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Protocol Number: GC2006
Protocol Version: 6.0
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STATISTICAL ANALYSIS PLAN

Version 2.0

A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Liquid Alpha$_1$-Proteinase Inhibitor (Human) plus Standard Medical Treatment (SMT) versus Placebo plus SMT in Hospitalized Subjects with COVID-19

STATISTICAL ANALYSIS PLAN

Version 2.0

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Author: [redacted]
Principal Biostatistician, [redacted]

DocuSigned by:
[redacted]
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Signing Reason: I am the author of this document
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[redacted] **Biostatistics Reviewer:** [redacted]
[redacted], Global Biostatistics [redacted]

DocuSigned by:
[redacted]
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Sponsor Approval: [redacted] PhD
[redacted] Biostatistics and Data Management
Grifols Therapeutics LLC.

DocuSigned by:
[redacted]
Signer Name: [redacted]
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Grifols Therapeutics LLC.

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Table of Contents

SAP REVISIONS

Version 1.0 of the SAP was finalized based on Protocol version 4.0 (02 March 2021). The following table details subsequent changes made to the SAP to match protocol amendment.

Revision History			
SAP Version #	SAP Section	Modification	Description and Rationale
2.0	1	1) Changed protocol version from 4.0 to 6.0, and protocol date from 02 March 2021 to 08 December 2021. 2) Updated the last paragraph to " This document details the statistical methods planned to perform the interim safety and futility, as well as the final analyses of the study".	1) and 2) Updated to match the protocol amendment.
2.0	3.1	Added the language for interim futility analysis.	Updated to match the protocol amendment.
2.0	6.1 and 6.2	Changed Fisher's exact method to Chi-square statistic.	Changed to reflect the planned analysis.
2.0	8	1) Added a section number and title "8.1 Interim Safety Analysis" for safety interim analysis. 2) Added Section 8.2 for interim futility analysis.	1) Clarify the original section is about Safety interim analysis. 2) Interim futility analysis was added to the protocol amendment, updated to match the protocol v6.0 and to provide the details of conditional power calculation.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
Alpha1-PI	Alpha 1-Proteinase Inhibitor
ANOVA/ANCOVA	Analysis of variance/covariance
ARDS	Acute respiratory disease syndrome
ATC	Anatomical, Therapeutic, and Chemical
BMI	Body mass index
CDF	Cumulative distribution function
CI	Confidence interval
CIF	Cumulative Incidence Function
COVID-19	Coronavirus disease 2019
CP	Conditional power
eCRF	Electronic Case Report Form
CRP	C-reactive protein
ECMO	Extracorporeal Membrane Oxygenation
FEU	Fibrinogen Equivalent Units
ICU	Intensive care unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	interleukin
IP	Investigational product
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
LS	Least-Squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
NAT	Nucleic acid amplification technology
NEWS	National Early Warning Score

Abbreviation	Definition
PCR	Polymerase chain reaction
PI	Principal Investigator
PP	Per-Protocol
PT	Preferred term
RT-PCR	Reverse transcriptase PCR
SAE	Serious adverse event
SAF	Safety
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMT	Standard medical treatment
SOC	System organ class
SaO_2	Arterial oxygen saturation
SpO_2	Oxygen Saturation by pulse oximetry
TEAE	Treatment-emergent adverse event
TNF-α	tumor necrosis factor-α
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # GC2006 Version 6.0, dated 08 December, 2021, and titled "A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Liquid Alpha$_1$-Proteinase Inhibitor (Human) plus Standard Medical Treatment (SMT) versus Placebo plus SMT in Hospitalized Subjects with COVID-19." See the study protocol for full details.

This document details the statistical methods planned to perform the interim safety and futility, as well as the final analyses of the study.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Efficacy Objective

To determine if Liquid Alpha$_1$-Proteinase Inhibitor (Human) **(**Liquid Alpha1-PI) plus SMT can reduce the proportion of subjects dying or requiring intensive care unit (ICU) admission on or before Day 29 or who are dependent on high flow oxygen devices or invasive mechanical ventilation on Day 29 versus placebo plus SMT in hospitalized subjects with COVID-19.

2.1.2 Secondary Efficacy Objectives

To compare Liquid Alpha1-PI plus SMT versus placebo plus SMT with regard to clinical efficacy as assessed by clinical severity, duration of hospital stay, dependency on oxygen or new need for ventilatory support, clinical response criteria including National Early Warning Score (NEWS)[1] and clinical status scale[2] through Day 29 in hospitalized subjects with COVID-19.

2.1.3 Exploratory Efficacy Objectives

The exploratory objectives of the study are:

- To evaluate the effect of Liquid Alpha1-PI (Human) plus SMT versus placebo plus SMT with regard to quantitative severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2) viral load and anti-SARS-CoV-2 antibodies in hospitalized subjects with COVID-19.
- To evaluate whether Liquid Alpha1-PI (Human) plus SMT versus placebo plus SMT reduces the frequency of hyperinflammation based on a pre-specified biochemical definition through Day 29.
- To evaluate cytokine profile changes from baseline for Liquid Alpha1-PI (Human) plus SMT versus placebo plus SMT through Day 29.
- To evaluate levels of alpha$_1$-proteinase inhibitor (alpha 1-PI, also known as alpha 1-antitrypsin [AAT]) activity and antigen through Day 29 (samples to be stored for measurement of both antigenic content and functional activity [potency] assays)

2.1.4 Safety Objective

To determine the safety and tolerability profile through Day 29 of Liquid Alpha1-PI (Human) plus SMT versus placebo plus SMT in hospitalized subjects with COVID-19.

2.2 Endpoints

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects dying or requiring ICU admission on or before Day 29 or who are dependent on high flow oxygen devices or invasive mechanical ventilation on Day 29.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Assessment of Clinical Severity: Change in NEWS from baseline (Day 1 through Day 29).

  The NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness [Alert, Voice, Pain, Unresponsive]).
- Time to clinical response: NEWS ≤ 2 maintained for 24 hours, Day 1 through Day 29
- Time to hospital discharge: defined as duration of hospitalization from Day 1 through Day 29
- If admitted to ICU post randomization: Duration of ICU stay through Day 29
- Duration of any oxygen use Day 1 through Day 29
- If requiring mechanical ventilation post randomization: Duration mechanical ventilation through Day 29
- Absolute value and mean change from baseline in the Ordinal scale Day 1 through Day 29

  The Ordinal scale is as follows:

  1) Death;
  2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
  3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
  4) Hospitalized, requiring supplemental oxygen;
  5) Hospitalized, not requiring supplemental oxygen;
  6) Not hospitalized, limitation on activities;
  7) Not hospitalized, no limitations on activities.
- Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29
- Time to sustained normalization of temperature and proportion of subjects with normalization of fever at all time points, defined as temperature <36.6 ºC armpit, <37.2 ºC oral, or <37.8 ºC rectal sustained for at least 24 hours
- Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS) through

Day 29

- Length of time to clinical progression through Day 29 (defined as the time to death, mechanical ventilation, or ICU admission)

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Change from baseline in quantitative SARS-CoV-2 viral load by nucleic acid amplification technology (NAT) or polymerase chain reaction (PCR; real-time reverse transcriptase [RT]-PCR) to Day 5± 1, Day 15± 1, and Day 29± 1
- Change from baseline in quantitative anti- SARS-CoV-2 immunoglobulin M (IgM) and IgG antibodies to Day 5± 1, Day 15± 1, and Day 29± 1
- Proportion of subjects with evidence of hyperinflammation on Day 1, Day 5, Day 15, and Day 29 defined as:
  a) Lymphocyte counts <1000 cells/μL, AND
  b) Two of the following 4 criteria:
     i) Ferritin > 500ng/mL,
     ii) LDH > 300 U/L,
     iii) D-Dimers > 1000 ng/mL (fibrinogen equivalent units [FEU]) or > 2 times upper normal limit,
     iv) C-reactive protein (CRP) > 70 mg/L
- Change from baseline in cytokine profile (cytokine panel includes interleukin (IL)-1β, IL-10, IL-6, IL-8 IL-2, interferon γ, and tumor necrosis factor-α [TNF-α]) to Day 5± 1, Day 15± 1, and Day 29± 1
- Change from baseline in levels of alpha 1-PI (AAT) activity and antigen through Day 29 (both plasma [sodium citrate] and serum samples to be stored for measurement of both antigenic content and functional activity [potency])

2.2.4 Safety Endpoints

The safety endpoints include:

- Cumulative incidence of treatment-emergent serious adverse events (SAEs) and potentially related SAEs through Day 90 phone check
- Cumulative incidence of Grade 3-5 treatment-emergent adverse events (TEAEs) and potentially related TEAEs through Day 29 as defined in the Common Terminology Criteria for Adverse Events (CTCAE), US Department of Health and Human Services, National Institutes of Health (NIH), and National Cancer Institute (NCI)
- Cumulative incidence of all TEAEs and potentially related TEAEs through Day 29

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a prospective, multi-center, randomized, double-blind, placebo-controlled study of Liquid Alpha$_1$-PI (Human) plus SMT versus placebo plus SMT in subjects with COVID-19 who are hospitalized. The first 6 subjects randomized will be staggered with an interval of no less than 1 week between subjects. If there are no definitely related SAEs reported by the time Day 8 is completed by the 6th subject, competitive enrollment would ensue thereafter. If a definitely related SAE were to be reported among these 6 subjects, and the subject was found by the Study-Independent Safety Review Committee (SISRC) to be randomized to the Liquid Alpha$_1$-PI (Human) plus SMT arm, the SISRC would carefully review and evaluate the case and make appropriate recommendations with regard to study status.

In this study, symptomatic subjects with positive PCR (RT-PCR), NAT for SARS-CoV-2 (or other commercial or public health assay approved by regulatory authorities) will receive placebo plus SMT or SMT plus Liquid Alpha$_1$-PI (Human) given as two intravenous (IV) doses of 120 mg/kg (body weight) one week apart (on Day 1 and Day 8); if the subject is discharged from the hospital then the 2nd infusion is not mandatory, and is at the discretion of the Principal Investigator (PI) and subject.

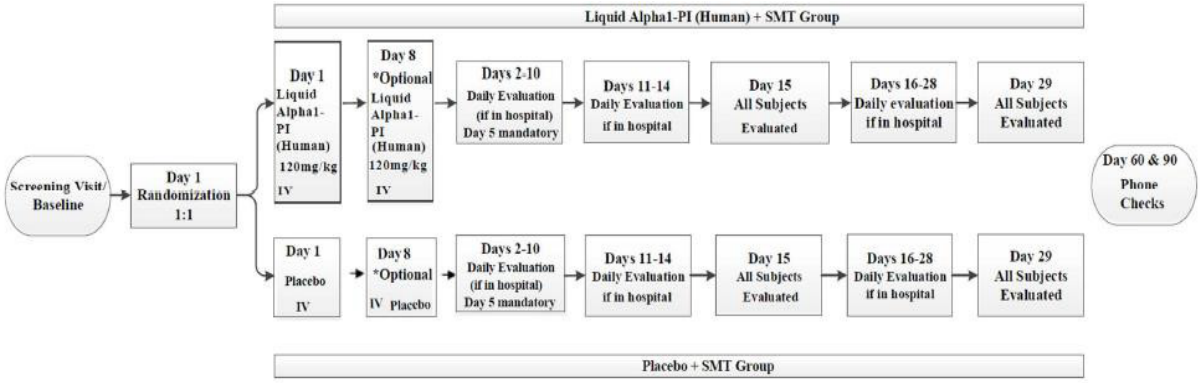
Specifically, subjects randomized to combination Liquid Alpha$_1$-PI (Human) will receive the first IV infusion of blinded Liquid Alpha$_1$-PI (Human) (120 mg/kg body weight) or Placebo on Day 1. A second Placebo/ Liquid Alpha1-PI (Human) dose of 120 mg/kg body weight will be administered a week later on Day 8. if the subject has been discharged from the hospital at the time of the Day 8 blinded Placebo/ Liquid Alpha$_1$-PI (Human) infusion, the 2nd infusion is not mandatory, and is at the discretion of the PI and subject.

Approximately 100 subjects (who meet the inclusion/exclusion criteria specified in Protocol Sections 5.1 & 5.2) will be randomized in a 1:1 [Liquid Alpha$_1$-PI (Human) plus SMT : Placebo plus SMT] ratio with an interim analysis after 50 subjects (approximately 25 per group). There will be no interruption in study conduct during interim analysis as this simply represents sponsor safety due diligence during the COVID-19 pandemic. An interim futility analysis will be conducted to assess whether the trial will be terminated due to lack of efficacy (futility) based on all available data assessable for the primary endpoint and key secondary efficacy endpoints.

All subjects will be followed daily through Day 10 (note: for Day 6 through Day 10, this stipulation is for as long as subjects are hospitalized). After Day 6, if subjects are discharged from the hospital, evaluations at Day 15 and 29 are required. Subjects remaining hospitalized will be followed daily through Day 29. Phone Checks will occur at Day 60 and Day 90 for vital status (living or deceased), any hospital re-admissions or serious/non-serious AEs after the Day 29 Final Clinic Visit. See Appendix A for the Schedule of Events.

Clinical trial finalization will coincide with the last study visit of the last subject enrolled in the clinical trial. For an individual subject, end of study for the purposes of determining disposition and successful study completion is the Day 29/Final Clinic Visit performed at the scheduled on-study timeframe.

An overview of the study design is presented below:



IV = intravenous; SMT = standard medical treatment

*Note: If the subject has been discharged from the hospital at the time of the Day 8 blinded Liquid Alpha-1 PI infusion, the 2nd infusion is not mandatory, and is at the discretion of the Principal Investigator and subject

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

Subjects will be randomized 1:1 to receive either combination treatment with Liquid Alpha$_1$-PI (Human) plus SMT or placebo plus SMT.

3.2.2 Blinding

The unblinded study pharmacist or designee will be the only unblinded study person at each site. Preparation and pooling of study drug [Liquid Alpha1-PI (Human) and placebo] will be the responsibility of the local unblinded pharmacist or designee.

3.2.3 Dosing Schedule

During this clinical trial, subjects randomized to receive combination Liquid Alpha$_1$-PI (Human) plus SMT will receive the first dose of blinded Liquid Alpha$_1$-PI (Human) given as an IV dose of 120 mg/kg (body weight) on Day 1. A second dose of blinded Liquid Alpha1-PI (Human) (120 mg/kg) will be infused on Day 8. If the subject has been discharged from the hospital at the time of the Day 8 blinded Liquid Alpha1-PI (Human) infusion, the 2nd infusion is not mandatory, and is at the discretion of the PI and subject.

3.2.4 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of the investigational product (IP) dose must be recorded in the subject's medical records.

The investigator or designee is responsible for maintaining accurate records of study medication administered at his/her study center.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Unless otherwise specified, continuous variables will be summarized using descriptive statistics

(n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage of subjects within each category.

Summary results will be provided for each treatment group. All tabulations will be based on pooled data across centers.

All statistical tests will be two-sided and tested at the 5% level of significance.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate. In the event that other software is used to perform some analyses, the details will be provided in the Clinical Study Report.

[redacted] will perform all efficacy and safety analyses described in this SAP and Grifols will review them.

Subject data will be listed, sorted by treatment group and subject number. When applicable, listings will be additionally sorted by visit and assessment date/time.

4.1 Data Quality Assurance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to [redacted] Biostatistics for final analysis.

Data may be pulled by [redacted] Biostatistics for interim analyses at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis data sets, tables, and listings are double programmed. The SAS outputs will be compared and the programs will be updated until the outputs match.

4.2 Analysis Populations

The following three analysis populations will be defined for this study:

The intent-to-treat (ITT) population is defined as all subjects who are randomized. All efficacy analyses will be carried out using the ITT population based on the randomized treatment.

The Per-Protocol (PP) population is defined as the subset of subjects included in the ITT population who do not present major protocol deviations which might have an impact on the primary efficacy endpoint, and complete at least 80% of the IP. The primary efficacy analyses will be carried out using the PP population if different from the ITT population.

The Safety (SAF) population is defined as the subset of subjects who receive at least any amount of Liquid $Alpha_1$-PI (Human) plus SMT or placebo plus SMT. All safety analyses will be carried out using the SAF population based on the treatment actually received rather than randomized treatment.

The validity of a subject for inclusion in each of these populations (ITT, Safety, and PP) will be assessed before unblinding the database and documented in a blinded review report.

4.3 Assessment Windows

Data will be summarized by nominal study visit recorded in the database.

4.4 Handling of Dropouts or Missing Data

Missing data will be treated as missing and no method for imputation is planned for study population or safety analyses except for the partial end dates/times for concomitant medications (Section 5.6) and partial onset dates/times for AEs (Section 7.2.1). When applicable, missing data for binary and selected continuous efficacy endpoints will be imputed using a most conservative/worst case approach, and the related details are described in Section 6.

Time to event endpoints will have events coded as right censored or competing events per the following table:

Table 1 Missing Data and Competing Events Coding for Time to Event Data Analyses

Endpoint	Right Censoring and Competing Events
Time to Clinical Response	Subjects who did not experience clinical response or died at any time during follow-up will be right censored as of the date of last non-missing assessment of NEWS on or prior to Day 29.
Time to Hospital Discharge	Subjects who did not discharge from the hospital at any time during follow-up will be right censored as of the date of last subject contact when the subject was known to be in the hospital. Subject death will be considered a competing event. Competing risk methods e.g., cumulative incidence function (CIF) will be used to account for competing events in the analysis.
Time to Sustained Normalization of Temperature	Subjects who did not meet the criteria for sustained normalization of temperature or died at any time during follow-up will be right censored as of the date of last non-missing assessment of temperature on or prior to Day 29.
Time to Clinical Progression (death, mechanical ventilation, or ICU admission)	Subjects who did not meet the criteria for clinical progression will be right censored as of the date of last subject contact on or prior to Day 29.

4.5 Multiple Comparisons

Because of the exploratory nature of this study, there will be no adjustment for multiple comparisons.

4.6 Data Derivations and Transformations

The following derivations will be used in this study:

Study Day:

- Date of assessment – 1st date of study drug administration + 1 for assessments done on or after the 1st date of study drug administration
- Date of assessment – 1st date of study drug administration for assessments done before the 1st date of study drug administration

Baseline Observation: the last non-missing value prior to the 1st study drug administration.

Duration:

- Duration in days = end date – start date + 1
- Duration in minutes = end time in minutes – start time in minutes

Origin or Start Date for Time to Event Endpoints:

- Time to Clinical Response: date of 1st study drug administration
- Time to Hospital Discharge: date of 1st study drug administration
- Time to Sustained Normalization of Temperature: date of 1st study drug administration
- Time to Clinical Progression: date of 1st study drug administration

Event Date for Time to Clinical Response and time to sustained normalization of temperature:

- If a subject met the criteria for clinical response or sustained normalization of temperature at multiple assessments, the date of the first assessment meeting the definition of clinical response or sustained normalization of temperature will be used as the event date for deriving time to clinical response or sustained normalization of temperature.

Event Date for Time to Clinical Progression

- The event date will be the date of death, the start date of mechanical ventilation, or the date of ICU admission, whichever occurs first.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A table of frequency counts and percentages of all subjects who are screened, randomized, and in each analysis population will be provided. Subject disposition including study completion status and reasons for early termination will be tabulated by treatment group and overall. A by subject listing will be provided.

5.2 Protocol Deviations

Distribution of the types of protocol deviations and the number of subjects that deviate from the protocol will be tabulated for the treatment groups in the ITT population. Protocol deviations will also be tabulated by severity (e.g., minor or major). A listing of all protocol deviations will be provided.

5.3 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (age, gender, race, ethnicity, height, weight, and Body Mass Index [BMI]) for the ITT population. A by subject listing will be provided.

5.4 Baseline Characteristics

Baseline characteristics of ITT subjects including historical SARS-CoV-2 results and pregnancy test will be listed and tabulated if appropriate.

5.5 Medical History

All medical conditions will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition will be presented for each SOC and PT for the ITT population.

5.6 Concomitant Medications

All concomitant medications collected will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percent of ITT subjects using concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) level 2 and by ATC level 4. If the ATC level 2 or 4 term is missing, the higher ATC level term will be used in the medication summary table and data listing.

Prior medications will be summarized separately from concomitant medications, for the overall ITT population.

Prior medications are defined as medications that ended prior to the date of 1st study drug administration. Concomitant medications are defined as medications that started at any time but ended on or after the date of 1st study drug administration, including those that are ongoing at study completion. In the case of a missing or partial end date/time, in order to determine whether a medication is prior or concomitant, the following conservative imputation rule will be used: the unknown portions of a medication end date/time will be imputed to the latest possible. The imputed medication end date/time will then be compared with the date of 1st study drug administration to determine if the medication is prior or concomitant.

Note the imputed end date/time will only be used to determine whether a medication is prior or concomitant. The actual date/time reported on the electronic case report forms (eCRFs) will be presented in the listings.

All concomitant medications collected will be reviewed in a data review meeting conducted prior to database lock. ATC or Preferred terms for COVID-19 specific, potentially disease modifying medications will be identified by the study team. Subsequently, a tabular summary by treatment group of these COVID-19 specific concomitant mediations based on the identified ATC or preferred terms will be generated. If clinically important imbalance was observed in the use of these medications between the 2 treatment groups, additional supplemental efficacy analyses may be performed in a post-hoc manner to adjust for the difference(s) in such medication use.

6. EFFICACY ANALYSES

All efficacy analyses will be carried out using the ITT population. Data on all efficacy endpoints will be listed and tabulated if appropriate.

6.1 Primary Efficacy Endpoint and Analysis

The primary efficacy analysis will be carried out on the ITT population. If there is difference between the PP population and ITT population, the analysis will be repeated using the PP population.

The primary efficacy variable is the proportion of subjects who die or require ICU admission on

or before Day 29, or who are dependent on high flow oxygen devices or invasive mechanical ventilation on Day 29. The primary efficacy endpoint will be derived based on the subject status (Alive/Death), ICU admission, mechanical ventilation and oxygen administration recorded in the database. Subjects who met any of the criteria listed below will be treated as meeting the primary efficacy endpoint:

1) Death is recorded on the eCRF All Visits page "General Duration of Hospitalization, & Overall Requirement for Mechanical Ventilation, ICU Admission and/or Oxygen Supplementation";
2) ICU admission date is recorded on the eCRF All Visits page "General Duration of Hospitalization, & Overall Requirement for Mechanical Ventilation, ICU Admission and/or Oxygen Supplementation";
3) On the eCRF Day 29 page "Mechanical Ventilation and Oxygen Administration":
    a. subject on mechanical ventilation is recorded in the mechanical ventilation record for that day, i.e., "Is the subject on a ventilator?" is recorded as "Yes";

       Or

    b. the modality of oxygen administration is recorded as "High flow oxygen devices"

If for a subject any of the 4 criteria above could not be assessed due to missing data, then the subject will be treated as meeting the endpoint in the primary efficacy analysis.

The null hypothesis is that there is no difference in the proportions of subjects who met the primary endpoint between randomized groups; H_0: $\pi_t - \pi_c = 0$. The alternative hypothesis is that the proportions of subjects who met the primary endpoint are different between the treatment groups; H_1: $\pi_t - \pi_c \neq 0$.

The proportion of subjects who met the criteria for the primary endpoint within each treatment group will be presented along with a two-sided exact (Clopper-Pearson) 95% confidence interval (CI).

The observed difference in the proportion of subjects meeting the criteria between treatment groups along with the exact unconditional 95% CI for risk difference will be calculated. The null hypothesis will be tested using Chi-square statistic and the p-value will be reported.

Subgroup analyses of the primary efficacy endpoint by baseline characteristics such as age group (with age cutoffs defined either by absolute values or by a summary metric [e.g., median] of the observed baseline values) and gender will be performed using the analysis method described above, if appropriate.

If for one or more subjects the actual treatment received is different from the randomized treatment and if deemed necessary, sensitivity analysis of the primary efficacy endpoint will be performed by repeating the primary efficacy analysis as described above in this section, but with subjects grouped according to the actual treatment received instead of the randomized treatment.

6.2 Secondary Efficacy Endpoints and Analyses

Assessment of clinical severity

The NEWS will be calculated based on 7 clinical parameters and recorded on the eCRF. The

absolute value and change from baseline in the total score from Day 1 through Day 29 will be summarized by treatment group and visit using descriptive statistics.

Change in NEWS total score through Day 29 will be evaluated by fitting a linear mixed-effects model for repeated measures (MMRM). The model will include change from baseline in NEWS total score as the repeated dependent variable; treatment (as a class variable), visit (as a class variable), and treatment-by-visit interaction as fixed effects; baseline NEWS total score, age and gender as covariates; and measures within subject at each visit as a repeated measure. An unstructured covariance matrix will be used to model the within-subject error. If the fit of the unstructured covariance structure fails to converge, a compound symmetry covariance structure will be used. Parameters will be estimated using restricted maximum likelihood with the Kenward-Roger method for calculating the denominator degrees of freedom. Data collected starting at the Day 2 visit and up to the Day 29 visit will be included in this analysis. Missing data will not be imputed. From this model, the least-squares (LS) means and 95% CIs for each treatment group, the treatment difference in the LS means, the 95% CI for the difference, and the associated p-value will be reported on Days 15 and 29, as well as for the average across all post-baseline visits.

Time to clinical response

Clinical response is defined as the NEWS score <=2 maintained for 24 hours from Day 1 through Day 29. The time to the first occurrence of clinical response will be estimated using the Kaplan-Meier (KM) method. The KM estimates along with 95% CI, and survival curves will be provided. Based on the KM estimates, the probabilities of achieving first clinical response and associated 95% CIs on Days 15 and 29 will be reported; in addition, the 25^{th} , 50^{th} (median), and 75^{th} percentiles of the time to first clinical response with associated 95% CIs will be provided, as data permit. The survival rates between treatment groups will be compared using Log-rank test. The p-value from Log-rank test will be presented.

Time to hospital discharge

Time to hospital discharge is defined as duration of hospitalization from Day 1 through Day 29. The proportion of subjects who are discharged from the hospital will be estimated using the CIF. Deaths that occur prior to discharge from the hospital will be treated as a competing risk. The estimated cumulative incidence and associated two-sided 95% CI on Days 15 and 29 will be displayed. Test for equality of the CIF between treatment groups will be conducted using Gray's test[3].

Duration of Hospitalization

The duration (number of days) of hospitalization from Day 1 through Day 29 will be calculated based on hospital admission and discharge dates recorded on the eCRF. Number of days in the hospital will be compared between treatment groups using an ANOVA model, including number of days in the hospital as a dependent variable and treatment group as a fixed effect. From this model, the LS means and 95% CIs for each treatment group, the treatment difference in the LS means, the 95% CI for the difference, and the associated p-value will be presented. If appropriate, an ANCOVA model may instead be used to additionally adjust for baseline characteristics such as age and gender.

Subjects who died while in the hospital will be assigned as in the hospital for the number of days remaining from the day of death to Day 29 for the analysis. Subjects who were in the hospital at

study completion will be assigned a hospitalization end date equals to the date of completion for the purpose of deriving the duration of hospitalization.

Duration of ICU stay

The duration (number of days) of ICU stay from Day 1 through Day 29 will be calculated based on ICU admission and discharge dates recorded on the eCRF. Number of days in the ICU will be compared between treatment groups using an ANOVA model, including number of days in the ICU as a dependent variable and treatment group as a fixed effect. From this model, the LS means and 95% CIs for each treatment group, the treatment difference in the LS means, the 95% CI for the difference, and the associated p-value will be presented. If appropriate, an ANCOVA model may instead be used to additionally adjust for baseline characteristics such as age and gender.

In the event the data is highly skewed, e.g. very few subjects with ICU admissions, a sensitivity analysis using a non-parametric Wilcoxon Rank Sum test will be performed. The p-value from Wilcoxon Rank Sum test, as wells as the Hodges-Lehmann estimate of the treatment difference and the corresponding 95% CI will be provided.

Subjects who died while in ICU will be assigned as in the ICU for the number of days remaining from the day of death to Day 29 for the analysis. Subjects who were at ICU at study completion will be assigned an ICU end date equals to the date of completion for the purpose of deriving number of ICU days. Subjects who are alive and never admitted into the ICU through Day 29 will be included in the analysis with a value of zero ICU days.

Duration of any oxygen use

The duration (number of Days) of any oxygen use from Day 1 through Day 29 will be calculated based on the start/stop date of using oxygen supplementation recorded on the eCRF All Visits page "General Duration of Hospitalization, & Overall Requirement for Mechanical Ventilation, ICU Admission and/or Oxygen Supplementation". Number of days on oxygen will be compared between treatment groups using an analysis of variance (ANOVA) model, including number of days on oxygen as a dependent variable and treatment group as a fixed effect. From this model, the LS means and 95% CIs for each treatment group, the treatment difference in the LS means, the 95% CI for the difference, and the associated p-value will be presented. If appropriate, an analysis of covariance (ANCOVA) model may instead be used to additionally adjust for baseline characteristics such as age and gender.

Subjects who died during the hospitalization without a stop date of using oxygen supplementation recorded on the eCRF will be assigned as being on oxygen for the number of days remaining to Day 29 for the analysis. Subjects who had oxygen use ongoing at study completion will be assigned an oxygen use end date equals to the date of completion for the purpose of deriving duration of oxygen use. Subjects who never received supplemental oxygen through Day 29 will be included in the analysis with a value of zero days of oxygen use.

A listing of all supplemental oxygen and saturation (SpO_2 and SaO_2) data collected throughout the study will be provided.

Duration of mechanical ventilation

The duration (number of days) on mechanical ventilation from Day 1 through Day 29 will be calculated based on the start/stop dates of mechanical ventilation recorded on the eCRF All Visits

page "General Duration of Hospitalization, & Overall Requirement for Mechanical Ventilation, ICU Admission and/or Oxygen Supplementation". Number of days on mechanical ventilation will be compared between treatment groups using an ANOVA model, including number of days on mechanical ventilation as a dependent variable and treatment group as a fixed effect. From this model, the LS means and 95% CIs for each treatment group, the treatment difference in the LS means, the 95% CI for the difference, and the associated p-value will be presented. If appropriate, an ANCOVA model may instead be used to additionally adjust for baseline characteristics such as age and gender.

In the event the data is highly skewed, e.g. very few subjects on mechanical ventilation, a sensitivity analysis using a non-parametric Wilcoxon Rank Sum test will be performed. The p-value from Wilcoxon Rank Sum test, as wells as the Hodges-Lehmann estimate of the treatment difference and the corresponding 95% CI will be provided.

Subjects who died during the hospitalization without a stop date of mechanical ventilation recorded on the eCRF will be assigned as being on mechanical ventilation for the number of days remaining to Day 29 for the analysis. Subjects who had mechanical ventilation ongoing at study completion will be assigned a mechanical ventilation end date equals to the date of completion for the purpose of deriving duration of mechanical ventilation. Subjects who are never placed on mechanical ventilation through Day 29 will be included in the analysis with a value of zero days on mechanical ventilation.

A listing of all mechanical ventilation and oxygen administration data collected throughout the study will be provided.

Ordinal scales

a) The absolute value and change from baseline in the Ordinal scale from Day 1 through Day 29 will be summarized by treatment group and visit using descriptive statistics.

   Mean change in Ordinal scales through Day 29 will be evaluated by fitting a linear MMRM similar to the one described above for "assessment of clinical severity."

b) The proportion of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29 will be tabulated. The difference in severity category distribution between treatment groups at Day 15 and Day 29 will be examined using proportional-odds cumulative logit model. The cumulative logits model will compare lower ordinal scales to higher ones, or equivalently, less favorable outcomes to more favorable ones. The model may be adjusted for baseline characteristics such as age and gender if appropriate. The estimated odds ratio and 95% CI will be presented. Graphical illustrations of the fitted model will also be presented for Day 15 and Day 29.

   The proportional odds assumption will be tested using a score test at the two-sided alpha level of 0.05. If the proportional odds assumption is not satisfied, given the anti-conservative nature of the score test, the proportional odds model will still be used for the analysis, and the results will be presented along with the score test p-value to help put these results in context. If the proportion odds assumption is rejected or if the proportional odds model fails to converge, a sensitivity or alternative analysis using a non-parametric Wilcoxon Rank Sum test will be performed. The p-value from Wilcoxon Rank Sum test, as well as the Hodges-Lehmann estimate of the treatment difference and the corresponding

95% CI will be provided.

Sustained normalization of temperature

Sustained normalization of temperature is defined as the temperature <36.6 ºC armpit (axillary), <37.2 ºC oral, or <37.8 ºC rectal sustained for at least 24 hours through Day 29.

- The time to the first occurrence of sustained normalization of temperature will be estimated using the KM method. The KM estimates along with 95% CI, and survival curves will be provided. Based on the KM estimates, the probabilities of achieving first sustained normalization of temperature and associated 95% CIs on Days 15 and 29 will be reported; in addition, the 25th 50th (median), and 75th percentiles of the time to first sustained normalization of temperature with associated 95% CIs will be provided, as data permit. The survival rates between treatment groups will be compared using Log-rank test. The p-value from Log-rank test will be presented.
- The proportion of subjects who have experienced sustained normalization of temperature at any timepoint through Day 29 within each treatment group will be presented along with a two-sided exact (Clopper-Pearson) 95% CI.

  The observed difference in the proportion of subjects who achieved sustained normalization of temperature at any timepoint between treatment groups along with the exact unconditional 95% CI for risk difference will be calculated. The null hypothesis of no between-treatment difference will be tested using Chi-square statistic and the p-value will be reported.

Number of subjects developed ARDS

Berlin criteria for ARDS will be assessed on Day 1, 5, 15, and 29. The presence of ARDS and the degree of ARDS by Berlin criteria (Mild, Moderate, Severe) will be tabulated by treatment group at each visit.

Time to clinical progression

Clinical progression is defined as death, start of mechanical ventilation, or ICU admission through Day 29, whichever occurs first. The time to clinical progression will be estimated using the KM method. The KM estimates along with 95% CI, and survival curves will be provided. Based on the KM estimates, the probabilities of experiencing clinical progression and associated 95% CIs on Days 15 and 29 will be reported; in addition, the 25th 50th (median), and 75th percentiles of the time to clinical progression with associated 95% CIs will be provided, as data permit. The survival rates between treatment groups will be compared using Log-rank test. The p-value from Log-rank test will be presented.

6.3 Exploratory Efficacy Endpoints and Analyses

- Change from baseline in quantitative SARS-CoV-2 viral load by NAT or PCR (RT-PCR) to Days 5±1, 15±1, and 29±1 will be summarized for each treatment group by visit.
- Change from baseline in quantitative anti- SARS-CoV-2 IgM and IgG antibodies to Days 5±1, 15±1, and 29±1 will be summarized for each treatment group by visit.
- The proportion of subjects with evidence of hyperinflammation on Days 1, 5, 15, and 29 will

be tabulated by treatment group. For this analysis, the denominator for calculating the proportion at each visit and within each treatment group will be the number of subjects with nom-missing values for Lymphocyte counts AND for at least 2 of the following 4 lab parameters: Ferritin, LDH, D-Dimers, and C-reactive protein (i.e., the number of subjects for whom evidence of hyperinflammation could be assessed).

- Change from baseline in cytokine profile (IL-1β, IL-10, IL-6, IL-8 IL-2, interferon γ, and TNF-α) to Days 5±1, 15±1, and 29±1 will be summarized for each treatment group by visit.
- Change from baseline in levels of alpha 1-PI (AAT) activity and antigen to Days 8, 15, and 29 will be summarized for each treatment group by visit.

7. SAFETY ANALYSIS

Safety assessments will include assessment of AEs, chemistry, hematology (complete blood count and differential), COVID-19 clinical features, vital signs, and hospital interventions. All safety summaries (or analyses if applicable) will be conducted using the SAF population. No formal hypothesis testing will be performed to compare differences between treatment groups.

7.1 Extent of Exposure and Compliance

The number of doses received, duration of infusion in minutes, infusion rate, the occurrence of dose interruption, whether 100% of study drug infused, total volume prepared, and total volume infused will be summarized by treatment group. In addition, treatment compliance will be calculated and summarized by treatment group. The summaries will include descriptive statistics of the treatment compliance as well as number and percentage of subjects with compliance between 80% and 120%.

Treatment compliance (%) will be calculated as follows:

(Total volume infused over all infusions [mL] /

Total volume prepared over all infusions [mL]) x 100.

7.2 Adverse Events

All AEs and SAEs occurring on Day 1 through the Day 29 (±1 day)/Final Visit must be fully recorded in the subject's medical record and eCRF, and SAE form (if serious). AEs will be classified by SOC and PT using the most recent version of MedDRA.

7.2.1 Treatment-emergent Adverse Events

For summary purposes, AEs will be classified as treatment-emergent AEs (TEAEs) or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the date of 1st study drug administration. A TEAE will be defined as an AE which occurred on or after the date of 1st study drug administration. For adverse events with incomplete start dates/times, the same imputation algorithm for missing or partial date/time information as described in Section 5.6 will be used for the determination of an AE being treatment emergent or not. Briefly, the unknown portions of an AE onset date/time will be imputed to the latest possible before being compared to the date of 1st study drug administration.

Non-TEAEs will be summarized separately from TEAEs by SOC and PT for each treatment group

and overall.

7.2.2 Adverse Event Severity

Refer to the study protocol, Section 8.3.5.

7.2.3 Adverse Event Relationship to IP

Refer to the study protocol, Section 8.3.4.

7.2.4 Serious Adverse Events

Refer to the study protocol, Section 8.3.7.

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring after randomization and before the end of study, regardless of relationship to IP, will be included and classified by SOC and PT using MedDRA.

For TEAEs, the following will be summarized and presented for the SAF population:

i. An overall summary of TEAEs, which includes:
    a. the number and percentage of subjects experiencing a TEAE
    b. the number and percentage of subjects experiencing a TEAE by strongest relationship to IP
    c. the number and percentage of subjects experiencing a TEAE by greatest severity
    d. the number and percentage of subjects experiencing a TEAE with Grade >=3
    e. the number and percentage of subjects experiencing a treatment-emergent SAE
    f. the number and percentage of subjects experiencing a TEAE leading to death
    g. the number and percentage of subjects experiencing a TEAE leading to study withdrawal

ii. the number and percentage of subjects experiencing a TEAE by SOC and PT.

iii. the number and percentage of subjects experiencing an adverse drug reaction (ADR; i.e., potentially related TEAE) by SOC and PT, where an ADR is defined as any TEAE with a casual relationship to IP assessed as 'Possibly Related' or 'Definitely Related'.

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to IP

v. the number and percentage of subjects experiencing a TEAE by SOC, PT and the greatest severity

vi. the number and percentage of subjects experiencing a TEAE with Grade >=3 by SOC and PT

vii. the number and percentage of subjects experiencing an ADR with Grade >=3 by SOC and PT

viii. the number and percentage of subjects experiencing a treatment-emergent SAE by SOC

and PT

ix. the number and percentage of subjects experiencing a potentially related treatment-emergent SAE by SOC and PT

x. the number and percentage of subjects experiencing a TEAE leading to death by SOC and PT

xi. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to IP, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC or PT will be counted only once in the total of subjects experiencing TEAEs in that particular SOC or PT.

All occurrences of all AEs and SAEs will be listed for each subject, grouped by treatment group. The listing will contain the following information: treatment group, verbatim term, SOC, PT, severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3-5]), relationship to IP, date/time and day of onset, date/time and day of resolution, action taken with regard to IP, whether additional non-drug or drug treatment was given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to study withdrawal, whether it occurred during IP infusion, and whether it is a TEAE. Listings will be sorted by treatment group, subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Clinical laboratory tests will be obtained at the time points presented in Appendix A. Continuous clinical laboratory values will be summarized by presenting descriptive statistics of raw data and change from baseline values at each time point for each treatment group, if feasible. If necessary, quantitative lab values reported in different units for the same lab parameter will be converted to the same units prior to being summarized. Qualitative results at each time point measured will be summarized by presenting the number and percentage of subjects for each category. Shift tables, based on the high/low flags, will also be summarized by treatment group at each visit for all laboratory tests with normal ranges, when available.

Laboratory parameter results from unscheduled visits will be excluded from table summaries but will be included in data listings. When there are repeat scheduled measurements for a given visit, only the last measurement will be used in the table summaries.

Listings will include flags for values outside of the reference ranges, when available, and clinical

significance if a laboratory result is deemed abnormal when applicable.

7.4 Vital Signs

Descriptive summaries of the vital signs (both raw and change from baseline values) including systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature will be prepared for each treatment group by visit.

Qualitative results at each time point measured, including severe dehydration (no/yes), sternal capillary refill time >2 seconds (no/yes/unknown), and clinically significant (no/yes), will be summarized by presenting the number and percentage of subjects for each category.

Vital signs will also be measured immediately before infusion, then after the first 5 minutes of infusion and subsequently at 5-10 minutes intervals during infusion until the end of infusion, and at a time point 2 hours after the end of infusion. The raw data and change from baseline values, as well as whether clinically significant at each time point will be summarized by treatment group.

Unscheduled visits will be excluded from the summaries but will be included in the data listings.

7.5 Other Safety Measures

Data for COVID-19 clinical features will be listed and tabulated.

Data for hospital interventions will be listed and summarized by presenting frequency counts and percentages for each category. The duration (number of days) of inotropes/vasopressors administration will be calculated based on the start/stop dates recorded on the eCRF and summarized descriptively. Subjects who were never on inotropes/vasopressors will be included in the descriptive summary with a value of zero days of duration.

8. INTERIM ANALYSES

8.1 Interim Safety Analysis

An interim analysis will be conducted after 50 subjects (approximately 25 per group) for safety variables through Day 29. Due to the exploratory nature of this phase 2 study, the multiplicity adjustments will not be considered. This interim evaluation simply represents Sponsor safety due diligence. This interim analysis will analyze safety variables including, but not limited to, the following: adverse events (see Section 7.2), clinical laboratory parameters (see Section 7.3), and vital signs (see Section 7.4). The relevant methods described in Section 7 (Safety Analysis) of this SAP intended for the final analysis will also be applicable to the interim analysis.

8.2 Interim Futility Analysis

An interim futility analysis will be conducted based on all available data assessable for the primary endpoint and key secondary efficacy endpoints to assess whether the trial will be terminated due to lack of efficacy (futility). The unblinded output will be reviewed by an independent unblinded team, and the study team will remain blinded. Determination of futility from the interim futility analysis will be based on the conditional power (the power conditional on the observed data accumulated at the interim analysis) for the primary outcome, as well as assessment of the secondary efficacy outcomes.

The futility analysis will include for the primary efficacy endpoint variable, all patients with data

through Day 29, and for the following secondary efficacy endpoint variables, all patients with data through Day 29, as specified for each endpoint:

- Assessment of Clinical Severity: Change in NEWS from baseline (Day 1 through Day 29)
- Time to clinical response: NEWS ≤ 2 maintained for 24 hours, Day 1 through Day 29
- Time to hospital discharge: defined as duration of hospitalization from Day 1 through Day 29 (and duration of hospitalization)
- If admitted to ICU post randomization: Duration of ICU stay through Day 29
- Duration of any oxygen use Day 1 through Day 29
- If requiring mechanical ventilation post randomization: Duration mechanical ventilation through Day 29
- Absolute value and mean change from baseline in the Ordinal scale Day 1 through Day 29
    - The Ordinal scale is as follows:
        1) Death;
        2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
        3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
        4) Hospitalized, requiring supplemental oxygen;
        5) Hospitalized, not requiring supplemental oxygen;
        6) Not hospitalized, limitation on activities;
        7) Not hospitalized, no limitations on activities.
- Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29
- Time to sustained normalization of temperature and proportion of subjects with normalization of fever at all time points, defined as temperature < 36.6 ° C armpit, < 37.2 ° C oral, or < 37.8 ° C rectal sustained for at least 24 hours
- Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS) through Day 29
- Length of time to clinical progression through Day 29 (defined as the time to death, mechanical ventilation, or ICU admission)

If the results of the interim futility analysis are not promising, the trial may be terminated. Otherwise the study will continue as originally planned unless discontinued for business or feasibility reasons.

The futility analysis will not inflate the type I error since the trial will not be stopped to claim efficacy. The primary and key secondary efficacy outcomes will be analyzed using the methods described above in Section 6.1 and 6.2. No subgroup or sensitivity analyses are planned for the futility analysis.

Suppose at the time of data-cut for the futility analysis, x_0 subjects meet the primary efficacy endpoint among m_0 subjects in the placebo group, and x_1 subjects have events among m_1 subjects in the active ($Alpha_1$-PI) group. Let $\tilde{p}_g = x_g/m_g$ for group g = 0, 1; and $\tilde{p} = (x_0 + x_1)/(m_0 + m_1)$. $Z_1 = \frac{\tilde{p}_1 - \tilde{p}_0}{\sqrt{(m_0^{-1} + m_1^{-1})\tilde{p}(1-\tilde{p})}}$ is the z-score corresponding to the Chi-square statistic.

Let the final sample size be n_0 and n_1 in the placebo and active ($Alpha_1$-PI) groups respectively. Let $Z_{1-\alpha/2}$ be the 1- α/2 = 97.5% percentile of the normal distribution, which can be calculated as the PROBIT function in SAS. Let $t = (n_0^{-1} + n_1^{-1})/(m_0^{-1} + m_1^{-1})$. The conditional power (CP) for the primary efficacy endpoint (active compares to placebo group) will be calculated using the formula:

$$CP = 1 - \Phi\left(\frac{Z_{1-\alpha/2} + Z_1/\sqrt{t}}{\sqrt{1-t}}\right)$$

where Φ is the cumulative distribution function (CDF) for *N* (0,1).

9. SAMPLE SIZE AND POWER CALCULATIONS

Because of the urgency and lack of previous prospective COVID-19 data, sample size estimation remains incompletely defined; however, the size of this pilot study is commensurate with other Phase 2 investigations ongoing during the COVID-19 pandemic. Approximately 100 subjects are allowed to be randomized as part of a humanitarian effort against COVID-19.

10. REFERENCES

1. https://www.mdcalc.com/national-early-warning-score-news

2. https://clinicaltrials.gov/ct2/show/NCT04280705

3. Gray, R.J. (1988). A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat, 16(3):1141-1154.

11. APPENDIX

11.1 Appendix A: Schedule of Events

Study Period	**Screen/ Baseline**	**IP**	**SMT and Daily Evaluations[l]**									**Follow-Up**	**Follow-Up Clinic Visit Day**				
Study Day **Procedures/assessments**	1	**1st IP infusion day**	2	3	4	5±1[m] day	6	7	8	9	10	11-14 **Daily** if in hospital	15± 1 day[m]	16-28 **Daily** if in hospital	29[e] ± 1 day[m]	Day 60 ± 2 days	Day 90 ± 2 days
Informed consent	X																
Inclusion/exclusion criteria	X																
Demography, (including age [year of birth], gender, race, and ethnicity), disease characteristics (date of exposure, date of onset[a])	X																
Pregnancy test[b]	X																
Ordinal Scale (at the 1st assessment of a given day)[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
National Early Warning Score (NEWS) (Appendix 2)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)	X	X[i]	X	X	X	X	X	X	X[i]	X	X	X	X	X	X		
Weight	X																
Record result of *historical* SARS-CoV-2 PCR (qualitative RT-PCR) or NAT or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19 in any specimen during the current hospital admission OR 96 hours prior to the hospital admission date and prior to randomization (the SARS-CoV-2 test results must be performed by a hospital laboratory and the documentation available) (eligibility criterion)	X																

Schedule of Events (Continued)

Study Period	**Screen/ Baseline**	**IP**	**SMT and Daily Evaluations[l]**									**Follow-Up**	**Follow-Up Clinic Visit Day**				
Study Day **Procedures/assessments**	1	**1st IP infusion day**	2	3	4	5±1[m] day	6	7	8	9	10	11-14 **Daily** if in hospital	15±1 day[m]	16-28 **Daily** if in hospital	29[e] ± 1 day[m]	Day 60 ± 2 days	Day 90 ± 2 days
Record any supplemental oxygen administration (type, %, flow start/end date/time)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
If subject requires mechanical ventilation post randomization: Record any mechanical ventilation (start/end date/time)			X	X	X	X	X	X	X	X	X	X	X	X	X		
Record oxygen saturation (specify on or off oxygen supplementation)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization *(after all Screen/Baseline assessments complete)*	X																
IV dose of blinded Liquid Alpha$_1$-PI (Human) 120 mg/kg body weight (or Placebo) given on Day 1 and Day 8		X							X[k]								
Record hospital admission and discharge dates	X														X[f]		
If subject requires ICU admission post randomization: Record ICU admission & discharge dates															X[f]		
Assessment of ARDS (Berlin Criteria) (Appendix 3)	X					X							X		X		
Respiratory sample for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab)	Pre randomized treatment[g]					X							X		X		
Sample for quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 (if antibodies cannot be determined quantitatively store serum samples frozen at -70°C for later analysis at an external lab)	Pre randomized treatment[g]					X							X		X		

Schedule of Events (Continued)

Study Period	Screen/ Baseline	IP	SMT and Daily Evaluations[l]									Follow-Up	Follow-Up Clinic Visit Day				
Study Day Procedures/assessments	1	1st IP infusion day	2	3	4	5±1[m] day	6	7	8	9	10	11-14 Daily if in hospital	15± 1 day[m]	16-28 Daily if in hospital	29[e] ± 1 day[m]	Day 60 ± 2 days	Day 90 ± 2 days
Serum Chemistry (creatinine, albumin, alanine aminotransferase [ALT], total bilirubin, lactate dehydrogenase [LDH])	Pre randomized treatment[g]					X							X		X		
Calculate an estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault formula	Pre randomized treatment[g]					X							X		X		
Ferritin, CRP, D-dimer	Pre randomized treatment[g]					X							X		X		
Hematology & absolute neutrophil & lymphocyte count (hemoglobin, hematocrit, platelet count, leukocyte count with differential)	Pre randomized treatment[g]					X							X		X		
Cytokine panel[h]	Pre randomized treatment[g]					X							X		X		
Levels of alpha 1-PI (AAT) activity and antigen (both plasma [sodium citrate] and serum samples to be stored for measurement of both antigenic content and functional activity [potency])	Pre randomized treatment[g]								X[gj]				X		X		
Record SAEs and TEAEs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Record standard care concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Phone Checks for Vital Status (living or deceased), any hospital re-admissions or SAEs/non-serious AEs after Day 29 Final Clinic Visit																X	X

a Date of first contact with the virus, date of first symptoms, date of PCR (RT-PCR)/NAT positive

b Human chorionic gonadotropin-based assay for women of childbearing potential (urine matrix is also valid).

c Ordinal scale measure of clinical status: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities.

d Grade 3-5 TEAEs will be defined according to CTCAE criteria, US Department of Health and Human Services, NIH, and NCI. In this clinical study, disease progression is defined as the worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the targeted disease and/or increases in the symptoms of the targeted disease. Anticipated symptoms of COVID-19 include fever, cough, hypoxia, dyspnea, hemoptysis, myalgia, fatigue, pharyngitis, which may develop at any time during the course of the disease. The development of COVID-19 symptoms during the clinical study should not be recorded as individual TEAEs, unless there is evidence suggesting a causal relationship between blinded Liquid Alpha$_1$-PI (Human)/Placebo and the TEAE.

e Final Clinic Visit, followed by Phone Checks.

f Record hospital and ICU discharge date on or before Day 29/Final Visit.

g All laboratory tests and serum and plasma samples must be obtained from all subjects; samples must be obtained prior to the blinded Liquid Alpha$_1$-PI (Human) infusion on Day 1 and Day 8. (Day 8 AAT levels only apply if second infusion given)

h Cytokine panel includes IL-1β, IL-10, IL-6, IL-8 IL-2, interferon γ, and TNF-α. Note: serum samples must be stored at -70° C for later analysis at a reference laboratory.

i. During study infusions on Day 1 and Day 8 vital signs will be measured immediately before the start of infusion, after the first 5 minutes of infusion, and subsequently at 5-10 minute intervals during infusion until the end of infusion. Vital signs will also be measured 2 hours after the end of study infusion.

j. Day 8 AAT measurement for activity and antigen is only required if subject is in hospital.

k. If the patient has been discharged from the hospital at the time of the Day 8 blinded Liquid Alpha1-PI (Human) or Placebo infusion, the 2nd infusion is not mandatory, and is at the discretion of the Principal Investigator and subject

l. Only applicable if subject remains hospitalized, except for Day 5 when all assessments are mandatory for all subjects.

m. Mandatory even if subject has been discharged from hospital

Note: For assessment for early withdrawal see Section 5.3.4.

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Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: D431E5ED-B26F-4E75-A11A-D083AEFDB1F6 Using IP Address: With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 12/13/2021 2:03:31 PM Viewed: 12/13/2021 2:15:34 PM Signed: 12/13/2021 2:17:49 PM
Electronic Record and Signature Disclosure: Accepted: 7/14/2020 11:54:42 PM ID: 2edc4721-867e-4245-8dad-1715494d30e0		
Grifols Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: EB645875-0999-448C-AD8F-1DC54F97A22A Using IP Address: With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 12/13/2021 2:03:33 PM Viewed: 12/13/2021 3:06:10 PM Signed: 12/13/2021 3:06:45 PM
Electronic Record and Signature Disclosure: Accepted: 12/13/2021 3:06:09 PM ID: a30279aa-92e5-46d3-9ea6-0c3f048b582d		

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 4858372B-8E7B-450B-9074-0B2A92108C37 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/13/2021 2:03:32 PM Viewed: 12/13/2021 2:08:06 PM Signed: 12/13/2021 2:08:52 PM
Electronic Record and Signature Disclosure: Accepted: 12/13/2021 2:08:06 PM ID: 7abf0426-ed91-42cf-9618-c27951b1bebe		
[redacted] Security Level: Email, Account Authentication (Required)	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 13-Dec-2021 | 12:05:14 PM PST E3B95A788F29468BBB17F43EB77602AB Signature Adoption: Pre-selected Style Signature ID: E3B95A78-8F29-468B-BB17-F43EB77602AB Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/13/2021 2:03:32 PM Viewed: 12/13/2021 3:04:49 PM Signed: 12/13/2021 3:05:15 PM
Electronic Record and Signature Disclosure: Accepted: 12/13/2021 3:04:49 PM ID: 29a1f73b-945d-48a3-b511-81786b8f427d		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: CEDDDA6A-450C-4590-B540-9E293574798C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 12/13/2021 2:03:32 PM Viewed: 12/13/2021 2:03:56 PM Signed: 12/13/2021 2:04:13 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	12/13/2021 2:03:33 PM
Certified Delivered	Security Checked	12/13/2021 2:03:56 PM
Signing Complete	Security Checked	12/13/2021 2:04:13 PM
Completed	Security Checked	12/13/2021 3:06:45 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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