Official Title: **A Multicenter, Randomized, Double-blind, Parallel Group Study to Evaluate the Safety and Efficacy of Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%) versus Placebo in Asymptomatic Ambulatory Outpatients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection**

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Protocol Number: GC2010
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STATISTICAL ANALYSIS PLAN

Version 2.0

The effective date of the document is the last date of approval of the document

A Multicenter, Randomized, Double-blind, Parallel Group Study to Evaluate the Safety and Efficacy of Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%) versus Placebo in Asymptomatic Ambulatory Outpatients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

STATISTICAL ANALYSIS PLAN

Version 2.0

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SAP REVISIONS

Version 1.0 of the SAP was finalized based on Protocol version 4.0 (28 June 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 5.0, and protocol date from 28 June 2021 to 13 October 2021. 2) Added "interim futility".	1) and 2) Updated to match the protocol amendment.
2.0	2.2.2	1) Added "Time to COVID-19 symptoms specifically defined as the time to fulfillment of the case definition used for the primary efficacy variable through Day 14". 2) Moved "[*Note: ICU level care is defined as the medical need for intensive or invasive monitoring; immediate or impending need for the support of the airway, breathing, or circulation; and/or stabilization of acute severe or life-threatening complications of COVID-19]" to the end of the section.	1) The new secondary efficacy endpoint was added to Protocol version 5.0. 2) Updated to match the protocol amendment.
2.0	4.1	Added "and interim futility".	Updated to match the protocol amendment.
2.0	4.4	Added right censoring rule for time to COVID-19 symptoms through Day 14.	Added to reflect the planned analysis for the new secondary efficacy endpoint.
2.0	4.6	Added start date and event date derivation for time to COVID-19 symptoms through Day 14.	Added to reflect the planned analysis for the new secondary efficacy endpoint.
2.0	6	For all efficacy analyses sections, changed Fisher's exact method to Chi-square statistic.	Changed to reflect the planned analysis.
2.0	6.1	For CMH test, changed odds ratio to common risk difference	Changed to reflect the planned analysis.
2.0	6.2	Added analysis for time to COVID-	Added to reflect the planned analysis for the new secondary

		19 symptoms through Day 14.	efficacy endpoint.
2.0	8	Changed section title from "INTERIM ANALYSE" to "DSMB ANALYSIS".	Clarify the section is about DSMB analysis.
2.0	9	Added the section for interim futility analysis	Interim futility analysis was added to the protocol amendment, updated to match the protocol v5.0 and to provide the details of conditional power calculation.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ATC	Anatomical, Therapeutic, and Chemical
BMI	Body mass index
C19-IG 20%	anti-COVID-19 Immune Globulin (Human) 20%
CDF	Cumulative distribution function
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CP	Conditional power
CRP	C-reactive protein
CTCAE	Common terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EUA	Emergency Use Authorization
ICU	Intensive care unit
IG	Immune globulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IP	Investigational product
ITT	Intention-to-treat
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LS	Least-Squares

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MMRM	Mixed-effects model for repeated measures
NAT	Nucleic acid amplification technology
NCI	National Cancer Institute
NEWS	National Early Warning Score
NIH	National Institutes of Health
PCR	Polymerase chain reaction
PI	Principal Investigator
PP	Per-Protocol
PT	Preferred term
RT-PCR	Reverse transcriptase PCR
SAE	Serious adverse event
SAF	Safety
SaO_2	Arterial oxygen saturation
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SOC	System organ class
SpO_2	Oxygen Saturation by pulse oximetry
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # GC2010 Version 5.0, dated 13 October, 2021, and titled "A Multicenter, Randomized, Double-blind, Parallel Group Study to Evaluate the Safety and Efficacy of Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%) versus Placebo in Asymptomatic Ambulatory Outpatients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection." See the study protocol for full details.

This document details the statistical methods planned to perform the Data Safety Monitoring Board (DSMB), interim futility and final analyses of the study.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Efficacy Objective

To compare C19-IG 20% (2 doses) versus Placebo with regard to proportion of asymptomatic subjects who remain asymptomatic, i.e., who do not develop symptomatic coronavirus disease 2019 (COVID-19) through Day 14 defined as any of the following:

> Experiencing at least TWO of the following systemic symptoms: (a) Fever (≥ 38ºC), (b) chills, (c) myalgia, (d) headache, (e) sore throat, (f) cough, (g) fatigue that interferes with activities of daily living, (h) new olfactory and taste disorder(s), (i) vomiting/diarrhea *(note that [h] new olfactory/taste disorder(s) & [i] vomiting/diarrhea Each Only count as ONE item of definition)*
>
> OR
>
> Experiencing at least ONE of the following respiratory signs/symptoms: new or worsening shortness of breath or difficulty breathing,
>
> OR
>
> Experiencing peripheral oxygen saturation by pulse oximetry (SpO2) < 94% on room air
>
> OR
>
> Radiographical evidence of pneumonia (radiographic infiltrates by imaging [chest X-Ray, CT scan, etc.]). Note radiographical studies are to be done for suspicion of pneumonia per standard of care

2.1.2 Secondary Efficacy Objectives

- To compare C19-IG 20% (2 doses) versus Placebo with regard to change in SARS-CoV-2 viral load (log_{10} copies/mL) from Baseline (Day 1) to Day 7 and to Day 14.
- To compare C19-IG 20% (2 doses) versus Placebo with regard to proportion of subjects who remain in an outpatient setting and maintain SpO2 ≥94% on room air on Day 3, Day 7, and Day 14.
- To compare C19-IG 20% (2 doses) versus Placebo with regard to proportion of subjects negative and time to negative SARS-Cov-2 by polymerase chain reaction (PCR) from

Baseline through Day 14 and through Day 29.

- To compare C19-IG 20% (2 doses) versus Placebo with regard to clinical efficacy in asymptomatic ambulatory outpatients as assessed by clinical evolution to overt COVID-19, new dependency on oxygen and if needed duration of oxygen supplementation, clinical response criteria including National Early Warning Score (NEWS) [1] and ordinal clinical status scale [2] through Day 29.
- To compare C19-IG 20% (2 doses) versus Placebo with regard to frequency of requirement for hospital-level medical care (i.e., hospitalization admission defined by need for medical intervention[s], not for quarantine purposes) and duration of hospitalization (if required) through Day 29.
- To compare C19-IG 20% (2 doses) versus Placebo with regard to proportion of asymptomatic subjects with COVID-19 who require at least one COVID-19 related medically attended visit for management/treatment of COVID-19 (apart from routinely scheduled study-directed visits) which may occur in any setting through Day 29 (e.g., Emergency department, urgent care, outpatient clinic or professional setting wherein direct in-person/telemedicine medical assessment and escalation of care for COVID-19 is provided by licensed healthcare personnel).

2.1.3 Exploratory Efficacy Objectives

The exploratory objectives of the study are:

- To evaluate the effect of C19-IG 20% (2 doses) versus Placebo with regard to change from baseline in inflammatory biomarkers specifically: interleukin 6 (IL-6); D-dimer; ferritin; C-reactive protein (CRP), and interferon γ through Day 14.
- To evaluate the effect of C19-IG 20% (2 doses) versus Placebo with regard to quantitative anti-SARS-CoV-2 antibodies through Day 14.
- Overall assessment of COVID-19 symptoms severity on Day 7 and Day 29.

2.1.4 Safety Objective

- To determine the safety and tolerability profile of C19-IG 20% (2 doses) versus Placebo through Day 29.
- To evaluate change from baseline in key biochemical parameters of organ function/dysfunction: alanine aminotransferase (ALT); lactate dehydrogenase (LDH); absolute lymphocyte count; creatinine through Day 14.

2.2 Endpoints

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of asymptomatic subjects who remain asymptomatic. See details above in Section 2.1.1.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Change in SARS-CoV-2 viral load (log_{10} copies/mL) from Baseline (Day 1) to Day 7 and to Day 14.
- Proportion of subjects who remain in an outpatient setting and maintain SpO2 ≥94% on room air on Day 3, Day 7, and Day 14.
- Proportion of subjects negative for SARS-CoV-2 by PCR at multiple time points through Day 14 and through Day 29.
- Time to negative SARS-CoV-2 PCR from Baseline through Day 29.
- Proportion of subjects who require O_2 supplementation on or before Day 29.
- If requiring supplemental oxygen post randomization: Duration of any oxygen through Day 29.
- Absolute value and mean change from baseline in the 7-point Ordinal scale Day 1, Day 7, Day 14, and Day 29:

  The 7-point 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 1, Day 7, Day 14, and Day 29.
- Assessment of Clinical Severity: Change in NEWS from baseline (at Day 7, Day 14, and 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]).
- Proportion of subjects who require at least one COVID-19 related medically attended visit for management/treatment of COVID-19 (apart from routinely scheduled study-directed visits) which may occur in any setting through Day 29 (e.g., Emergency department, urgent care, outpatient clinic or professional setting wherein direct in-person/telemedicine medical assessment and escalation of care for COVID-19 is provided by licensed healthcare personnel).
- Proportion of subjects who require hospital admission for medical care (non-quarantine purpose) through Day 29.

- If admitted to hospital post randomization: Duration of hospital stay through Day 29.
- Proportion of subjects who require ICU admission or initiation of ICU-level care* through Day 29.
- If admitted to ICU post randomization: Duration of ICU stay through Day 29.
- Proportion of subjects requiring invasive mechanical ventilation through Day 29.
- If requiring invasive mechanical ventilation post randomization: Duration of invasive mechanical ventilation through Day 29
- All-cause mortality through Day 29.
- Incidence of critical COVID-19 illness, defined as any one of the following: (a) requiring ICU admission or ICU level of care*, (b) invasive mechanical ventilation, or (c) resulting in death by Day 29.

- Length of time to clinical progression to critical COVID-19 illness through Day 29 (defined as the time to death, invasive mechanical ventilation, or ICU admission/requiring ICU level of care).
- Time to COVID-19 symptoms specifically defined as the time to fulfillment of the case definition used for the primary efficacy variable through Day 14.

[*Note: ICU level care is defined as the medical need for intensive or invasive monitoring; immediate or impending need for the support of the airway, breathing, or circulation; and/or stabilization of acute severe or life-threatening complications of COVID-19]

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Change from baseline in inflammatory biomarkers specifically: IL-6; D-dimer; ferritin; CRP; interferon γ through Day 14.
- Change from baseline in quantitative anti-SARS-CoV-2 IgM and IgG antibodies through Day 14.
- Overall assessment of COVID-19 symptoms severity (No symptoms; Mild; Moderate; Severe; Potentially Life-threatening) on Day 7 and Day 29.

2.2.4 Safety Endpoints

The safety endpoints include:

- Cumulative incidence of treatment-emergent serious adverse events (SAEs) and potentially related SAEs through Day 60 Phone Check.
- Cumulative incidence of Grade 3-5 treatment-emergent adverse events (TEAEs) and potentially related severe 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) through Day 29.

- Cumulative incidence of all TEAEs and potentially related TEAEs through Day 29.
- Change from baseline in key biochemical parameters of organ function/dysfunction: ALT; LDH; absolute lymphocyte count; creatinine through Day 14.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a prospective, multi-center, randomized (1:1:1), double-blind study of C19-IG 20% at 1 of 2 dose levels versus Placebo in asymptomatic, ambulatory outpatients aged ≥18 years who are SARS-CoV-2 positive. Participants will be stratified by age <65 years vs ≥65 years of age. The study will enroll asymptomatic subjects with laboratory-confirmed novel coronavirus (SARS-CoV-2) infection as determined by qualitative PCR (reverse transcriptase [RT]-PCR), or other commercial or public health assay approved by regulatory authorities as a diagnostic for COVID-19 (inclusive of SARS-CoV-2 antigen testing or other approved rapid testing platforms) in any specimen obtained ≤ 5 days prior to randomized treatment (≤ 5 days is the post-sampling timeframe from date specimen obtained to administration of blinded study drug). Every effort should be made to reduce this time interval to the minimum as nearly immediate treatment is key for successful intervention.

Approximately 801 subjects (267 per arm) will be randomized (1:1:1). Subjects randomized to C19-IG 20% will receive a blinded subcutaneous (SC) infusion on Day 1 at a dose of either 1 gram or 2 grams, according to the randomized dose assigned. Subjects randomized to Placebo will receive a SC infusion of sterile 0.9% sodium chloride injection, United States Pharmacopeia (0.9% NaCl, USP) or equivalent. Blinded study drug will be prepared and administered by an unblinded study nurse who is entirely independent of the evaluating study team with SC infusions using 2 separate syringes as follows:

- Placebo (*two* syringes each containing 5 mL 0.9% NaCl);
- 1 gram C19-IG 20% (one syringe containing 5 mL C19-IG 20% *Plus* one syringe containing 5 mL 0.9% NaCl)
- 2 grams C19-IG 20% (*two* syringes each containing 5 mL C19-IG 20%).

An independent DSMB will review interim safety data when approximately 399 patients have been randomized and treated with follow-up through Day 29 (approximately 133 patients per randomized group).

Subjects will receive one C19-IG 20%/Placebo dose via SC route on Day 1; for all subjects monitoring and surveillance will be continued throughout the subject's participation in the study. The total estimated maximum duration of a subject's participation in terms of actual Healthcare Provider Visits will be up to 30 days. Additionally, a Phone Check will occur at Day 60 for complete follow-up. Thus, subject participation (from Screening Visit to the Final Phone Check) will be approximately 60 days.

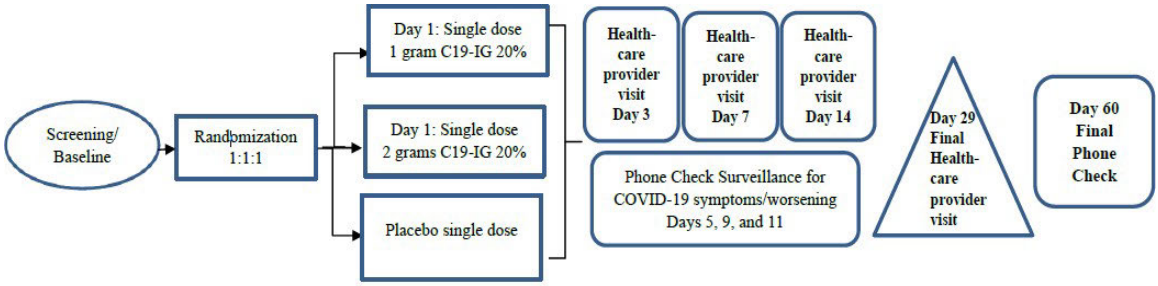
At the Healthcare Provider visit on Day 1, all subjects will receive a pulse oximeter for home use and daily recording of SpO2 in order to monitor for development of hypoxia (SpO2 < 94% on room air). All subjects will also be instructed to measure, monitor, and record body temperature daily. Subjects will be evaluated at Healthcare Provider Visits on Day 3, Day 7, Day 14, and Day

29 (or if hospitalized, assessments required for Day 7, Day 14, and Day 29 will be performed in hospital).

Additionally, subjects will be assessed as outpatients by Phone Check on Day 5, Day 9, and Day 11. The Phone Checks serve as surveillance for development of symptomatic COVID-19, sentinel alarm symptoms or symptoms that may indicate clinical deterioration (e.g., dyspnea) and to record the patient's daily entries for SpO2 and body temperature.

Following the Day 29 assessment time point, one more final Phone Check will be performed at Day 60 for vital status (living or deceased), any hospital admissions, ICU admissions, requirement for invasive mechanical ventilation, need for oxygen supplementation, or serious/non-serious adverse events after the Day 29 Healthcare Provider Visit, and to confirm resolution of any COVID-19 sequelae. See Appendix A for the Schedule of Events.

An overview of the study design is presented below:



Note: All subjects will receive a pulse oximeter for home use and daily recording of SpO2 in order to monitor for development of hypoxia (SpO2 < 94% on room air). All subjects will also be instructed to measure, monitor, and record body temperature daily. For single dose administrations all doses will be given in 2 syringes to maintain the blind. Note that given the pandemic setting it is likely that Healthcare Provider Visits may consist either of evaluations at the subject´s usual residence (home) justified because subject is in confinement or at an alternate site, e.g., Clinic, always under the care and supervision of trained healthcare personnel.

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

Eligible subjects will be randomized 1:1:1 to Placebo or to C19-IG 20% via a SC infusion on Day 1 at a dose of either 1 gram or 2 grams, according to the randomized dose assigned. A central randomization stratified by age group (age <65 years versus ≥ 65 years) will be used for this study. Randomization will be centralized and will be performed via an Interactive Web Response System after subject inclusion. A randomization list containing the randomization numbers and the corresponding randomized treatment assignments will be generated and stored in a secured area that is only accessible to the randomization team.

3.2.2 Blinding

There will be a designated unblinded study nurse for preparation and administration of study drug who is entirely independent of the team evaluating the patient with SC infusions using 2 separate syringes as described above in Section 3.1.

The designated unblinded study nurse will be the only unblinded study person at each site. Preparation of study drug (Anti-COVID-19 Immune Globulin [Human] and placebo) and SC administration of study drug will be the responsibility of the local unblinded study nurse.

Since this is a double-blind, placebo-controlled study, measures will be taken to assure that the

placebo infusion will be indistinguishable in terms of commensurate volume from Anti-COVID-19 Immune Globulin (Human) infusion volume to that required for the appropriate dose of Anti-COVID-19 Immune Globulin (Human) to maintain blinding. For all 3 arms a 10-mL volume (2 syringes each containing 5 mL volumes of various composition) will be prepared so that there is no difference in infusion volume or apparent configuration.

Furthermore, results of the central laboratory analysis of quantitative viral load and quantitative IgM and IgG anti-SARS-CoV-2 antibodies will not be shared with the Investigator, blinded study staff, clinical research organization or blinded Sponsor personnel involved in study conduct.

3.2.3 Dosing Schedule

Subjects randomized to C19-IG 20% will receive a blinded single dose via SC infusion of C19-IG 20%. Randomization to active treatment arms will specify either a dose of 1 gram or 2 grams C19-IG 20%. Subjects randomized to Placebo will receive blinded sterile 0.9% sodium chloride injection United States Pharmacopeia (0.9% NaCl, USP) or equivalent. Blinded study drug will be prepared and administered by an unblinded study nurse who is entirely independent of the evaluating study team with SC infusions using 2 separate syringes as described above in Section 3.1.

3.2.4 Treatment Compliance

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

The investigator or designee is responsible for maintaining accurate records of C19-IG 20%/Placebo 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.

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

All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001'. Minimum and maximum values will be reported in the units of collection with 3 decimals being maximum value; the mean will be presented with 1 decimal place more and the standard deviation 2 decimal places more than the units of collection. Percentages for categorical summaries will be represented to 1 decimal place.

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 Analysis Quality Control Procedures

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 the DSMB and interim futility 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 four analysis populations will be defined for this study:

The intent-to-treat (ITT) population is defined as all subjects who are randomized.

The modified intent-to-treat (mITT) population is defined as the subset of subjects included in the ITT who are also dosed. The mITT population will be used for all efficacy analyses. As sensitivity analysis, the primary efficacy analysis will also be carried out using the ITT population if different from the mITT population.

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

The Safety (SAF) population is defined as subjects who receive at least any amount of blinded C19-IG 20%/Placebo. 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, mITT, 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.

Missing data on the time to event endpoints will have events coded as right censored per the

following table:

Table 1 Missing Data Coding for Time to Event Data Analyses

Endpoint	Right Censoring
Time to negative SARS-CoV-2 by PCR	Subjects who did not have negative SARS-CoV-2 by PCR will be right censored as of the date of last non-missing assessment of SARS-CoV-2 by PCR on or prior to Day 29.
Time to Clinical Progression (death, invasive mechanical ventilation, or ICU admission/requiring ICU level of care)	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.
Time to COVID-19 symptoms (fulfillment of the case definition used for the primary efficacy variable through Day 14)	Subjects who did not meet the criteria will be right censored as of the date of last non-missing assessment of clinical features/symptoms on or prior to Day 14.

4.5 Multiple Comparisons

A hierarchical ordered testing procedure will be employed for handling the multiplicity issue to maintain the overall family-wised alpha level at 0.05 for comparisons between each dose and placebo. The null hypothesis for 1g vs placebo is tested only if the superiority for the 2g dose compared to placebo has been shown at a two-sided significance level of 5%. The order in which the null hypotheses are tested for the primary endpoint is predetermined as below:

1. H_{01}: no difference between 2g and placebo on primary efficacy endpoint
2. H_{02}: no difference between 1g and placebo on primary efficacy endpoint

The primary efficacy analysis will be carried out on the mITT population and repeated on the ITT and PP population (if different from the mITT population).

There will be no adjustment for multiple comparisons on secondary and exploratory efficacy endpoints.

4.6 Data Derivations and Transformations

The following derivations will be used in this study:

Study Day:

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

Baseline Observation: the last non-missing value prior to 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 negative SARS-CoV-2 by PCR: date of study drug administration
- Time to Clinical Progression: date of study drug administration
- Time to COVID-19 symptoms through Day 14: date of study drug administration

Event Date for Time to negative SARS-CoV-2 by PCR:

- The date of the first negative result from the SARS-CoV-2 assessment by PCR will be used as the event date for deriving time to negative SARS-CoV-2.

Event Date for Time to Clinical Progression

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

Event Date for Time to COVID-19 symptoms through Day 14

- The event date will be the first time point when any element of the case definition for primary efficacy variable is fulfilled through Day 14

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 mITT 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 mITT population. A by subject listing will be provided.

5.4 Baseline Characteristics

Baseline characteristics of mITT subjects including historical SARS-CoV-2 results, comorbidity, and pregnancy test will be listed and summarized by treatment group and overall 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 mITT 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 mITT 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 mITT population.

Prior medications are defined as medications that ended prior to the date of study drug administration. Concomitant medications are defined as medications that started at any time but ended on or after the date of 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 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.

6. EFFICACY ANALYSES

All efficacy analyses will be carried out using the mITT 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 mITT population. The analysis will be repeated using the ITT and PP population if different from the mITT population,

The primary efficacy variable is the proportion of asymptomatic subjects who remain asymptomatic through Day 14. Subject clinical features/symptoms and radiographical evidence of pneumonia will be recorded in the database; the oxygen saturation by pulse oximetry on room air will be recorded daily through Day 14 by subject at home on the "SpO_2 and Temperature Log", as well as on the "Patient's Measured Oxygen Saturation" eCRF at the protocol-specified healthcare provider visits. In the case when multiple SpO_2 values are recorded on the same day, the lower value will be used for the analysis.

The null hypothesis is that the proportion of subjects who meet the primary endpoint in a given C19-IG 20% dose group (2 g and 1 g) will be no different than the proportion of subjects in placebo group; H_0: $\pi_t - \pi_c = 0$. The alternative hypothesis is that the proportion of subjects who meet the primary endpoint at Day 14 in a given C19-IG 20% dose group will be different than the proportion

of subjects in placebo; H_1: $\pi_t - \pi_c \neq 0$.

Separate comparisons will be made for each C19-IG 20% dose group. If the 2 g dose group fails to demonstrate superiority compared to placebo at two-sided significance level of 5%, the test for 1 g dose group compared with placebo will be considered as exploratory rather than as confirmatory.

The proportion of subjects who meet 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 who meet the primary endpoint between each C19-IG 20% dose group and placebo 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.

Sensitivity analysis on primary endpoint will be performed using the Cochran-Mantel-Haenszel (CMH) test, stratified by randomization strata (age <65 years versus ≥ 65 years). The common risk difference in the proportion of subjects meeting the primary endpoint between each C19-IG 20% dose group and placebo, together with the associated 95% CIs and p-value will be presented.

Subgroup analyses based on the presence of comorbidities associated with increased risk of serious COVID-19 will be performed on the primary endpoint using the method described above with Chi-square test, if appropriate. If data permit, a subgroup analysis based on the number of comorbidities (<2 comorbidities vs. >=2 comorbidities) will also be performed.

Subgroup analyses by perceived comorbidities will include the following conditions: Cancer; Chronic kidney disease; Chronic obstructive pulmonary disease (COPD); Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies; Immunocompromised state from solid organ transplant; Obesity (BMI of 30 kg/m2) or higher; Diabetes mellitus. The information of subject comorbidity will be recorded on the eCRF.

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.

Data for COVID-19 clinical features/symptoms will be listed and summarized by treatment group at each time point. Radiographic evidence of pneumonia data will be presented in a listing.

6.2 Secondary Efficacy Endpoints and Analyses

Change in SARS-CoV-2 viral load

Change in SARS-CoV-2 viral load (log_{10} copies/mL) from Baseline to Day 7 and to Day 14 will be compared between each C19-IG 20% dose group and placebo using the analysis of covariance (ANCOVA) model, including the change from baseline value as a dependent variable; treatment group as a fixed effect; and baseline SARS-CoV-2 viral load value, age and gender as covariates. 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 at Day 7 and Day 14.

Subgroup analyses based on the presence of comorbidities associated with increased risk of serious

COVID-19 will be performed on change in SARS-CoV-2 viral load using the method described above with ANCOVA model at Day 7 and Day 14. If data permit, a subgroup analysis based on the number of comorbidities (<2 comorbidities vs. >=2 comorbidities) will also be performed.

Proportion of subjects remain in an outpatient setting and maintain SpO2 ≥94%

Subjects remain in an outpatient setting is defined as no hospitalization or ICU admission through Day 3, Day 7, and Day 14.

In the case when multiple SpO_2 values are recorded on the same day, e.g. SpO_2 values from subject self-reported at home and from healthcare provider visit on the same day, the lower value will be used for the analysis.

The proportion of subjects who remain in an outpatient setting and maintain SpO_2 ≥94% on room air at each timepoint 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 remain in an outpatient setting and maintain SpO_2 ≥94% on room air at any timepoint between each C19-IG 20% dose group and placebo 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. .

Proportion of subjects negative for SARS-CoV-2 by PCR through Day 14 and Day 29

The proportion of subjects with negative SARS-CoV-2 by PCR through Day 14 and Day 29 within each treatment group will be presented along with a two-sided exact (Clopper-Pearson) 95% CI.

At each time point, the observed difference in the proportion of subjects with negative PCR test results between each C19-IG 20% dose group and placebo 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.

Time to negative SARS-CoV-2 PCR from Baseline through Day 29

The time from baseline to the first occurrence of negative SARS-CoV-2 by PCR through Day 29 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 negative SARS-CoV-2 by PCR and associated 95% CIs on Days 14 and 29 will be reported; in addition, the 25th, 50th (median), and 75th percentiles of the time to negative SARS-CoV-2 by PCR with associated 95% CIs will be provided, as data permit. The survival rates between each C19-IG 20% dose group and placebo will be compared using Log-rank test. The p-value from Log-rank test will be presented.

Proportion of subjects requiring O2 supplementation on or before Day 29

The proportion of subjects requiring oxygen supplementation 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 requiring oxygen supplementation between each C19-IG 20% dose group and placebo 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.

Duration of any oxygen use through Day 29

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 each C19-IG 20% dose group and placebo using an ANCOVA model, including number of days on oxygen as a dependent variable, treatment group as a fixed effect, and baseline characteristics such as age and gender as covariates. 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.

In the event the data is highly skewed, e.g. very few subjects received supplemental oxygen, 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 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 from both subject self-monitoring at home and health provider visits 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 mixed-effects model for repeated measures (MMRM). The model will include change from baseline in Ordinal scale as the repeated dependent variable; treatment (as a class variable), visit (as a class variable), and treatment-by-visit interaction and as fixed effects; baseline Ordinal scale, 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 at Days 3, 7, 14, and 29 visits 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 3, 7, 14, and 29.

b) The proportion of subjects in each severity category of the 7-point Ordinal scale at Days 1, 3, 7, 14, and 29 visits will be summarized by treatment group. The difference in severity

category distribution between each C19-IG 20% dose group and placebo at Day 3, Day 7, Day 14, 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 3, Day 7, Day 14, 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.

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 at Days 3, 7, 14, and 29 visits 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 for Day 3, Day 7, Day 14, and Day 29.

Proportion of subjects requiring at least one COVID-19 related medically attended visit through Day 29

The proportion of subjects requiring at least one COVID-19 related medically attended visit for management/treatment of COVID-19 (apart from routinely scheduled study-directed visits) 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 requiring at least one COVID-19 related medically attended visit between each C19-IG 20% dose group and placebo 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.

A listing of all medically attended visit data collected through the study will be provided.

Proportion of subjects requiring hospital admission through Day 29

The proportion of subjects requiring hospital admission 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 requiring hospital admission between each C19-IG 20% dose group and placebo 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.

Duration of Hospitalization through Day 29

The duration (number of days) of hospitalization from post-randomization 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 each C19-IG 20% dose group and placebo using an ANCOVA model, including number of days in the hospital as a dependent variable, treatment group as a fixed effect, and baseline characteristics such as age and gender as covariates. 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.

In the event the data is highly skewed, e.g. very few subjects hospitalized, 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 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. Subjects who never been hospitalized through Day 29 will be included in the analysis with a value of zero days in the hospital.

Proportion of subjects requiring ICU admission through Day 29

The proportion of subjects requiring ICU admission 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 requiring ICU admission between each C19-IG 20% dose group and placebo 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.

Duration of ICU stay through Day 29

The duration (number of days) of ICU stay from post-randomization 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 each C19-IG 20% dose group and placebo using an ANCOVA model, including number of days in the ICU as a dependent variable, treatment group as a fixed effect, and baseline characteristics such as age and gender as covariates. 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.

In the event the data is highly skewed, e.g. very few subjects admitted to ICU, 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 the 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 the number of ICU days. Subjects who never been in the ICU through Day 29 will be included in the analysis with a value of zero days in the ICU.

Proportion of subjects requiring invasive mechanical ventilation through Day 29

The proportion of subjects requiring invasive mechanical ventilation 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 requiring invasive mechanical ventilation between each C19-IG 20% dose group and placebo 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.

Duration of invasive mechanical ventilation through Day 29

The duration (number of days) on invasive mechanical ventilation from post randomization through Day 29 will be calculated based on the start/stop dates of invasive 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 invasive mechanical ventilation will be compared between each C19-IG 20% dose group and placebo using an ANCOVA model, including number of days in on invasive mechanical ventilation as a dependent variable, treatment group as a fixed effect, and baseline characteristics such as age and gender as covariates. 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.

In the event the data is highly skewed, e.g. very few subjects on invasive 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 invasive 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 invasive 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 invasive mechanical ventilation through Day 29 will be included in the analysis with a value of zero days on mechanical ventilation.

Data collected on "Respiratory Support" eCRF through Day 60/Final Phone Check visit will be presented in a listing.

Mortality rate through Day 29

Subject status (Alive/Death) will be recorded in the database. If the vital status of the subject is missing, then the subject will be treated as death for the analysis.

The proportion of subjects who die 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 mortality rate (proportion of deceased subjects) between each C19-IG 20% dose group and placebo 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.

Subject status after Day 29 (vital status [living or deceased], any hospital admissions, ICU admissions, requirement for invasive mechanical ventilation, need for oxygen supplementation) collected at Day 60/Final Phone Check visit will be presented in a listing.

Proportion of subjects with critical COVID-19 illness through Day 29

Critical COVID-19 illness is defined as any of the following: (a) requiring ICU admission or ICU level of care, (b) invasive mechanical ventilation, or (c) resulting in death by Day 29.

The proportion of subjects with critical COVID-19 illness defined above 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 with critical COVID-19 illness between each C19-IG 20% dose group and placebo 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.

Time to clinical progression (critical COVID-19 illness) through Day 29

Clinical progression is defined as death, start of invasive mechanical ventilation, or ICU admission/requiring ICU level of care 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 14 and 29 will be reported; in addition, the 25%, 50% (median), and 75% percentiles of the time to clinical progression with associated 95% CIs will be provided, as data permit. The survival rates between each C19-IG 20% dose group and placebo will be compared using Log-rank test. The p-value from Log-rank test will be presented.

Time to COVID-19 symptoms through Day 14

Time to COVID-19 symptoms is defined as the time from study drug administration to the first time point when any element of the case definition for primary efficacy variable is fulfilled through Day 14. The time to COVID-19 symptoms 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 COVID-19 symptoms and associated 95% CIs at Day 14 will be reported; in addition, the 25%, 50% (median), and 75% percentiles of the time to COVID-19 symptoms with associated 95% CIs will be provided, as data permit. The survival rates between each C19-IG 20% dose group and placebo 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 inflammatory biomarkers specifically: IL-6; D-dimer; ferritin; CRP; interferon γ through Day 14 will be summarized for each treatment group by visit.
- Change from baseline in quantitative anti-SARS-CoV-2 IgM and IgG antibodies through Day 14 will be summarized for each treatment group by visit.
- Overall assessment of COVID-19 symptoms severity on Day 7 and Day 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, and vital signs. 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 duration of infusion in minutes, total volume prepared, and total volume infused will be summarized by treatment group. For each syringe, the occurrence of dose interruption and whether 100% of study drug infused will also be summarized by treatment group. In addition, treatment compliance will be calculated and summarized for each 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% in each treatment group.

Treatment compliance (%) will be calculated as follows:

(Total volume infused [mL] / Total volume prepared [mL]) x 100.

7.2 Adverse Events

All AEs and serious AEs (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). At the time of the Day 60 (±2 days) Phone Check any additional SAEs/non-serious AEs will also be collected and recorded. 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/time of study drug administration. A TEAE will be defined as an AE which occurred on or after the date/time of 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/time of 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 8.2.5.

7.2.3 Adverse Event Relationship to IP

Refer to the study protocol, Section 8.2.4.

7.2.4 Serious Adverse Events

Refer to the study protocol, Section 8.2.7.

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring from Day 1 through 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:
    1. the number and percentage of subjects experiencing a TEAE
    2. the number and percentage of subjects experiencing a TEAE by strongest relationship to IP
    3. the number and percentage of subjects experiencing a TEAE by greatest severity
    4. the number and percentage of subjects experiencing a TEAE with Grade >=3
    5. the number and percentage of subjects experiencing a treatment-emergent SAE
    6. the number and percentage of subjects experiencing a TEAE leading to death
    7. 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 causal 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 and grade (mild [Grade 1], moderate [Grade 2], severe [Grade 3], Life-threatening [Grade 4], Fatal [Grade 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

All routine laboratory analyses including serum chemistry (creatinine, albumin, ALT, total bilirubin, and LDH) and hematology (hemoglobin, hematocrit, platelet count, absolute neutrophil & lymphocyte count, leukocyte count with differential) will be conducted by a central laboratory.

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. 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.

When there are repeat scheduled measurements for a given visit, only the last measurement will be used in the table summaries.

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

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 including clinically significant change from baseline (no/yes) will be summarized by presenting the number and percentage of subjects for each category at each post-baseline time point.

8. DSMB ANALYSIS

An independent DSMB will review interim safety data when approximately 399 patients have been randomized and treated with follow-up through Day 29 (approximately 133 patients per randomized group).

The DSMB's specific activities will be defined by a mutually agreed charter, which will define the DSMB's membership, conduct and meeting schedule.

9. INTERIM FUTILITY ANALYSIS

An interim analysis will be conducted in the December 2021 timeframe 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.

The decision for the interim 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 14, and for the following secondary efficacy endpoint variables, all patients with data through Day 14 or Day 29, as specified for each endpoint:

- Time to COVID-19 symptoms specifically defined as the time to fulfillment of the case definition used for the primary efficacy variable through Day 14.
- Proportion of subjects who remain in an outpatient setting and maintain SpO2 ≥94% on room air on Day 3, Day 7, and Day 14.
- Proportion of subjects who require O_2 supplementation on or before Day 29.
- If requiring supplemental oxygen post randomization: Duration of any oxygen through Day 29.
- Absolute value and mean change from baseline in the 7-point Ordinal scale at Day 1, Day 7, Day 14, and Day 29
- Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale at Day 1, Day 7, Day 14, and Day 29.
- Assessment of Clinical Severity: Change in NEWS from baseline (at Day 7, Day 14, and

Day 29).

- Proportion who require at least one COVID-19 related medically attended visit for management/treatment of COVID-19 (apart from routinely scheduled study-directed visits) which may occur in any setting through Day 29 (e.g., Emergency department, urgent care, outpatient clinic or professional setting wherein direct in-person/telemedicine medical assessment and escalation of care for COVID-19 is provided by licensed healthcare personnel).
- Proportion of subjects who require hospital admission for medical care (non-quarantine purposes) through Day 29.
- If admitted to hospital post randomization: Duration of hospital stay through Day 29.
- Proportion of subjects who require ICU admission or initiation of ICU-level care* through Day 29.
- If admitted to ICU post randomization: Duration of ICU stay through Day 29.
- Proportion of subjects requiring invasive mechanical ventilation through Day 29.
- If requiring invasive mechanical ventilation post randomization: Duration of invasive mechanical ventilation through Day 29.
- All-cause mortality through Day 29.
- Incidence of critical COVID-19 illness, defined as any one of the following: (a) requiring ICU admission or ICU level of care*, (b) invasive mechanical ventilation, or (c) resulting in death by Day 29.
- Length of time to clinical progression to critical COVID-19 illness through Day 29 (defined as the time to death, invasive mechanical ventilation, or ICU admission/requiring ICU level of care).

After this interim analysis, the 1 gram dose arm may be terminated, the trial may be terminated (if the 2 gram dose is discontinued, the 1 gram dose will also be terminated), or the study will continue as originally planned unless discontinued for business or feasibility reasons in a setting of changing epidemic dynamics in the geographic catchment of the trial.

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 treatment group (1 gram or 2 grams C19-IG 20%). 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 treated (1 gram or 2 grams C19-IG 20%)

groups respectively. Let $Z_{1-\alpha/2}$ be the 1- $\alpha/2$ = 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 (each of C19-IG 20% dose groups compares to placebo) 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).

10. 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 study is commensurate with other Phase 3 investigations ongoing during the COVID-19 pandemic.

For overall context, one may reference the mAb data for casirivimab and imdevimab (Regeneron cocktail) in support of their Emergency Use Authorization (EUA) granted 20 November 2020. The R10933-10987-COV-2067 study on which the data analysis for the EUA was based included 799 enrolled subjects (~266/arm).

If it is assumed that 80% of patients in the Placebo control arm will remain asymptomatic at Day 14 [3] (subset of ~314 patients PCR + at baseline) then the sample size projections in the table below emerge for various degrees of C19-IG 20% treatment effect (delta).

Practically speaking then the sample size becomes ~240 patients/arm for a significance level alpha (0.025) and 80% power (Table 2). Assuming a 10% withdrawal rate, 267 patients per arm would be needed. Furthermore, this calculation provides a per group sample size commensurate with the per arm group size supporting Regeneron's EUA for casirivimab and imdevimab.

Table 2 Sample Size Estimation

Control Success % (proportion remaining *Asymptomatic*) (reference)	**Absolute Delta C19-IG 20%**		**C19-IG 20% Success % (proportion remaining *Asymptomatic*)**		**Sample Size (total)**	
80% (Mitja et al., NEJM 2020)	*5%*	**10%**	*85%*	**90%**	*1094/arm*	**238/arm**

[Sample sizes in table were calculated using https://www.sealedenvelope.com/power/binary-superiority/]

Based on the above extrapolation/estimate, and allowing for a total of 3 arms, randomized 1:1:1 to Placebo and 2 dose levels of C19-IG 20% approximately 801 subjects are allowed to be randomized as part of a humanitarian effort against COVID-19. N=267 subjects per group should allow differentiation in disease evolution for patients randomized to C19-IG 20% versus the control Placebo arm.

Sample size estimation was also calculated with regard to consideration of the viral load first secondary endpoint. A sample size of ~172 patients/arm would theoretically provide the trial with 80% power to detect a difference of 0.5 $\log_{10}$ in the mean reduction of SARS-CoV-2 viral load at a two-sided significance level of $\alpha = 0.025$, assuming an expected standard deviation of 1.5 [3, 4]. A 0.5 $\log_{10}$ copies/mL difference in reduction was chosen to represent the minimal threshold for a

biologically relevant change for analyses based on analogy with other viruses[5]. However, it is unknown whether this degree of viral load reduction will be realized as a result of the planned dosages of C19-IG 20% within this clinical setting. The larger sample size per arm provides a greater level of assurance in this regard.

11. REFERENCES

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12. APPENDIX

12.1 Appendix A: Schedule of Events

Study Period	**Screen/ Baseline Healthcare Provider Visit[h]**		**Phone Check Surveillance for COVID-19 symptoms/worsening & Healthcare Provider Visits Day 3 & Day 7**			**Continued Phone Check Surveillance**		**Follow-Up Healthcare Provider Visits**		**Final Phone Check**
Study Day **Procedures/assessments**	1	**IP administration Day 1**	3 Healthcare Provider Visit[g]	5	7 Healthcare Provider Visit[g]	Day 9	Day 11	14±1 day[g]	Final Healthcare Provider Visit 29±1 day[g]	60[e] ± 2 days
Informed consent	X									
Inclusion/exclusion criteria	X									
Demography, disease characteristics (date of exposure, date of onset[a])	X									
Medical history	X									
Record specific comorbidities which may increase risk of severe COVID-19 disease: Cancer; Chronic kidney disease; chronic obstructive pulmonary disease (COPD); Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies; Immunocompromised state from solid organ transplant; Obesity (body mass index [BMI] of 30 kg/m^2) or higher; Diabetes mellitus	X									
Ordinal Scale (at the last assessment of a given day)[b]	X		X		X			X	X	
National Early Warning Score (NEWS) (Appendix 2)	X		X		X			X	X	

Schedule of Events (Continued)

Study Period	**Screen/ Baseline Healthcare Provider Visit[h]**		**Phone Check Surveillance for COVID-19 symptoms/worsening & Healthcare Provider Visits Day 3 & Day 7**			**Continued Phone Check Surveillance**		**Follow-Up Healthcare Provider Visits**		**Final Phone Check**
Study Day **Procedures/assessments**	1	**IP administration Day 1**	3 Healthcare Provider Visit[g]	5	7 Healthcare Provider Visit[g]	Day 9	Day 11	14±1 day[g]	Final Healthcare Provider Visit 29±1 day[g]	60[e] ± 2 days
Provide subjects with pulse oximeter for home use and SpO_2 monitoring on room air (train subjects in use of pulse oximeter)	X									
Subjects record SpO_2 at home using pulse oximeter (self monitoring at home daily through Day 14)		X---------	----------	-------	----------	----------	----------	----------X		
Subjects record body temperature (non-axillary) and whether any antipyretic was taken on each day (self monitoring at home daily through Day 14)		X---------	----------	-------	----------	----------	----------	----------X		
Record key clinical features/symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.			X	X	X	X	X	X	X	
Phone Check Surveillance for COVID-19 symptoms and *for site to record subject's SpO2, temperature, and key COVID-19 clinical features/symptoms*				X		X	X			
Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)	X		X		X			X	X	
Weight, Height, BMI	X									

Schedule of Events (Continued)

Study Period	Screen/ Baseline Healthcare Provider Visit[h]		Phone Check Surveillance for COVID-19 symptoms/worsening & Healthcare Provider Visits Day 3 & Day 7			Continued Phone Check Surveillance		Follow-Up Healthcare Provider Visits		Final Phone Check
Study Day **Procedures/assessments**	1	**IP administration Day 1**	3 Healthcare Provider Visit[g]	5	7 Healthcare Provider Visit[g]	Day 9	Day 11	14±1 day[g]	Final Healthcare Provider Visit 29±1 day[g]	60[e] ± 2 days
Record result of *historical* SARS-CoV-2 qualitative PCR (RT-PCR), or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19 in any specimen (≤ 5 days prior to randomized treatment. Note: Every effort should be made to reduce this time interval to the minimum as nearly immediate treatment is key for successful intervention. For instance if SARS-CoV-2 antigen testing is used for diagnostic purposes the subject may be able to receive the study drug the same day testing is performed.)	X									
Record oxygen saturation (specify on or off oxygen supplementation; Note must be off oxygen at Screening on Day 1). Use subject's home recorded SpO_2 value for Non-healthcare provider visit days.	X		X	X	X	X	X	X	X	
Overall Assessment of COVID-19 Symptoms Severity [c]					X				X	
Randomization *(after all Screen/Baseline assessments complete)*	X									

Schedule of Events (Continued)

Study Period	**Screen/ Baseline Healthcare Provider Visit[h]**		**Phone Check Surveillance for COVID-19 symptoms/worsening & Healthcare Provider Visits Day 3 & Day 7**			**Continued Phone Check Surveillance**		**Follow-Up Healthcare Provider Visits**		**Final Phone Check**
Study Day **Procedures/assessments**	1	**IP administration Day 1**	3 Healthcare Provider Visit[g]	5	7 Healthcare Provider Visit[g]	Day 9	Day 11	14±1 day[g]	Final Healthcare Provider Visit 29±1 day[g]	60[e] ± 2 days
C19-IG 20% or Placebo: SC administration of blinded C19-IG 20%/Placebo		X								
Record medically attended visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting (eg, Emergency department, urgent care, outpatient clinic/professional setting for direct in-person/telemedicine medical assessment and care of COVID-19 provided by licensed healthcare personnel)		X	X	X	X	X	X	X	X	
If subject requires supplemental oxygen post randomization: Record any supplemental O_2 administration (type, %, flow start/end date/time)		X	X	X	X	X	X	X	X	X
If subject requires invasive mechanical ventilation post randomization: Record any invasive mechanical ventilation details (start/end date/time)		X	X	X	X	X	X	X	X	X
If subject requires hospital admission post randomization: Record hospital admission & discharge dates		X	X	X	X	X	X	X	X	X

Schedule of Events (Continued)

Study Period	**Screen/ Baseline Healthcare Provider Visit[h]**		**Phone Check Surveillance for COVID-19 symptoms/worsening & Healthcare Provider Visits Day 3 & Day 7**			**Continued Phone Check Surveillance**		**Follow-Up Healthcare Provider Visits**		**Final Phone Check**
Study Day **Procedures/assessments**	1	**IP administration Day 1**	3 Healthcare Provider Visit[g]	5	7 Healthcare Provider Visit[g]	Day 9	Day 11	14±1 day[g]	Final Healthcare Provider Visit 29±1 day[g]	60[e] ± 2 days
If subject requires ICU admission post randomization: Record ICU admission & discharge dates		X	X	X	X	X	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)	Before rand[f]		X		X			X	X	
Sample for quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 (store serum samples frozen at -70°C for later analysis at an external lab)	Before rand[f]				X			X		
Sample for possible additional quantitative neutralizing antibody versus SARS-CoV-2 (serum sample reserved for neutralizing antibody testing if such testing becomes feasible stored frozen at -70°C for later analysis at an external lab).	Before rand[f]				X			X		
Sample for IL-6; interferon γ, & possibly autoantibodies against type 1 interferons (may store serum samples frozen at -70°C for later analysis at an external lab)	Before rand[f]				X			X		

Schedule of Events (Continued)

Study Period	Screen/ Baseline Healthcare Provider Visit[h]		Phone Check Surveillance for COVID-19 symptoms/worsening & Healthcare Provider Visits Day 3 & Day 7			Continued Phone Check Surveillance		Follow-Up Healthcare Provider Visits		Final Phone Check
Study Day **Procedures/assessments**	1	**IP administration Day 1**	3 Healthcare Provider Visit[g]	5	7 Healthcare Provider Visit[g]	Day 9	Day 11	14±1 day[g]	Final Healthcare Provider Visit 29±1 day[g]	60[e] ± 2 days
Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)	Before rand[f]				X			X		
Hematology & absolute neutrophil & lymphocyte count (hemoglobin, hematocrit, platelet count, leukocyte count with differential)	Before rand[f]				X			X		
Ferritin, CRP, D-dimer	Before rand[f]				X			X		
Pregnancy test (hCG-based assay for women of childbearing potential [urine matrix is also valid])	Before rand[f]									
Record SAEs and TEAEs[d]	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X

a Date of first contact with the virus, date of PCR (RT-PCR), or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19.

b 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.

c Overall assessment of COVID-19 symptoms severity will be graded as follows:

No symptoms: No COVID-19 symptoms present.

Mild: Mild symptoms causing no or minimal interference with ability to perform usual activities with intervention not indicated (note: limitations due to quarantine do not count towards grading assignment)

Moderate: Moderate symptoms causing greater than minimal interference with usual functional activities with intervention indicated (note: limitations due to quarantine do not count towards grading assignment)

Schedule of Events (Continued)

Severe: Severe symptoms causing inability to perform usual functional activities with intervention or hospitalization indicated.
Potentially Life-threatening: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

d Grade 3-5 TEAEs and potentially related TEAEs through Day 29 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 C19-IG 20%/placebo and the TEAE.

e Final Phone Check Study Contact.

f All laboratory tests and serum samples must be obtained from all patients; samples must be obtained prior to blinded C19-IG 20%/Placebo SC infusion on Day 1.

g Note that given the pandemic setting it is likely that Healthcare Provider Visits may consist either of evaluations at the subject´s usual residence (home) justified because subject is in confinement or at an alternate site, e.g., Clinic, always under the care and supervision of trained healthcare personnel.

h Potential eligible participants will be contacted by the Investigator through their database systems for SARS-CoV2 positive subjects nationwide. Since potential participants (SARS-CoV-2 positive subjects) will be confined, they will be contacted over the phone and asked to participate into the clinical trial by providing the oral consent form. After that, the Investigator will review eligibility criteria and if eligible, the screening visit will continue subject's residence. Once there, the Investigator will obtain the written informed consent, eligibility criteria will be reassessed and if eligible, baseline assessments will be performed, and the subject will be randomized to one of the treatment arms. The IP will be administered by an unblinded study nurse at subject's residence. The subject will receive a pulse oximeter for home use and daily recording of SpO2 in order to monitor for development of hypoxia (SpO2 < 94% on room air). Subject will also be instructed to measure, monitor, and record body temperature daily.

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