

Study Title:

A Phase 2 Trial Evaluating Sargramostim in Patients with COVID-19 Associated Acute Hypoxemia

iLeuk Pulm

Study Sponsor:

Partner Therapeutics, Inc.

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Prepared by:

[redacted]

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1 Signature Page

Documents Prepared by:

[redacted] _____ _____
Date
Statistician
[redacted]

Reviewer

[redacted]	Consultant – Regulatory, Biostatistics & Data Management
Printed Name	Title
Signature	dd-mmm-yyyy

Approval

The undersigned have reviewed and approved the Statistical Analysis Plan and find the document to be consistent with the requirements of the Protocol.

[redacted]	Consultant – Regulatory, Biostatistics & Data Management
Printed Name	Title
Signature	dd-mmm-yyyy

[redacted]	Executive Director Medical Immunology Oncology
Printed Name	Title
Signature	dd-mmm-yyyy

2 Amendment/Modification History

The following table documents any changes made to the previously approved versions of the document.

Version #	Page # / Section	Summary of Changes	Date
1.0	Original	NA	17-Mar-2021

3 Abbreviations

ADR:	adverse drug reaction
ADL:	activities of daily living
AE:	adverse event
ALT:	alanine aminotransferase
ARDS:	acute respiratory distress syndrome
AST:	alanine aminotransferase
BAL:	bronchoalveolar lavage
BUN:	blood urea nitrogen
CRF:	case report form
CRP:	C-reactive protein
Cstat:	static compliance
CT:	Computed tomography
CTCAE:	Common Terminology Criteria for Adverse Events
DSMB:	Data Safety Monitoring Board
ECG:	electrocardiogram
FiO_2:	fraction of inspired oxygen
GCS:	Glasgow coma score
GM-CSF:	granulocyte macrophage colonystimulating factor
HLA-DR:	human leukocyte antigen – DR isotype
ICF:	Informed consent form
IL-1:	Interleukin-1
IL-6:	Interleukin-6
IV:	Intravenous
LDH:	lactate dehydrogenase
NEWS-2:	National Early Warning Score 2
$P(A\text{-}a)O_2$:	gradient (alveolar-arterial) oxygen gradient
$PaCO_2$:	partial pressure of carbon dioxide
PaO_2:	partial pressure of oxygen
PCR:	polymerase chain reaction
PEEP:	positive end expiratory pressure
PI:	Principal Investigator
Pplat:	plateau pressure
PTX:	Partner Therapeutics
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	Standard of care
SOFA:	sequential organ failure assessment
SpO_2:	peripheral oxygen saturation
SUSAR:	suspected unexpected serious adverse reaction
US:	United States
USP:	United States Pharmacopoeia
WBC:	white blood cells

4 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methodologies that will be used in the analysis and reporting of results for Partner Therapeutics Protocol PTX-001-002.

This document is prepared based on the following documents:

- the study protocol version 2.0 dated 02 December 2020;
- the Case Report Form version 1.7 dated 08 January 2021.

Readers are referred to the final study protocol (and any amendments or addenda), the case report form (CRF), and CRF completion guidelines for details of the study design, conduct and data collection. Any significant changes to these documents in terms of the principal features of the study analyses may result in an SAP amendment; any other changes will be denoted in the Clinical Study Report as changes to the planned analyses.

This SAP must be finalized prior to the locking of the clinical database for this study. The mock summary tables, figures and by subject data listings (TFLs) are provided in a separate document.

5 Study Objectives and Endpoints

5.1 Study Objectives

The aim of the study is to determine if inhaled sargramostim, as an adjunct to institutional SOC, improves clinical outcomes in patients with COVID-19-associated acute hypoxemia.

5.2 Study Endpoints

5.2.1 Primary Endpoints

- Change in oxygenation parameter of $P(A\text{-}a)O_2$ gradient by Day 6 and % of patients who have been intubated by Day 14

5.2.2 Secondary Endpoints

- Change in ordinal scale.

- All cause 28-day mortality.
- Number of patients with treatment-emergent serious adverse events or clinically significant adverse drug reactions (ADRs).
- Survival time and causes of death.
- Time to improvement in oxygenation (PaO_2/FiO_2 ratio, SpO_2/FiO_2 ratio and $P(A\text{-}a)O_2$ gradient).
- Rate of nosocomial infection (as determined by local institution practice).
- Duration of hospitalization.
- Number of patients requiring initiation of mechanical ventilation.
- Duration of invasive and non-invasive ventilation and/or supplemental oxygen.
- Time to normalization of WBC and lymphocytes.

5.2.3 Exploratory Endpoints

- National Early Warning Score (NEWS-2).
- Sequential organ failure assessment (SOFA) scores.
- ROX Index.
- Progression to ARDS.
- Changes on chest X-ray or CT.

6 Study Design

6.1 Study Design Overview

This study is a randomized two-arm open-label study. This Phase 2 study will randomize approximately 120 patients with COVID-19: of which 80 will receive sargramostim + SOC, and 40 patients who will receive SOC alone. Refer to Section 5.1 of the Study Protocol for a more detailed description of the study. Section 1 of the Study Protocol is a schematic of the study design.

6.2 Randomization

Per Section 5.2 of the Study Protocol, randomization will be performed, using a 2:1 randomization ratio, with the strata defined as:

- investigational site,
- SOFA score (<6 versus ⩾ 6)

6.3 Study Schedule

The scheduled assessments will be carried out during the study as described in Section 10 of the Study Protocol.

6.4 Study Duration and Early Termination

6.4.1 Patient Discontinuation Criteria

Refer to Section 11.1 of the Study Protocol

6.4.2 Study Completion

Refer to Section 11.2 of the Study Protocol

6.4.3 Duration of Treatment (Days 1-5)

Refer to Section 11.3 of the Study Protocol.

6.4.4 Duration of Study Period (Days 6-28)

Refer to Section 11.4 of the Study Protocol.

6.4.5 Duration of Follow-up (up to 30 days following end of study visit)

Refer to Section 11.5 of the Study Protocol.

6.5 Study Drug Administration

Refer to Section 7.1 of the Study Protocol.

6.6 Study Assessments

6.6.1 Safety Evaluations

Safety evaluations and definitions are described in Sections 8, 10, and 10.1 of the Study Protocol.

6.6.2 Efficacy Evaluations

Efficacy evaluations are described in Section 10.2 of the Study Protocol.

7 Statistical Analysis Methods

7.1 General Considerations

All safety analyses will be based on Safety Population; all efficacy analyses will be based on Modified Intent-to-Treat population, unless otherwise specified. Some specific sensitivity analyses of efficacy may be based on ITT and Per Protocol populations (for primary endpoints only). See Section 7.4 below for definitions of each analysis population.

All analyses will be considered as descriptive analyses. Derivation of two-sided 95% confidence intervals and p-values will be generated where applicable.

Time to event endpoints will be defined as the start date/time to the end date/time; censoring dates will be the last date/time the patient was determined to be event-free. Kaplan Meier methods will be used for time to event endpoint analyses; a log-rank test will be performed to compare the two survival curves. Timepoints estimates and median survival will be derived from the Kaplan Meier analysis. A Cox proportional hazards model may also be used to compare the two treatment arms using a hazard ratio.

Categorical endpoints will be calculated as the percentage of patients with the event, relative to the number of patients in a given analysis population (see Section 7.4). Stratified logistic regression approaches and/or repeated measures statistical approaches may be used to compare patients on the sargramostim and control arms, in addition to Fisher's Exact or Chi^2 tests (as appropriate). The randomization stratification factor for the baseline SOFA score (<6 versus ≥ 6) will be considered for any stratified analysis.

Continuous endpoints will be summarized by n, means, medians, minimum, maximum, and 25^{th} and 75^{th} percentiles. Analysis of variance, analysis of covariance, and/or repeated measures statistical approaches may be used to compare patients on the sargramostim and control arms.

In the event that the underlying assumptions and/or distributions for a given statistical method are not satisfied, alternative statistical methods will be employed.

Additional exploratory analyses may be performed to evaluate the robustness and sensitivity of the study results, including but not limited to, additional evaluation of endpoints on other

analysis populations, subgroup analyses, treatment interactions, adjusted or stratified analyses, and/or alternative statistical methods.

7.1.1 Study Day

Study day will be calculated as follows:

- For the sargramostim arm: Assessments/events prior to the first sargramostim dose date, study day will be the assessment date minus the first dose date. The end of treatment is the date/time of the last administered dose of sargramostim.
- For the control arm, the randomization date will be used as the first dose date. The treatment completion or discontinuation date/time from the treatment disposition CRF page will be considered the end of treatment for the SOC arm.
- Assessments/events on or after the first dose date, study day will be the assessment date minus the first dose date plus one.
- The duration of SOC (for both treatment arms) will be based on the start date of randomization, and the end date as latest of 1) any concomitant medication end date with indication "COVID-19", or 2) any end date of procedure with indication "COVID-19", or 3) any end date of transfusion, ventilation or supplemental oxygen.

For assessments captured as an unscheduled visit, if the date of assessment is the same as a date of another visit (e.g., Day 6, Day 14, Day 28, Day 58, Day 90), then the visit label for the unscheduled assessment can be re-assigned to the appropriate visit label (e.g., Day 6, Day 14, Day 28, Day 58, Day 90). Other appropriate data handling approaches may be used to ensure data is analyzed in the appropriate timepoint analysis.

7.1.2 Baseline Definition

For both treatment arms, baseline is considered any observation that occurs prior to, or on the date of randomization, unless otherwise specified. That is, baseline date $\leq$ randomization date.

Additionally, for the sargramostim arm, baseline assessments must also be prior to the first sargramostim dose date/time.

If there are multiple baseline assessments, the latest one will be used for analysis purposes.

For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured, will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries, change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The % change from baseline will be calculated as (post-baseline value - baseline value) / baseline value x 100.

7.1.3 Analysis Period

The main analysis period would be the Treatment Emergent period.

For all treatment emergent adverse events, it is defined as the period from the date of the first dose until the earliest of the following 1) date of Study Day 58; or 2) date of early discontinuation from study, or 3) data cutoff date. However, SAEs will include all the serious adverse events collected after the first dose.

The analysis period used for abnormalities in laboratory evaluations is defined as the period from the date of the first dose until the earliest of the following 1) date of Study Day 90; or 2) date of Early discontinuation from study, or 3) data cutoff date.

Analysis period for efficacy parameters would be the period from the date of the first dose until the earliest of the following 1) Date of Study Day 90; or 2) Date of Early discontinuation from study, or 3) data cutoff date.

7.1.4 Post-Treatment: Up to Day 6 (or Discharge, whichever is earlier)

The post-treatment evaluation is one of the main timepoints for evaluation of efficacy endpoints, particularly measures of oxygenation. In the protocol, this is referred to as the Day 6 evaluation. In the context of this document, this will be presented as “Up to Day 6”.

For the **sargramostim arm**: any assessment that is performed within 24 hours after the last treatment administration date/time may be considered as the “Up to Day 6” evaluation. That is, within last dose date/time + 24 hours. If there are no assessments in that timeframe, then the last

post-baseline observation prior to last dose date/time will be used. To address any missing dose times for the known dose dates:

- if the start time of inhalation dosing is known, then the end time can be assumed to be 15 minutes later (i.e., end time = start time + 15 minutes)
- otherwise, the end time will be assumed to be 23:59

For patients who received **standard of care alone**, any assessment that is within 1 calendar day after the later of, the treatment completion (or treatment discontinuation date) [from the treatment disposition CRF page] or Day 6/Post-Treatment visit date, may be considered as the "Up to Day 6" evaluation. If there are no assessments in that timeframe, then the last post-baseline observation prior to latter of, the treatment completion (or treatment discontinuation date) or Day 6/Post-Treatment visit date, will be used.

7.1.5 Missing Data Handling

In general, no imputation of missing data is planned for the primary analyses. However, for purposes of any sensitivity analyses, missing data may be imputed using last-observation-carried forward, or other advanced statistical imputation methods.

For the efficacy analyses based on oxygenation parameters, up to Day 6, if the assessment on Day 6 is not available, then the last prior non-missing value, after baseline will be used. See Sections 7.1.2, 7.1.3, and 7.1.4 for algorithm on determining assessments to be used for analysis.

Imputation for $P(A\text{-}a)O_2$ gradient, intubation rate and ordinal scale will not be performed.

If using last observation carried forward, a missing follow-up visit value will be imputed as that patient's previously observed value.

In the absence of any other specifications, the following rule will be used for missing time-to-event data:

- Patients who are alive (not lost to follow up) and did not experience the event of interest will be censored at the date last known to be alive and to be event-free.

7.2 Sample Size

Approximately 120 patients will be randomized: of which 80 will receive sargramostim + SOC, and 40 patients who will receive SOC alone to evaluate the clinical efficacy and safety of sargramostim in patients with COVID-19 associated acute hypoxemia.

The sample size was based on practical and clinical considerations to ensure that the efficacy endpoints and safety profile could be appropriately evaluated and was not based on any statistical assumptions or hypotheses. As a result, the analyses of this study will be considered as descriptive analyses.

7.3 Data Safety Monitoring Board

The DSMB will comprise of independent external experts to review the safety and benefit/risk data. See Section 12.2 of the Study Protocol and/or DSMB Charter for further information.

7.4 Analysis Population

The following analysis populations will be used to summarize the results from this study.

- **Safety Population** includes all patients who received at least one dose of sargramostim and/or SOC based on actual treatment received. Patients who did not receive any study treatment (either sargramostim and/or SOC) will be excluded from Safety Population. All safety analyses will be based on the Safety Population.
- **Intent-to-treat Population (ITT)** includes all patients who were randomized, and analyzed per the treatment arm as randomized. Selected efficacy analysis ($P(A\text{-}a)O_2$ and intubation rate) may also be performed based on ITT population for the purpose of sensitivity, unless otherwise specified.
- **Modified Intent-to-treat Population (MITT):** a subset of the ITT population that received at least one dose of any study treatment (either sargramostim and/or SOC). Efficacy analyses will be based on the MITT Population.
- **Per Protocol Population (PP)** includes all patients who were randomized and received at least one dose of sargramostim and/or standard of care based on the treatment assigned

at randomization and meet the eligibility criteria of this study. Selected efficacy analyses may also be performed based on the Per Protocol Population, unless otherwise specified.

- If the ITT, and PP populations are identical, or less than 10% different compared to the MITT population, then the selected efficacy analyses may not be repeated across the ITT and PP analysis population.
- **Enrolled Population** includes all patients who were eligible and signed informed consent form (ICF).

7.5 Patient Disposition

Descriptive statistics by treatment will be used to summarize the number of patients enrolled, the number of screening failures, the number of patients in Safety Population, ITT, MITT, and PP, number of patients who completed key study timepoints of interest (Days 1-5, Up to Day 6, Day 14, Day 28, Day 58), and who completed treatment period, completed the study, withdrew from treatment, and withdrew from the study, and reasons for withdrawals from treatment and from study. The descriptive statistics will include numbers and percentages of patients in each identified category by treatment arms. A patient's data listing will be provided for disposition that includes patients who are excluded from each analysis populations (and reasons for exclusion); who prematurely withdrew from the study and for early treatment discontinuation, along with the associated reasons.

7.6 Protocol Deviations

All reported protocol deviations will be reviewed, and determined to be major or minor, based on the potential impact to efficacy and/or safety.

A subject listing of protocol deviations data will be presented.

The following general categories will be considered major deviations include, but are not limited to:

- Deviation 1: Patients randomized but who did not receive study drug or standard of care (i.e., not treated)
- Deviation 2: Patients who deviate from the following key entry criteria:

- Inclusion:
- Exclusion:

- Deviation 3: Patients randomized who received treatment other than that to which they were randomized to (i.e., received the other treatment).

7.7 Demographics and Baseline Disease Characteristics

Demographic information for MITT Population will be summarized. The demographic data consists of age, gender, race, ethnicity, baseline height, body weight, body mass index (BMI), Body Surface Area (BSA). The baseline disease assessment scales, including the SOFA score (including categorization of <6 versus ≥ 6) , ordinal scale, and National Early Warning System 2 Score will be summarized. The baseline COVID-19 diagnostic information will also be summarized.

Individual demographics and other baseline factors will be listed by patient.

Continuous variables (for example, age, height, body weight, body mass index, body surface area, disease assessment scales) will be summarized by n, means, medians, minimum, maximum, and 25^{th} and 75^{th} percentiles. Number of patients and percentages will be used to describe categorical (discrete) variables (for example, gender, race, ethnicity and SOFA score <6 versus ⩾ 6).

If there is a difference between the MITT and the Safety Population, the summary of baseline and disease characteristics may be repeated on the Safety Population.

7.8 Medical History

Medical condition and/or significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later, and listed by reported term, System Organ Class and Preferred Term (PT). The number and percentage of patients will be summarized by System Organ Class and PT by treatment for MITT Population, and listed.

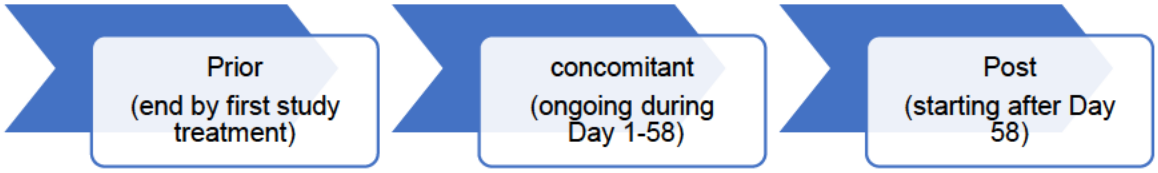
7.9 Concomitant Medications

All medications will be coded using WHO Drug Enhanced Dictionary (March 2020 Version or later) and categorized as Prior Medication, Concomitant Medication, or Post Medication based on the following:

- Prior medications include medications that have a start date and end date before the date/time of the first dose of the study treatment;
- Concomitant medications include medications that start date prior to, or after the date of first dose, that is administered any time through Day 58 and could continue on into follow up period;
- Post medications include medications that have a start date after Day 58.

Depending on the start and end date/time, medications are categorized as prior, concomitant, or post, as displayed in Figure 1 below.

Figure 1: Concomitant Medication Categorization



Concomitant medications will be summarized by treatment, Anatomical Therapeutic Chemical (ATC) classes, and Preferred Term for MITT Population. Prior and Post Medications will be included in the patient's listing of medications including the start and end dates, prior/concomitant/post flag, whether it is ongoing, dose, unit and indication.

Standard of Care treatments for COVID-19 will be tabulated separately from other concomitant medications. These treatments may be given prior to entry into study, or during the study.

7.10 Extend of Exposure and Treatment Compliance

Study days, including first and last dose, to enable deviation of treatment durations for both treatment arms are defined in Section 7.1.1.

Treatment duration and treatment compliance will be summarized for the Safety Population. For each patient, the treatment duration is defined as the number of days from the first treatment date to the last treatment date, and can be calculated as:

Treatment Duration (Days) = (Date and Time of Last Treatment – Date and Time of First Treatment)/24 +1.

The result of treatment duration will be rounded to the nearest integer. For example, if the calculation results in 5.4 days, then the final result of treatment duration will be 5 days.

See Section 7.1.4 for handling missing treatment times. Otherwise, if time of the last treatment is not available, the end time of the treatment duration will be imputed using the earliest of 1) End time of treatment Day 5; or 2) Time of patient's early discontinuation from the treatment or from the study (where available). Treatment duration will be calculated for both treatment arms, and will include any treatment, sargramostim, and standard of care durations.

For each patient who received sargramostim, the treatment compliance is defined as the actual treatment received as percentage of the planned treatment (K days). It can be calculated as:

> Treatment Compliance = 100*(Treatment Duration– Number of Days without Study Treatment)/K

In this study, the prespecified treatment duration of sargramostim is 5 days (K=5).. For discontinued patients, K would be equal to the number of days from the date the sargramostim study drug is first received to the date of early discontinuation.

K can be smaller than 5 1) if the end of the treatment/early discontinuation of treatment before Day 5; 2) if the patient has not completed 5 days of sargramostim treatment and has not discontinued treatment/study early by the time of the data cut.

Since there is no planned or prespecified treatment duration for the standard of care therapies, compliance with standard of care cannot be determined or summarized.

7.11 Efficacy Evaluations

The primary and secondary efficacy endpoints of the study (as defined above in Sections 5.2.1 and 5.2.2 above) will be analyzed as specified below. If the primary and secondary efficacy endpoints show meaningful results, then the exploratory efficacy endpoints (Section 5.2.3 above) will be summarized.

Key timepoints of interest for endpoints include Days 1-6, Day 14, and Day 28, where data are assessed and/or available, unless otherwise specified. All available efficacy data will be tabulated and presented for all patients in the Modified Intent-to-Treat (MITT) Population; see Section 7.4.

7.11.1 Primary Efficacy Evaluations

For primary efficacy measures based on oxygenation parameters, the main timepoints of interest for analyses are baseline, up to Day 6 for P(A-a)O_2 gradient, and by Day 14 for rate of intubation, where data are available, unless otherwise specified.

See Sections 7.1.2, 7.1.3, and 7.1.4 for algorithm on determining assessments to be used for analysis.

As ABG was required only at baseline and at Day 6/Post-Treatment visit (or day of discharge if earlier), the number of patients with complete data at all study visit days is expected to quite limited. Therefore, the primary timepoint for analyses for data based on ABG will be up to Day 6.

7.11.1.1 Oxygenation Up to Day 6

The P(A-a)O_2 gradient will be derived using arterial blood gas assessment via arterial puncture at baseline and up to Day 6, or day of discharge whichever is earlier. See Sections 7.1.2, 7.1.3, and 7.1.4 for algorithm on determining assessments to be used for analysis.

The change from baseline and percentage from baseline is defined as:

Percentage Change from Baseline= Change from Baseline/ Baseline

The P(A-a)O_2 gradient, the percent change from baseline up to Day 6 will be tabulated based on "unchanged or deteriorated" [no difference or positive percent change from baseline] and "improved" [negative percent changer from baseline] by 10% change increments. In addition,

the percentage of patients with a ≥ 33% improvement for each treatment arm will be provided. For both of these analyses, a Chi-square, or Fisher's exact test (or stratified logistic model) will be generated to compare the treatment arms. Alternative cutoffs for defining meaningful improvement may be used (e.g., 25%, 50%), with similar analyses methods as above.

The maximum change from baseline and maximum percentage change from baseline will be summarized up to Day 6 , and for the study duration.

Maximum percentage change from baseline is defined as:

Maximum Percentage Change from Baseline= Maximum Change from Baseline/ Baseline

For these analyses, the baseline is defined as the last available assessment prior to administration of study drug (see Section 7.1.2 above). Except as noted in Section 7.1.1, unscheduled records will be excluded from the summaries at specific timepoints but will be included in the maximum change from baseline.

A listing of all P(A-a)O_2 gradient measurements will be provided.

A Mixed Model Repeated Measures (MMRM) model will be used to evaluate the change in P(A-a)O_2 gradient, in which the change of P(A-a)O_2 gradient from baseline on each study day up to Day 6 (or day of discharge) will be included as dependent variable and treatment, study day (categorical), and treatment-by-study-day as fixed effects, patient as random effect, and the baseline value as a continuous covariate. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the compound symmetry will be used. The change in P(A-a)O2 gradient up to Day 6 will be evaluated by this MMRM model.

Change in oxygenation/respiratory parameter of P(A-a)O_2 gradient will also be presented by waterfall plot.

7.11.1.2 **Rate of Intubation, and any other Respiratory Support**

Another key primary endpoint will be the rate of intubation by Day 14. That is, any occurrence of intubation (mechanical ventilation, or ECMO) at any point time in time between Days 1 and

14, will be considered to be an event. In addition, any intubation at any point during the study will be tabulated. The treatment arms will be compared using a Fisher's Exact or Chi2 test.

Furthermore, the various types of respiratory support will be summarized as specified below, including invasive ventilation (ventilator or ECMO), non-invasive ventilation by CPAP or BiPAP, high flow oxygen, low flow oxygen or no oxygen support required.

The durations of respiratory support (days) are defined as:

$$\text{Duration of respiratory support} = \sum_{k_i=0}^{N_i} (\text{End Date/time on Day } k_i - \text{ Start Date/time on Day} k_i)/24$$

Where, N_i is the total number of available study days for any patient i. Respiratory support includes invasive ventilation, non-invasive ventilation and supplemental oxygen. Duration of oxygen support will be summarized by treatment arm; p-values generated from t-tests will compare the differences in the mean values between two treatment arms. These analyses will be generated for any oxygenation support, and for invasive ventilation separately.

Status of requiring respiratory support of each patient, including durations of any respiratory support (by type) will be listed.

7.11.1.3 **Sensitivity analysis**

To evaluating the sensitivity and robustness of the primary analyses using the MITT population, the above analyses may be repeated in the ITT and PP Populations. Baseline factors, including demographics, disease characteristics, medical history, concomitant medication may be repeated for each analysis population. See Section 7.4 for further discussion on analyses populations.

7.11.1.4 **Subgroup analysis**

For the purpose of evaluating the sensitivity and robustness of the primary analyses, subgroup analyses including, but not limited to, the following subgroups may be performed:

- Age
- Gender
- Race

- Investigational sites
- COVID-19 standard of care treatments received:
    - systemic steroids such as dexamethosone
    - remdesivir

Baseline factors, including demographics, disease characteristics, medical history, concomitant medication may be repeated for each subgroup evaluated. If warranted, safety analysis may be repeated across subgroups.

7.11.2 Secondary Efficacy Evaluations

For secondary efficacy measures. the main timepoints of interest for analyses are baseline, Days 6, 14, 28, where data is available, unless otherwise specified.

7.11.2.1 Change in Ordinal Scale

Ordinal scale will be assessed at the Screening/Baseline, during the 5 days of treatment administration, and at any days where the patients are hospitalized through Day 28 and at Day 90. Baseline for the following analyses is defined as the last ordinal scale prior to administration of study drug. The number of patients with an improvement in the ordinal scale, defined as a change from baseline of ≥ 2 points, will be tabulated.

A MMRM model will be used to evaluate the change in ordinal scale, in which the change of ordinal scale from baseline on each timepoint of interest will be included as dependent variable and treatment, timepoint (categorical), and treatment-by-timepoint as fixed effects, patient as random effect, and the baseline value as a continuous covariate. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the compound symmetry will be used.

Descriptive statistics for the overall treatment effect based on the MMRM model will include the least-squares (LS) mean difference, LS mean change from baseline for each treatment arm, their corresponding 95% CIs, and the p-values associated with the treatment difference compared to SOC. In addition, LS Means for the treatment differences at each timepoint of interest between treatment arms may also be provided with the same set of statistics derived from the same MMRM model defined above based on the MMRM estimates.

Additionally, the non-model based descriptive statistics for the corresponding change from baseline (overall) in the ordinal scale at each visit or timepoint of interest, change from baseline and maximum change from baseline will be evaluated and summarized by treatment arm. Except as noted in Section 7.1.1, unscheduled records will be excluded from the summaries at specific timepoints but will be included in the maximum change from baseline.

All available values of the ordinal scale, including change from baseline and maximum change from baseline will be listed by arm and patient. Refer to Appendix C of the Study Protocol for the ordinal scale categories.

7.11.2.2 **Mortality**

Survival status will be collected up to Day 90 +/- 30 days. Death is considered as an event. All the mortality events and cause of death will be listed by treatment arm and by patient.

Patients who did not experience death within the first 90 days will be censored on the date of Day 90 visit or the date of last contact from the study which ever is earlier.

The number of patients who died and survival time will be summarized by treatment arm. Survival time will also be listed by patient. The probability function of death will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. Cumulative progression rates estimated by the KM method for up to day 6, 14, 28, 90 and the 95% confidence intervals will be reported.

The hazard ratio will be estimated by the Cox proportional hazards model with treatment arm as a covariate in the model. Relevant hazard rates, hazard ratio between treatment arms and associated p-values will be tabulated.

7.11.2.3 **Time to Improvement in Oxygenation**

The secondary endpoint of time to improvement in oxygenation will be assessed in terms of the analysis in oxygenation parameters by visit. That is, evaluation of an improvement in oxygenation parameters will be assessed on the basis of the change from baseline analysis at the study timepoints of interest.

Oxygenation parameters including PaO_2/FiO_2 ratio, SpO_2/ FiO_2 ratio and $P(A-a)O_2$ gradient (alveolar-arterial) will be measured at the Screening visit, any days the patient is hospitalized (and where data is available) from Day 1 through Day 28 and at Day 90. On days where arterial blood gas test data is not available, PaO_2 may be estimated using pulse oximetry when required for calculating the PaO_2/FiO_2 ratio.

Oxygen saturation (SpO_2), SpO_2/FiO_2 ratio, and PaO_2/FiO_2 ratio will be summarized, along with the change from baseline and percentage change from baseline, and at all available study visits during Days 1-6, Day 14, Day 28, and Day 90 (where available). See Sections 7.1.2, 7.1.3, and 7.1.4 for algorithm on determining assessments to be used for analysis.

Percentage change from baseline is defined as:

Percentage Change from Baseline= Change from Baseline/ Baseline

For the percent change from baseline in these parameters, deterioration is defined as a negative percent change from baseline, while improvement is a positive percent change from baseline.

Change in PaO_2/FiO_2 ratio will also be presented by waterfall plot.

7.11.2.4 **Nosocomial Infections**

A listing of nosocomial infections identified through adverse events will be produced.

7.11.2.5 **Hospitalization**

The duration of hospitalization (days) is defined as:

Duration of hospitalization (Days) = Date of Discharge – Date of Randomization + 1. In this context, the date of hospital discharge is the earliest hospitalization discharge date on/after the treatment completion/discontinuation date from the Treatment Disposition CRF page. Moving a patient from ICU to a regular hospital ward, would not be considered as a hospital discharge date, in this case.

However, duration of ICU (days) = Date of ICU Discharge – Date of ICU admission + 1. In this context, moving a patient from ICU to a regular hospital ward, would be considered as ICU discharge date.

For patients who died in hospital prior to Day 28, alternative methods to account for these cases, such as assigning the duration of hospitalization as 28 days, may be considered.

Duration of hospitalization will be listed for each patient, and summarized by treatment arm.

7.11.2.6 Normalization of WBC and Lymphocytes

White Blood Cell (WBC) count and lymphocytes counts will be performed at the Screening visit and any days the patient is hospitalized from Day 1 through Day 28 and at Day 90.

Normalization of WBC and lymphocyte count is defined as whether WBC and lymphocyte count results are normal or below normal or above normal ranges at available visits. A summary table and listing will be generated for normalization of WBC and lymphocytes.

7.11.3 Exploratory Efficacy Evaluations

For exploratory efficacy measures. the main timepoints of interest for analyses are baseline, Days 6, 14, 28, where data are available, unless otherwise specified.

7.11.3.1 National Early Warning Score (NEWS-2)

The calculated total National Early Warning Score (NEWS-2) (See the scoring in Appendix D of the Study Protocol) will be summarized by treatment arm for each available timepoint of interest using descriptive analyses. Individual measures and overall score will be provided in patient data listing.

7.11.3.2 Sequential Organ Failure Assessment (SOFA)

Sequential Organ Failure Assessment (SOFA) are based on six different scores, including respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. The overall calculated SOFA score will be summarized by treatment arm for each available timepoint.

Individual SOFA scores and its components such as the Glasgow Coma Score will be provided in a patient data listing.

The Glasgow Coma Score and the SOFA Scores are defined in Appendices A and B of the Study Protocol, respectively.

7.11.3.3 ROX Index

The ROX Index assessment is described in Appendix E of the Study Protocol.

ROX Index calculation = SpO_2/FiO_2 ratio/ Respiratory rate (breaths/min).

The ROX Index will be summarized by treatment arm . The ROX Index Score and its components will be listing by patient.

7.11.3.4 **ARDS progression and Changes on Chest X-ray or CT**

The exploratory endpoints of progression to ARDS and changes on chest x-ray or CT will be evaluated in terms of determining ARDS progression.

Chest X-ray or CT may be performed at the Screening visit, Treatment period Days 1-5, Post-treatment period at Day 6 or day of discharge (whichever is earlier), Days 7-27 (or until hospital discharge), Day 28, and Day 90.

Percentage of patients in whom ARDS or ARDS progression is documented post-baseline will be summarized. Potential available data sources for the diagnosis of ARDS/ARDS progression include adverse events, physical examination findings, imaging studies such as Chest X-ray, CT, treatment or study discontinuation reasons, etc.

7.12 Safety Evaluations

Safety assessments will include monitoring of available assessments of vital signs, adverse events (AEs), clinical laboratory tests, and physical examinations. The main analysis period would be the Treatment Emergent period which is defined as the period from the date of the first dose until the end of earliest of the following 1) date of Study Day 58 for AEs and date of Study Day 90 for the rest; or 2) date of early discontinuation from study; or 3) data cutoff date. This analysis period will be used for all treatment emergent adverse event, laboratory evaluations. However, serious adverse events analysis will include all the serious adverse events collected after the first dose.

Safety variables will be tabulated and presented for all patients in the Safety Population.

7.12.1 Adverse Event

All adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 (or later). Adverse events will be categorized as prior events, treatment emergent adverse events, and post treatment adverse events:

- Prior Events includes all adverse events with a start date before the first dose of the study drug regardless of the end date.
- Treatment-emergent adverse events (TEAE) are defined as adverse events with a start date (or date of worsening) on or after the first dose of the study drug and no later than the earliest of the following 1) the date for the Day 58; 2) date of early discontinuation from study, or 3) data cutoff date.
- All adverse event started after study day 58 will be considered post-treatment.

All TEAE will be summarized by treatment arm and presented by:

1) system organ classification and preferred term (PT);
2) PT;
3) system organ classification, PT and the maximum severity.

Treatment-related TEAE, serious TEAE and treatment-related serious TEAE will be summarized by MedDRA System Organ Class and PT , and the maximum severity. SAEs and deaths will be listed by patient.

For patients at sites where Aerogen devices were supplied by PTX, the following analyses will be performed:

- All device-related TEAEs will be summarized by treatment arm;
- All device-related TE-SAEs will be summarized by treatment arm;
- All device-related AEs will be listed by patient.

The frequency of treatment-emergent serious adverse events (TESAEs) will be summarized by arm, SOC, and preferred term. Severity (using CTCAE) and relationship of TEAEs to treatment (sargramostim, sargramostim inhalation device or standard of care) will be analyzed as recorded on eCRF (also refer to Section 8 of the Study Protocol for definitions).

Clinically significant adverse drug reactions (ADRs) are treatment-emergent drug-related AEs and SAEs (as discussed above).

If a patient experiences more than one TEAE within a preferred term, the patient will be counted only once in the calculation of incidence of TEAE within that preferred term. Similarly, if a

patient experiences more than one TEAE within a system organ class, the patient will be counted only once in the calculation of incidence of TEAE within that system organ class. If a patient experiences more than one TEAE within a preferred term (or system organ class), the occurrence with the highest severity will be used in the calculation of the incidence of TEAE within that preferred term (or system organ class) with regards to severity. If a patient experiences more than one TEAE within a preferred term (or system organ class), the occurrence considered most closely related to study drug will be used in the calculation of the incidence of TEAE with that preferred term (or system organ class) with regards to relationship .

Data listings for all AEs, and for serious AEs, will be provided with flags for TEAE, relatedness and CTCAE severity.

7.12.2 Laboratory data

Laboratory data, as performed and collected as part of SOC in both arms (see Section 10 in the Study Protocol), will be collected and include the following:

- Hematology laboratory parameters: complete blood count with differential, hemoglobin, hematocrit, and absolute counts for white blood cells, platelets, neutrophils, lymphocytes, eosinophils and monocytes.
- Chemistry laboratory parameters: albumin, amylase, lipase, BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, bicarbonate, calcium and uric acid.
- Required laboratory measurements of ferritin, d-dimer and C-reactive protein should also be collected at screening, Days 1-6 and any other time it is performed as part of SOC.
- Immune profiling, if performed, including CD4+, CD8+, HLA-DR, IL-6, IL-1, GM-CSF

Descriptive statistics for baseline value, actual value at a given visit, and change from baseline to each scheduled postbaseline visit will be provided by arm for the clinical hematology, chemistry laboratory, ferritin, d-dimer, CRP, and immune profiling (where available) tests described above. In addition, the neutrophil/lymphocyte ratio will also be summarized and listed. Baseline for these tests is defined as the last assessment prior to administration of study drug (see Section 7.1.2). Conventional Units will be used for reporting the laboratory test results.

Serum pregnancy test results will be listed. Values for any chemistry, hematology, ferritin, d-dimer, CRP, and immune profiling values outside the clinical reference ranges (where available) will be flagged on the individual patient data listings.

7.12.3 Physical Examination

Physical examination findings will be listed by arm and patient.

7.12.4 Vital Signs

Vital signs (including temperature, respiratory rate, and blood pressure and pulse) will be measured during the Screening visit, Treatment period Days 1-5, Post-treatment period at Day 6 or day of discharge (whichever is earlier), Day 28, and Day 90.

Baseline for vital signs is defined as the last assessment prior to administration of study drug (see Section 7.1.2).

All vital sign data including unscheduled records will be listed. Unscheduled records will be excluded from the summary statistics. Vital sign data including baseline value, actual value at a given visit, and change from baseline to each post-baseline visit will be summarized by arm and timepoint.

7.12.5 Electrocardiogram (ECG)

Electrocardiogram examination findings for ECGs will be listed by arm and patient for each ECG parameter.

7.12.6 Patient Profiles

Key lab parameters for patients with SAEs, discontinuation due to AE, and deaths will be presented in patient profiles, in which the demographics and treatment data will be included. Additional profiles may be generated for any identified suspected unexpected serious adverse reactions (SUSARs).

8 Data Presentation

8.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the table, such as, “None reported”.

9 Revision History

10 Reference