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

NCT Number: NCT04847141

Document Date: Protocol Amendment 4, Version 5.0: 13 October 2021

Completion of the signature block below signifies the review and approval of this document.

Signed by:	Reason:	Date / Time (UTC):
[redacted]	Owner	08-Oct-2021 14:33:03
[redacted]	[redacted]	13-Oct-2021 12:24:49

Clinical Study Protocol

Protocol 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
Investigational Product:	Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%)
Sponsor's Name and Address:	Grifols Therapeutics LLC 79 TW Alexander Drive Research Triangle Park, NC 27709
Study Number	GC2010
Additional Identifier	C19-IG 20% in COVID-19
EUDRACT Number:	2021-000269-34
Development Phase:	3
Sponsor Signatory:	[redacted], M.D. [redacted] Grifols Therapeutics, LLC. email address: [redacted] Phone: [redacted] [redacted] Grifols Bioscience Industrial Group Email address: [redacted] Telephone number: [redacted]

Protocol Version History

Protocol Version	Approval/Effective Date
5.0 Amendment 4 + Integrated Protocol	See left margin
4.0 Amendment 3 + Integrated Protocol	28 June 2021
3.0 Amendment 2 + Integrated Protocol	27 April 2021
2 Amendment 1 + Integrated Protocol	05 March 2021
1.0 Original	28 Jan 2021

Amendment 4

The protocol for GC2010 (Version 4.0, dated 28 June 2021) has been amended as Protocol Amendment 4, Version 5.0. See the table on the next page for a summary of changes for Protocol Amendment 4.

SUMMARY OF CHANGES

(Note: Administrative changes including minor administrative corrections are not included in Protocol Summary of Changes)

Sections	Change From: (Version 4.0, dated 28 June 2021)	Change To: (Version 5.0)	Rationale:
Synopsis, 4.1.2, 7.1.2	*New secondary efficacy 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.	Addition of a secondary efficacy endpoint for time to COVID-19 symptoms based on a priori case definition.
Synopsis, 4.2, 9.1	*New section for Interim Futility Analysis*	Interim Analysis An interim futility analysis will be conducted to assess whether the trial will be terminated due to lack of efficacy (futility) in the December 2021 timeframe based on all available data assessable for the primary endpoint and key secondary efficacy endpoints.	Addition of an interim futility analysis which will be conducted to provide guidance in the setting of dynamic changes within the context of an evolving epidemic.
9.3	*New section for Interim Futility Analysis*	**9.3 Interim 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	Addition of an interim futility analysis which will be conducted to provide guidance in the setting of dynamic changes within the context of an evolving epidemic.

Sections	Change From: (Version 4.0, dated 28 June 2021)	Change To: (Version 5.0)	Rationale:
		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.	

Sections	Change From: (Version 4.0, dated 28 June 2021)	Change To: (Version 5.0)	Rationale:
		• 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.	

Sections	Change From: (Version 4.0, dated 28 June 2021)	Change To: (Version 5.0)	Rationale:
		• 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). [*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] 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.	

Sections	Change From: (Version 4.0, dated 28 June 2021)	Change To: (Version 5.0)	Rationale:
		The primary outcome will be analyzed according to Section 9.1.	

PROTOCOL SYNOPSIS

Title of Study: 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)

Short Title: Study to Evaluate the Safety and Efficacy of C19-IG 20% in SARS-CoV-2 Infected Asymptomatic Ambulatory Outpatients

Study Number: GC2010

Phase: 3

Study Objectives:

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

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) and ordinal clinical status scale 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).

<u>Exploratory Efficacy Objectives</u>

- 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.

<u>Safety Objectives</u>

- 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.

Overall Study Design and Description:

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 test 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. 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.

Participants 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. Participants 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%).

C19-IG 20% is a human immune globulin preparation for SC administration, manufactured by essentially the same process as Gamunex-C, which has been commercially available as an intravenous (IV) immunoglobulin G (IgG) product since 2003 and is licensed in Spain and most of the European countries with >15 years in the market without safety issues. C19-IG 20% is a more concentrated form containing a 200 mg/mL concentration of immunoglobulin in order to reduce administration volume and is made from the plasma of convalescent donors who have recovered from COVID-19. The conventional commercial form of Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is currently approved in the United States and Canada for SC administration in the treatment of primary (congenital) humoral immunodeficiency (PI) for IgG replacement and is under evaluation by the European regulatory authorities for this indication.

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 investigational product (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.

As described above at the Healthcare Provide Visit on Day 1, all subjects will receive a pulse oximeter for home use and daily recording of SpO_2 in order to monitor for development of hypoxia (SpO_2 < 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. 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. If hospitalized, assessments required for Day 3, 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, and Days 9 and 11. Phone Check surveillance is specifically targeted to detecting development of symptomatic COVID-19, to determine presence of sentinel alarm symptoms or symptoms that may indicate worsening (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, Intensive Care Unit (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. Details are provided in Appendix 1 (Schedule of Study Procedures).

An independent Data Safety Monitoring Board 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).

Number of Subjects Planned:

Approximately 801 subjects (267 per arm) will be randomized (1:1:1).

Diagnosis and Main Criteria for Eligibility

Inclusion Criteria:

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Ambulatory male or female outpatients ≥ 18 years of age who have laboratory-confirmed SARS-CoV-2 infection as determined by qualitative PCR (RT-PCR), or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19 (inclusive of SARS-CoV-2 antigen testing or other approved rapid testing platforms) in any specimen ≤ 5 days prior to randomized treatment. (Note: ≤ 5 days is the post-sampling timeframe from date specimen obtained to administration of blinded study drug).

   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.
2. Asymptomatic with no constitutional COVID-19 illness (evident symptoms), specifically no fever, cough, shortness of breath, fatigue, anorexia, vomiting/diarrhea, headache that is unrelated to pre-existing medical conditions (eg, migraine), sore throat that is unrelated to other pre-existing medical conditions (eg, allergies, gastroesophageal reflux disease), myalgias, olfactory disorders unrelated with previous medical condition, or evidence of pneumonia at Screening.
3. Pulse oximetry SpO2 (oxygen saturation) on room air > 94% (i.e., 95% to 100%) at Screening.
4. National Early Warning Score (NEWS) ≤ 2 points (Appendix 2) at Screening.
5. Subject provides informed consent (informed consent form [ICF]) prior to initiation of any study procedures.

Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Subjects who are admitted to hospital or for whom hospital admission is being planned at the time of Screening.
2. Subjects requiring any form of oxygen supplementation at Screening.
3. Concurrent or planned treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 including remdesivir.
4. Prior, concurrent or planned treatment with monoclonal antibodies (mAbs) against SARS-CoV-2.
5. Have participated in a previous SARS-CoV-2 vaccine study OR outside of a study have received any SARS-CoV-2 vaccine of any kind.
6. Have a history of convalescent COVID-19 plasma treatment at Screening.

7. Fever (temperature ≥38.0° C [≥100.4° F]) measured orally, requirement for antipyretics to reduce temperature (administered for fever), and/or respiratory symptoms (cough, dyspnea) at Screening.
8. Clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may place the subject at undue medical risk for study treatment.
9. The subject has had a known (documented) history of serious anaphylactic reaction to blood, any blood-derived plasma product or commercial immunoglobulin, or has known selective immunoglobulin A (IgA) deficiency with anti-IgA antibodies.
10. Decompensated congestive heart failure or renal failure with fluid overload. This includes currently uncontrolled congestive heart failure New York Heart Association Class III or IV stage heart failure.
11. Subjects for whom there is limitation of therapeutic effort such as "Do not resuscitate" status.
12. Currently participating in another interventional clinical trial with investigational medical product or device.
13. Subjects with known (documented) thrombotic complications to polyclonal intravenous immune globulin (IVIG) therapy in the past.
14. Subject has medical condition (other than COVID-19) that is projected to limit lifespan to ≤ 1 year.
15. Subject has history of drug or alcohol abuse within the past 12 months.
16. Subject is unwilling to commit to follow-up visits.
17. Women who are pregnant or breastfeeding, or if of childbearing potential, unwilling to practice a highly effective method of contraception (oral, injectable, or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom, or occlusive cap with spermicidal foam/gel/cream/suppository, male sterilization, or true abstinence*) throughout the study.

    * True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

Note: Women who are > 55 years and with absence of menses in the last 12 months are considered Not to be of childbearing potential. Female subjects of child-bearing potential must have a negative test for pregnancy blood or urine human chorionic gonadotropin (HCG)-based assay at Screening/Baseline Visit.

Investigational Product, Dose and Mode of Administration

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% 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%).

Since the immunoglobulin concentration is 200 mg/mL subjects randomized to receive 1 gram of C19-IG 20% will be administered 5 mL via SC infusion. Subjects randomized to receive 2 grams of C19-IG 20% will be administered 10 mL, via SC infusion (administered as described above to maintain the blind).

These doses are selected with the aim of providing at least the same neutralizing antibody capacity as transfusion of 1 unit of Convalescent plasma donated by people fully recovered from COVID-19.

All C19-IG 20%/Placebo administrations will be undertaken by a trained medical professional.

C19-IG 20%/Placebo will be administered into the SC fat by direct push via syringe in a residence/clinic/healthcare setting and will be supervised by a healthcare professional. A 10-mL Luer lock syringe is recommended for ease in manual push administration due to viscosity, and SC infusion lines specifically designed for SC infusion should be used to facilitate manual push infusion. SC infusion lines have perpendicular needles that are easily inserted perpendicularly into the SC fat and are designed with very little dead space (minimizing product loss within the lines); they are designed with easily secured tabs for stable placement during the SC push administration. SC infusion sets with 24-gauge needle size are recommended and needle length is dependent upon SC fat layer (either 9 mm or 12 mm in most adults).

SC infusion is a slow push administration. It may take approximately 1-2 minutes for each mL of C19-IG 20% to infuse. Ancillary supplies (for example, SC infusion lines with 24-gauge perpendicular needles of 9 mm and 12 mm length or appropriate alternatives) will be supplied by the Sponsor.

There is extensive experience with conventional Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) based on considerations of tolerability in patients with SC administration of subcutaneous immunoglobulin (SCIG) for PI. Experience with conventional IGSC 20% in phase 3 study GTI1502 provides useful metrics for tolerability of SC infusions in PI patients. In the adult population, defined in GTI1502 as > 16 years, the mean dose per infusion was 179.5 mg/kg, the median number of SC sites utilized per infusion was 4 sites, and the mean volume per site was 21.7 mL/site. Participants in study GTI1502 tolerated SC infusions of IGSC 20% very well. In the current study, a dose of 1 or 2 grams of C19-IG 20% is selected. This translates, to a volume of 5 or 10 mL (blinded C19-IG 20%), thus providing a margin and buffer with regard to the weekly metrics from the pivotal study described above. This approach is anticipated to translate into good tolerability.

Duration of Treatment:

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.

Reference Therapy, Dose and Mode of Administration:

Placebo with surveillance of asymptomatic subjects: SC administration of sterile 0.9% sodium chloride injection, United States Pharmacopeia (0.9% NaCl, USP) or equivalent

Key Study Variables:

The primary efficacy variable is:

- Proportion of asymptomatic subjects who remain asymptomatic, i.e., who do not develop symptomatic COVID-19 through Day 14 defined as any of the following:

  Experiencing at least TWO of the following systemic symptoms: (a) Fever (≥ 38°C), (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 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.

The secondary efficacy variables include:

- 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]).
  https://www.mdcalc.com/national-early-warning-score-news (Appendix 2)
- 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).
- 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]

The exploratory efficacy variables 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 symptom severity on Day 7 and Day 29

  No symptoms: No COVID-19 symptoms present.

  Mild: Mild symptoms causing no or minimal interference with ability to perform usual functional 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)

  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

The safety variables 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.

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.

Study Assessments and Procedures:

A complete schedule of study procedures and events are located in Appendix 1.

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.

For this study, the eligible population is asymptomatic ambulatory outpatients with COVID-19 who will be evaluated on Day 1 for Screening/Baseline assessments and if eligible will be randomized on Day 1. Subjects randomized to C19-IG 20% will receive either 1 gram or 2 grams blinded C19-IG 20% (according to randomization assignment) via SC infusion on Day 1. Subjects randomized to Placebo will receive blinded sterile 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%).

At the Healthcare Provider visit on Day 1, all subjects will receive a pulse oximeter for home use and daily recording of SpO_2 in order to monitor for development of hypoxia

(SpO_2 < 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).

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.

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 (eg, 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.

The Ordinal Scale and NEWS will be assessed at Screening/Baseline, and at Day 3, Day 7, Day 14, and Day 29 visits. The NEWS calculation is delineated in Appendix 2 and can be calculated using the on-line web tool at https://www.mdcalc.com/national-early-warning-score-news.

Basic chemistry analytes (creatinine, albumin, ALT, total bilirubin, LDH) will be assessed on Day 1 prior to blinded IP infusion, and on Day 7 and Day 14 (± 1 day). Hematology (hemoglobin, hematocrit, platelet count, absolute neutrophil & lymphocyte count, leukocyte count with differential) will be assessed on Day 1 prior to blinded IP infusion, and on Day 7, and Day 14 (± 1 day). Samples will be drawn for D-dimer, CRP, and ferritin prior to blinded IP infusion, and on Day 7, and Day 14 (± 1 day). Serum samples will be obtained on Day 1 prior to blinded IP infusion and at Day 7 and Day 14 (±1 day) (which may be stored at -70° C) for later analysis at a reference laboratory for the following parameters: IL-6; interferon γ; autoantibodies against type 1 interferons; quantitative measurement of IgM and IgG antibodies to SARS-CoV-2; and for possible additional quantitative neutralizing antibody versus SARS-CoV-2 (sample reserved for neutralizing antibody testing if such testing becomes feasible).

Respiratory samples for quantitative measurement of SARS-CoV-2 viral load by nucleic acid amplification technology (NAT) or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab) will be obtained for central laboratory analysis on Day 1 prior to blinded IP infusion, and on Day 3, Day 7, Day 14, and Day 29 (± 1 day).

Statistical Methods:

Descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum values for the continuous/quantitative

data or absolute and relative frequency counts and percentages for categorical/qualitative data. All statistical tests will be 2-sided at a significance level of 0.05.

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 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

Primary efficacy endpoint of proportion of asymptomatic subjects who remain asymptomatic will be compared between 2 doses of C19-IG 20% and Placebo by Fisher's exact test or Chi-square test. Sensitivity analysis stratified by age group will be performed using Cochran-Mantel-Haenszel (CMH) test. The first secondary efficacy endpoint of change in SARS-CoV-2 viral load (log_{10} copies/mL) from Baseline (Day 1) to Day 7 and to Day 14 will be analyzed by analysis of covariance (ANCOVA) with treatment and randomization strata as fixed effects and baseline value as covariate.

Determination of Sample Size

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.

Assumptions for the purposes of sample size estimation in this setting are difficult.

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). The reduction in medically attended visits (MAVs) in patients given mAb was substantial (at least half), and in higher risk individuals this was even more pronounced, though the overall rate of MAVs was low in all arms including control (45). Among other caveats, a different population of patients was evaluated (albeit non-hospitalized outpatients) who already had mild/moderate COVID-19 symptomatology; additionally, the endpoint was needed for a higher threshold intervention (MAVs), and not maintenance of an asymptomatic state. However, this does provide a benchmark and context for subsequent sample size extrapolations.

If it is assumed that 80% of patients in the Placebo control arm will remain asymptomatic at Day 14 (42 [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. 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.

Control Success % (proportion remaining *Asymptomatic*) (reference)	**Absolute Delta C19-IG 20%**		**C19-IG 20% Success % (proportion remaining *Asymptomatic*)**		**Sample Size (total)**	
80% (42)	*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 (42, 43). 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 (44). 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.

Interim Futility Analysis

An interim futility analysis will be conducted to assess whether the trial will be terminated due to lack of efficacy (futility) in the December 2021 timeframe based on all available data assessable for the primary endpoint and key secondary efficacy endpoints.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

GLOSSARY AND ABBREVIATIONS

ACE2	Angiotensin-converting enzyme 2
ADE	antibody dependent enhancement
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
ARDS	acute respiratory disease syndrome
AUC	area under the concentration versus time curve
BMI	body mass index
C3PO	COVID-19 Convalescent Plasma in Outpatients
C19-IG 20%	anti-COVID-19 Immune Globulin (Human) 20%
CD4	cluster of differentiation 4
CDC	Center for Disease Control
CHO	Chinese hamster ovary
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CJD	Creutzfeldt-Jakob disease
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CoVs	coronaviruses
COVID-19	coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DAF	dose adjustment factor
EAP	Expanded Access Program
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HCoVs	highly pathogenic CoVs
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IFA	indirect fluorescent antibody
IgA	immunoglobulin A

IgG	immunoglobulin G
IgG1	human immunoglobulin G-1
IGIV-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IL-6	interleukin-6
IP	investigational product
IQR	interquartile range
IRB/EC	Institutional Review Board/Ethics Committee
mITT	modified intention to treat
IV	intravenous
IVIG	intravenous immune globulin
LSM	least-squares means
mAb	monoclonal antibody
MAVs	medically attended visits
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
NAT	nucleic acid amplification technology
NCI	National Cancer Institute
NEWS	National Early Warning Score
NIH	National Institutes of Health
PCR	polymerase chain reaction
PI	primary immunodeficiency
PK	pharmacokinetic
PP	Per Protocol
PS80	polysorbate 80
RBD	receptor binding domain
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase PCR
RT-qPCR	reverse transcription quantitative real-time PCR
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBIs	serious bacterial infections
SCIG	subcutaneous immunoglobulin
SD	standard deviation
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral oxygen saturation by pulse oximetry
TEAE	treatment-emergent adverse event
TWA	time weighted average
US	United States
vCJD	variant Creutzfeldt-Jakob disease
WBC	white blood cell
WHO	World Health Organization

1 GENERAL INFORMATION

Protocol title and other key study information are provided on the title page. Information regarding additional key personnel and organizations involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the sponsor and at the investigator sites within the study reference manual/file.

Investigators and staff will receive training in appropriate individual site training session(s) depending on what is feasible, given the emergency epidemic situation.

2 BACKGROUND INFORMATION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that was first recognized in Wuhan, China, in December 2019 (1). Genetic sequencing of the virus suggests that SARS-CoV-2 is a betacoronavirus closely linked to the severe acute respiratory syndrome (SARS) virus (2). While most people with COVID-19 develop mild or uncomplicated illness, approximately 14% develop severe disease requiring hospitalization and oxygen support and 5% require admission to an intensive care unit (2). In severe cases, COVID-19 can be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury (3). Older age and co-morbid disease have been reported as risk factors for death, and recent multivariable analysis confirmed older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer > 1 µg/L on admission were associated with higher mortality. The observed median duration of viral RNA detection was 20.0 days (interquartile range [IQR] 17.0–24.0) in survivors, but SARS-CoV-2 virus was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days (4, 5).

Apart from Veklury® (remdesivir) which is approved in the United States (US) for COVID-19 there are no fully approved treatments for COVID-19 and no other fully approved post-exposure prophylactic or therapeutic treatment modalities currently in existence for SARS-CoV-2. While the mAb bamlanivumab, mAb cocktail of casirivimab and imdevimab, and convalescent plasma have emergency use authorizations (EUA) before licensure granted by the US Food and Drug Administration (FDA), efficacy remains to be further defined.

Results for remdesivir have been encouraging. The NIAID Adaptive COVID-19 Treatment Trial, showed that subjects receiving remdesivir had a shorter median time to recovery compared with those receiving placebo (11 vs 15 days; p<0.001) with a trend toward a survival benefit, and mortality rate of 8.0% vs 11.6% by day 29 (p=0.06) (6). A smaller randomized study from China did not show a significant benefit for remdesivir in a similar hospitalized population (hazard ratio for time to clinical improvement 1.23 [95% CI 0.87–1.75]); however, that trial was stopped early due to slow enrolment and power was substantially less than planned (58% instead of 80%) (7). Additional studies in the FDA approved labeling were also supportive of efficacy or remdesivir in COVID-19 (8).

The EUA to permit the emergency use of the unapproved product bamlanivimab (LY-CoV555) and also the mAb cocktail of casirivimab and imdevimab specifies treatment of mild to moderate COVID-19 in adults and pediatric outpatients (≥12 years of age) with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization (9).

Bamlanivimab is a recombinant neutralizing human immunoglobulin G-1 (IgG1)κ mAb to the spike protein of SARS-CoV-2, and is unmodified in the Fc region. Bamlanivimab blocks spike protein attachment to the human Angiotensin-converting enzyme 2 (ACE2) receptor with an IC_{50} value of 0.025 µg/mL. The data supporting this EUA are based on an interim analysis from Part A of BLAZE-1 that occurred after all enrolled subjects completed at least Day 29 of the trial and showed that patients receiving bamlanivimab had fewer emergency room visits or hospitalizations than occurred in the placebo arm (9).

Both components of Regeneron's mAb cocktail casirivimab (IgG1κ) and imdevimab (IgG1λ) are recombinant human mAbs which are unmodified in the Fc regions and are produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 and block RBD binding to the human ACE2 receptor with IC_{50} values of 56.4 pM, 165 pM and 81.8 pM, respectively for the components and the combination. The EUA was based on a study in which the primary endpoint was the difference in time weighted average (TWA) change from baseline in viral load (log_{10} copies/mL), as measured by reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR) in nasopharyngeal swab samples. TWA from Day 1 through Day 7 for the pooled doses of casirivimab and imdevimab compared with placebo (n=665) was highly significant ($p<0.0001$). Medically attended visits (MAVs) which comprised hospitalizations, emergency room visits, urgent care visits, or physician office/telemedicine visits for COVID-19 were also diminished. A lower proportion of subjects treated with casirivimab and imdevimab had COVID-19 related MAVs (2.8% for combined treatment arms vs 6.5% placebo). In post-hoc analyses, a lower proportion of subjects treated with casirivimab and imdevimab had COVID-19-related hospitalizations or emergency room visits compared to placebo (10).

Convalescent plasma and hyperimmune immune globulin, such as Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%) are examples of passive immunotherapies involving administration of antibodies against SARS-CoV-2 derived from donors who have recovered from infection. Convalescent plasma was previously evaluated in an uncontrolled study for SARS-CoV-1 illness in Hong Kong. This was shown to be more effective when administered early, and in those who were polymerase chain reaction (PCR) positive and seronegative (25). In a pilot uncontrolled study of convalescent plasma containing COVID-19 antibodies in China, one unit of 200 ml with neutralizing antibody titers ≥1:640 dilution was used in 10 patients with severe COVID-19 (11). This was shown to be safe and showed a possible improvement in clinical outcomes. Another study in New York reported that 39 patients receiving convalescent plasma had in improvements in supplemental oxygen requirements and survival compared to retrospectively matched controls (12). In a prospective, propensity score-matched study by Salazar and colleagues assessing the efficacy of COVID-19

convalescent plasma transfusion versus standard of care as treatment for severe and/or critical COVID-19 in 8 Houston hospitals, an interim analysis of 316 transfused patients (136 transfused patients meeting 28-day outcome measure vs 251 matched controls) demonstrated a significant survival benefit for earlier transfusion with high-titer units (13). In the United States (US) the Expanded Access Program (EAP) resulted in over 100,000 COVID-19 patients enrolling at over 2,700 sites across the US, and although uncontrolled, demonstrated that convalescent plasma had no safety issues and was associated with significantly diminished mortality in the subset of patients ≤ 80 years, transfused earlier in disease course with higher titer units (14, 15).

Efficacy of high-titer convalescent plasma in outpatients has recently been demonstrated in a randomized, double-blind, placebo-controlled study in Argentina wherein symptomatic COVID-19 patients aged ≥ 65 years were evaluated for severe respiratory progression based on oxygen saturation on room air and/or tachypnea (16). In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P = 0.03. A modified intention-to-treat analysis that excluded 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20 to 0.81) (16). This profound effect was demonstrable with early intervention within 3 days of symptoms. As such this study supports the concept of evaluating novel passive antibody transfer treatments early in the course of disease (as outpatients) in populations vulnerable to COVID-19.

Hyperimmune globulin preparations have been described to have therapeutic utility in varicella zoster, cytomegalovirus (CMV) pneumonitis (17), parvovirus induced red cell aplasia (18), and respiratory syncytial virus (RSV) infection (18) in patients with underlying impairments of immunity. In addition, hyperimmune globulins for hepatitis A (20), hepatitis B (21), and rabies (22) have proven prophylactic efficacy and their use is recommended in clinical guidelines. For measles prophylaxis, Gamunex-C 400 mg/kg may be administered either as pre-exposure prophylaxis or post-exposure prophylaxis in vulnerable individuals (23). The potential utility of this approach has also been explored in severe respiratory infections caused by other pathogens including influenza (24) and SARS (25, 26, 27). However, the evidence for efficacy of hyperimmune globulin in SARS infection is limited because in that disease outbreak, its use was assessed only in small, poorly controlled clinical studies (28). While there are some mechanistic similarities between hyperimmune intravenous immune globulin (IVIG) and convalescent plasma (29), individual doses of neutralizing antibody in convalescent plasma are inherently variable from unit to unit. Unlike hyperimmune purified IgG products, convalescent plasma cannot be standardized as a therapeutic product at the required scale. In contrast to convalescent plasma where generally a single unit of plasma obtained from a single ABO compatible donor is used, hyperimmune IgG is a highly purified preparation containing high titers of neutralizing antibodies pooled from multiple donors and would be safer and have higher activity than convalescent plasma. As an extension of the convalescent plasma concept for passive humoral immunity, highly

purified IgG products have been manufactured from plasma collected from convalescent donors who have recovered from COVID-19. These concentrated hyperimmune products, such as C19-IG 20%, allow greater IgG content to be administered since the IgG is concentrated and IgG dose is not limited by fluid volume constraints.

Given the still emerging data and imminent need for intervention, many approaches and combination strategies are being employed. The subjects enrolled in this study will be those who test positive for SARS-CoV-2 by a regulatory-authority-approved diagnostic assay who are asymptomatic but are vulnerable to evolution to overt COVID-19 manifestations by virtue of their age (≥ 18 years). While the majority of infected patients will recover, a significant number require hospitalization; and morbidity and sequelae can be severe (30).

In addition to the information provided here and below, please also refer to the full C19-IG 20% Investigator's Brochure (IB), and any additional data supplied by the sponsor.

2.1 Name and Description of the Investigational Product(s)

See Section 4.4 Study Treatments for detail.

The investigational product (IP) is a hyperimmune immune globulin, Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%). C19-IG 20% is a formulation of hyperimmune immunoglobulin manufactured with human plasma from those who have recovered from coronavirus disease 2019 (COVID-19) with antibodies to SARS-CoV-2, which may benefit people suffering from COVID-19.

For C19-IG 20% the criteria for selection of convalescent plasma units specify a titer threshold, specifically: anti-SARS-Cov-2 antibody titer corresponding to ≥10.0 using the Ortho-Vitros anti-SARS-CoV-2 antibody test.

C19-IG 20% is manufactured using the same production process as commercially approved Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%), also known as XEMBIFY®. IGSC 20% is approved by the US FDA and Health Canada for subcutaneous (SC) injection indicated for treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older.

The following IP will be used in this clinical trial (Table 2-1):

Table 2-1 Investigational products

Investigational Products	
Test Product: **Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%)**	Vials containing sterile liquid preparation of Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%) (200 mg/mL) in single use vials of 2 vial sizes (1 gram in 5 mL; 2 grams in 10 mL)

C19-IG 20% will be the investigational product being tested versus Placebo in asymptomatic outpatients with documented SARS-CoV-2 virus infection via regulatory-approved diagnostic assay.

C19-IG 20% is a sterile preservative-free and pyrogen-free liquid formulation containing 20% human immune globulin (IgG) formulated in 0.16 to 0.26 M glycine and 10 to 40 µg/mL polysorbate 80 at pH of 4.1 to 4.8. It has been purified from human plasma via a multi-step process and consists of purified protein from pooled plasma donations of which not less than 98% of the protein has the electrophoretic mobility of IgG. Also present are trace levels of protein aggregates and fragments and immune globulin A (IgA) (average about 0.1 mg/mL).

2.2 Relevant Findings from Nonclinical and Clinical Trials

C19-IG 20% is manufactured using the same production process as commercially approved IGSC 20% (XEMBIFY). Because of this, the attributes of IGSC20% are described herein in terms of clinical experience.

There is no clinical experience to date with C19-IG 20%.

In animal studies, the toxicity profile of IGSC 20% was remarkably similar following single or repeated SC administration in New Zealand White rabbits to Grifols commercial 10% product, Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C 10%) which is licensed in the US (trade name Gamunex®-C,), in Europe (Gamunex®), and in a number of other countries around the world.

In a single dose toxicity study, the SC dosing was well tolerated, and no adverse effects were observed at dose levels as high as 1500 mg/kg. In a repeat dose toxicity study, the safety and toxicity profiles of IGSC 20% and IGIV-C 10% were remarkably similar following 5 consecutive daily SC administrations in New Zealand White rabbits. The repeat dose study employed the daily dosing strategy to minimize xenogeneic immunity issues. This dosing was essentially cumulative because of the long terminal half-life ($t_{1/2}$) (>100 hours) in rabbits. The final cumulative IGSC 20% doses were 2500, 5000, and 7500 mg/kg, respectively (5 days × 500, 1000, and 1500 mg/kg/day). The final cumulative dose of IGIV-C 10% was 7500 mg/kg (5 days × 1500 mg/kg/day). Clinical signs in the affected animals were only seen after the administration of the fifth and final highest dose levels of IGSC 20% or IGIV-C 10% and the frequency was similar between commercial product IGIV-C 10% and IGSC 20%. Manifestations were morbidity/mortality in several animals dosed at the highest cumulative dose levels of human IGSC 20% and IGIV-C 10% related to immune-mediated hemolytic anemia. Injection site histopathology was similar between the high dose IGSC 20% and IGIV-C 10% groups.

In improper delivery route studies, IGSC 20% administered as a single intravenous (IV), intra-arterial, and perivascular dose of 100 mg/kg was well tolerated in rabbits. Pathological findings in these studies were either considered non-adverse or within standard norms for the given routes of administration in rabbits.

In conclusion, the safety and toxicity profile of IGSC 20% was remarkably similar to subcutaneously administered IGIV-C 10% on a mg/kg basis in animal studies.

Two Phase 3 clinical trials (Study GTI1502 conducted in North America [US and Canada] and Study GTI1503 conducted in the European Union [EU] and Australia) evaluated IGSC 20% in subjects with PI.

Study GTI1502 (IGSC 20%)

On the basis of the GTI1502 Phase 3 study, IGSC 20% received US FDA approval for XEMBIFY® for SC injection indicated for treatment of PI in patients 2 years of age and older, which includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

In Study GTI1502, a total of 53 subjects with PI were enrolled. Participants received IGIV-C 10% intravenously (IV) followed by 24 weeks of weekly IGSC 20% administered subcutaneously using an IV to SC dose adjustment factor (DAF) of 1.37. Non-inferiority and bioequivalence of IGSC 20% to IGIV-C 10% were demonstrated in terms of the area under the concentration versus time curve (AUC) comparing IgG pharmacokinetic (PK) profiling of IV IGIV-C 10% to SC IGSC 20% at SC Weeks #13 to 14. The $AUC_{(0\text{-}7days)}$ geometric least-squares means (LSM) ratio was 1.04 (90% confidence interval [CI] 1.00, 1.07). In study GTI1502, little variation in IgG trough values was observed during IGSC 20% treatment from SC Week #5 onwards. Average total IgG steady-state mean trough during SC administration of IGSC 20% was 1244.8 mg/dL, demonstrating a 33% increase relative to average steady state mean IgG trough during IV infusions of IGIV-C 10% (957.1 mg/dL). IGSC 20% provided good protection from serious bacterial infections (SBIs) with a rate per person per year of 0.049 (95% CI 0.020, 0.098).

Experience with conventional IGSC 20% in this phase 3 study provides useful metrics for tolerability of SC infusions in PI patients. In the adult population, defined in GTI1502 as >16 years, the mean dose per infusion was 179.5 mg/kg, the median number of SC sites utilized per infusion was 4 sites, and the mean volume per site was 21.7 mL/site. Participants in study GTI1502 tolerated SC infusions of IGSC 20% very well. In the current study, a dose of 1 or 2 grams of C19-IG 20% is selected. This translates, to a volume of 5 or 10 mL (blinded C19-IG 20%), thus providing a margin and buffer with regard to the weekly metrics from the pivotal study described above. This approach is anticipated to translate into good tolerability in the current study.

Study GTI1503 (IGSC 20%)

In the second Phase 3 study (GTI1503), subjects received 12 months of IGSC 20% given SC at weekly intervals. IGSC 20% was given at an equivalent dose to the subject's previous IgG replacement regimen.

In Study GTI1503, a total of 61 subjects with PI were enrolled, and these included 29 children and 32 adults. Participants received 52 weeks of IGSC 20% administered via SC route. A weekly dose of IGSC 20% equivalent to the subject's previous immune globulin

replacement was administered for all prior regimens, both SCIG and IVIG. No DAF was applied for subjects entering on IVIG although a minimum dose of IGSC 20% was set to 100 mg/kg/week.

The primary efficacy endpoint was rate of SBIs per person per year, which was 0.017 on IGSC 20% treatment. The 1-sided 99% upper confidence limit was 0.036, which was less than 1, hence the null hypothesis that the SBI rate per person per year is ≥1 was rejected at 1-sided α=0.01 level. Thus, the primary efficacy endpoint was met.

The rate of hospitalization due to infection per person per year 0.017 (2-sided 95% confidence interval: 0.008-0.033) overall. Weekly administration of IGSC 20% resulted in mean trough serum concentrations of total IgG that were comparable to the mean trough IgG levels obtained with the previous IgG replacement regimen. The mean trough ratio (SC phase:Previous Regimen phase) was 1.078 (range: 0.83 to 1.54), and the average of the steady state mean trough concentrations of total IgG over all subjects during the Previous Regimen and SC phases were 891.37 mg/dL and 947.64 mg/dL, respectively.

Experience with conventional IGSC 20% in this phase 3 study also provides useful metrics for tolerability of SC infusions in PI patients. In the adult population, defined in GTI1503 as >16 years, the mean dose per infusion was 129.9 mg/kg, the median number of SC sites utilized per infusion was 2 sites, and the mean volume per site was 21.4 mL/site. Participants in study GTI1503 tolerated SC infusions of IGSC 20% very well. In the current study, a dose of 1 or 2 grams of C19-IG 20% is selected. This translates, to a volume of 5 or 10 mL (blinded C19-IG 20%), thus providing a margin and buffer with regard to the weekly metrics from the pivotal study described above over the course of 12 months of treatment with conventional IGSC 20%. This approach is anticipated to translate into good tolerability.

Important nonclinical and clinical data related to efficacy and safety of C19-IG 20% is summarized in the IB.

2.3 Known and Potential Risks and Benefits to Human Subjects

2.3.1 Benefits

Convalescent plasma and hyperimmune plasma-derived products have been used to successfully treat a number of acute infectious diseases. Among the most remarkable is Argentine Hemorrhagic Fever wherein the mortality was reduced from 16.5% to 1.1% in a randomized, controlled trial of 188 patients transfused 500 mL convalescent plasma versus placebo (31).

Similar to convalescent plasma currently used in the COVID-19 pandemic, the antibody distribution in C19-IG 20% is broad, including antibodies specific to SARS-CoV-2 as well as antibodies to other pathogens. However, compared to convalescent plasma, C19-IG 20% is available in a more concentrated form (higher IgG concentration), therefore higher antibody doses may be administered, and there is no requirement for ABO blood type compatibility (as needed for convalescent plasma).

While there are no direct data to draw upon with regard to dose selection for C19-IG 20% treatment of COVID-19. There are some historical precedents with other infectious diseases. A dose of 400 mg/kg for hyperimmune IVIG was employed by Hung and colleagues in their study of H1N1 influenza (32). These investigators reported a multicenter, prospective, double-blind, randomized controlled trial. Convalescent plasma from patients who recovered from the 2009 pandemic influenza A(H1N1) (A[H1N1]) infection was fractionated to hyperimmune IVIG by CSL Biotherapies. Patients with severe A(H1N1) infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive hyperimmune IVIG or normal IVIG manufactured before 2009 as control. A single dose of 400 mg/kg of hyperimmune IVIG (treatment) or 400 mg/kg normal IVIG (control) was administered according to randomized treatment assignment. Between 2010 and 2011, 35 patients were randomized to receive hyperimmune IVIG (17 patients) or IVIG (18 patients). Serial respiratory viral load demonstrated that hyperimmune IVIG treatment was associated with significantly lower day 5 and 7 posttreatment viral load when compared with the control ($p=0.04$ and $p=0.02$, respectively). The initial serum cytokine level was significantly higher in the hyperimmune IVIG group but fell to a similar level 3 days after treatment. Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that hyperimmune IVIG treatment was the only factor that independently reduced mortality (odds ratio, 0.14; 95% CI, 0.02-0.92; $P = 0.04$). Treatment of severe A(H1N1) infection with hyperimmune IVIG within 5 days of symptom onset was associated with a lower viral load and reduced mortality (32).

In Israel, Makhoul and colleagues also employed a dose of 400 mg/kg (for 5 days) to a small group of 8 patients with worsening West Nile virus (WNV) encephalopathy with apparent benefit. The study was uncontrolled, and the net cumulative dose was high (2 g/kg) (33); this dose is similar to that used for myasthenia gravis exacerbations, Kawasaki disease, Guillain-Barré syndrome (GBS), and as the initial loading dose for chronic inflammatory demyelinating polyneuropathy (CIDP).

The role of hyperimmune IVIG to treat serious influenza A and B infection in combination with antivirals (eg, oseltamivir) remains incompletely defined (24). The INSIGHT FLU-IVIG Study Group conducted a large study funded by the National Institutes of Health, NIAID, Bethesda, MD. However, the dose selected in this sentinel study was lower (a single 250 mg/kg dose, with a weight cap of 100 kg). Limitations of the study included the possibility that it was not feasible to demonstrate incremental therapeutic benefit over coadministration of active antivirals (oseltamivir) to virtually all patients.

Briefly, Davey and colleagues (INSIGHT FLU-IVIG Study Group) conducted an international randomized, double-blind, placebo-controlled trial over five influenza seasons from 2013–14 to 2017–18. Adults (≥18 years of age) were admitted for hospital treatment with laboratory-confirmed influenza A or B infection and were randomly assigned (1:1) to receive standard care plus either a single 500 mL infusion of high-titer hyperimmune IVIG (250 mg/kg body weight, capped at 100 kg maximum) or saline placebo (placebo group). Standard of care included antivirals effective against influenza, most commonly oseltamivir in 95% of patients. Eligible patients had a National Early Warning Score (NEWS) of 2 points or greater at the time of screening and their symptoms began no more than 7 days before randomization. The primary endpoint was a six-category ordinal outcome of clinical status at

day 7, ranging in severity from death to resumption of normal activities after discharge. It was analyzed with a proportional odds model, using all six categories to estimate a common odds ratio. An odds ratio greater than 1 indicated that, for a given category, patients in the hyperimmune IVIG group were more likely to be in a better category than those in the placebo group. There were 308 patients included in the primary analysis (156 hyperimmune IVIG, 152 placebo). Hyperimmune IVIG treatment produced a robust rise in hemagglutination inhibition titers against influenza A and smaller rises in influenza B titers. Based on the proportional odds model, the odds ratio on day 7 was 1.25 (95% CI 0.79–1.97; p=0.33). In subgroup analyses for the primary outcome, the odds ratio in patients with influenza A was 0.94 (0.55–1.59) and was 3.19 (1.21–8.42) for those with influenza B (interaction p=0.023). When administered alongside standard care (most commonly oseltamivir), hyperimmune IVIG was not superior to placebo for adults hospitalized with influenza infection. However, the investigators found a clinical benefit of hyperimmune IVIG for patients with influenza B which was supported by antibody affinity analyses, although it was considered that this finding warranted further confirmation (24).

Taken together these data in the context of existing experience with convalescent plasma in the COVID-19 pandemic, suggest the potential benefit of C19-IG 20% as a therapeutic intervention for asymptomatic outpatients infected with SARS-CoV-2 with age-related increased risk of progression to overt COVID-19. The ability to concentrate antibody and administer a potent dose in a smaller volume with no constraints regarding ABO compatibility are additional advantages in this regard.

Additionally, C19-IG 20% is manufactured from convalescent plasma units with anti-SARS-Cov-2 antibody titers ≥7.0 using the Architect-Abbott method or ≥10.0 using the Vitros-Ortho method. Thus, the product is targeted for highly concentrated antibody delivery.

2.3.2 Risks

When highly purified IgG is given by the SC route, the systemic ARs associated with IVIG such as headaches, fever, chills, and myalgia are diminished, and repeated SC infusions of IgG cause few systemic ARs (34, 35). These characteristics with SCIG and conventional IGSC 20% are expected to be reflected similarly in clinical experience with C19-IG 20%.

In the 2 pivotal studies of IGSC 20% in PI the most common adverse events were local infusion site reactions which were not dose limiting over the course of up to 1 year of administration, were generally mild or moderate, and were without serious manifestations.

As with conventional IGSC 20%, antibodies in C19-IG 20% may interfere with the response to live viral vaccines such as measles, mumps, polio, rubella, and varicella. Therefore, immunization with live viral vaccines should be deferred until approximately 6 months after IGSC 20% administration when possible.

It is recommended that SARS-CoV-2 vaccination for participants in Study GC2010 be deferred for 90 days after receipt of blinded study drug. This is in accordance with available guidance from the Center for Disease Control (CDC) to avoid potential interference of the antibody therapy with vaccine-induced immune responses.

C19-IG 20% should not be administered to patients with known (documented) history of serious anaphylactic reaction to blood, any blood-derived plasma product or commercial immunoglobulin, or those with known selective IgA deficiency with anti-IgA antibodies.

Because IGSC 20% is a biological product, it may carry a risk of transmitting infectious agents (eg, viruses and, theoretically, the variant Creutzfeldt-Jakob disease (vCJD) and CJD agents). The risk that C19-IG 20% can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and by the inclusion of steps in the manufacturing process with the demonstrated capacity to inactivate and/or remove pathogenic agents. Despite these measures, a risk of transmitting infectious agents cannot be entirely ruled out.

Theoretical risk involves the phenomenon of antibody dependent enhancement of infection (ADE). ADE can occur in several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described, and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain (36). It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for Middle East respiratory syndrome (MERS) (36).

Structural and functional analysis of the SARS-CoV-2 shows that the SARS-CoV-2 S protein binds the ACE2 receptor on human alveolar epithelial cells, suggesting SARS-CoV-2 uses the same receptor, ACE2, as SARS-CoV. However, the SARS-CoV-2 S protein binds ACE2 with higher affinity than SARS-CoV S. The high affinity of the S protein for human ACE2 may lead to the great human-to-human transmission of SARS-CoV-2. Due to the key role of the S protein, it is the main target for antibody mediated neutralization (Zhou and Zhao, 2020). Although SARS-CoV-2 shows the high homology with SARS-CoV, antibody cross-reactivity is limited between the two virus S proteins. Several published SARS-CoV neutralizing antibodies do not have appreciable binding to SARS-CoV-2 S protein (37).

ADE of viral entry has been observed for many viruses. It was shown that antibodies target one serotype of viruses but only sub neutralize another, leading to ADE of the latter viruses. ADE occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells. ADE has been observed most notably for flaviviruses (e.g., dengue virus) (36). It has been shown that when patients are infected by one serotype of dengue virus (i.e., primary infection), they produce neutralizing antibodies targeting the same serotype of the virus. However, if they are later infected by another serotype of dengue virus (i.e., secondary infection), the preexisting antibodies cannot fully neutralize the virus. Instead, the antibodies first bind to the virus and then bind to the IgG Fc receptors on immune cells and mediate viral entry into these cells (36). Thus, sub neutralizing antibodies (or non-neutralizing antibodies in some cases) are responsible for ADE of these viruses (36).

Additionally, Yip and colleagues discuss experiments which suggest for SARS that in vitro potential ADE resulted in abortive infection in vitro (38). They state that despite being increasingly susceptible to infection, macrophages did not support productive replication of the virus, or modify expression of some pro-inflammatory cytokines/chemokines upon antibody-mediated invasion (38). Their findings point towards the likely occurrence of ADE

infection of immune cells by SARS-CoV, but the outcomes of such an alternative infection pathway on the cell functionality/homeostasis remained unclear. It appeared that antibody-mediated enhancement of SARS-CoV infection in primary macrophages lead to abortive infection and that the ADE infection pathway did not alter the profile of cytokine/chemokine produced by primary human macrophages (38).

While the possibility of ADE from administration of C19-IG 20% cannot be entirely ruled out. The available data from the earlier SARS epidemic, and currently the extensive EAP experience with convalescent plasma as a source of neutralizing antibodies suggest that the over-riding effect of hyperimmune immune globulin is salutary.

Therefore, the premise of the current study is that C19-IG 20% may produce therapeutic benefit in outpatients aged ≥ 18 years who are infected with SARS-CoV-2 to prevent evolution of symptomatic COVID-19.

2.4 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

2.4.1 Administration of Investigational Product

Subjects will be randomized to either of 2 dose levels of C19-IG 20% or Placebo. Randomization to active treatment arms will specify either a blinded 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 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%).

Subjects randomized to C19-IG 20% will receive a blinded single dose via SC infusion of C19-IG 20%. Subjects randomized to blinded Placebo will receive sterile 0.9% sodium chloride injection United States Pharmacopeia (0.9% NaCl, USP) or equivalent.

Since the immunoglobulin concentration is 200 mg/mL subjects randomized to receive 1 gram of C19-IG 20% will be administered 5 mL via SC infusion. Subjects randomized to receive 2 grams of C19-IG 20% will be administered 10 mL via SC infusion (administered as described above to maintain the blind).

All C19-IG 20%/Placebo administrations will be undertaken by a trained medical professional under the supervision of a healthcare provider.

C19-IG 20%/Placebo will be administered into the SC fat by direct push via syringe in a residence/clinic/healthcare setting and will be supervised by a healthcare professional. A 10-

mL Luer lock syringe is recommended for ease in manual push administration due to viscosity, and SC infusion lines specifically designed for SC infusion should be used to facilitate manual push infusion. SC infusion lines have perpendicular needles that are easily inserted perpendicularly into the SC fat and are designed with very little dead space (minimizing product loss within the lines); they are designed with easily secured tabs for stable placement during the SC push administration. SC infusion sets with 24-gauge needle size are recommended and needle length is dependent upon SC fat layer (either 9 mm or 12 mm in most adults).

SC infusion is a slow push administration. It may take approximately 1-2 minutes for each mL of C19-IG 20% to infuse. Ancillary supplies (for example, SC infusion lines with 24-gauge perpendicular needles of 9 mm and 12 mm length or appropriate alternatives) will be supplied by the Sponsor.

2.4.2 Justification for Selection of Doses/Timing of Investigational Product

For C19-IG 20% the criteria for selection of convalescent plasma units for manufacture of the hyperimmune specify a certain minimum titer threshold. Specifically, to be used in hyperimmune manufacture the donated plasma must have an anti-SARS-Cov-2 antibody titer ≥7.0 using the Architect-Abbott method or ≥10.0 using the Vitros-Ortho method.

The doses of C19-IG 20% in this study are selected with the aim of providing at least the same neutralizing antibody capacity as transfusion of 1 unit of Convalescent plasma donated by people fully recovered from COVID-19.

2.5 Compliance Statement

This study will be conducted under the conditions described in this protocol and in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and all applicable regulatory requirements.

2.6 Study Population

The purpose of this study is to determine if fixed dose C19-IG 20% can reduce the proportion of subjects developing overt COVID-19 symptoms.

Approximately 801 subjects (n=267/arm) will be randomized (1:1:1).

2.7 Relevant Data and Literature Review

2.7.1 COVID-19 Therapeutic Approaches

Coronaviruses (CoVs) typically affect the respiratory tract of mammals, including humans, and lead to mild to severe respiratory tract infections. In the past two decades, two highly pathogenic human CoVs (HCoVs), including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerging from animal reservoirs, have led to global epidemics with high morbidity and mortality.

Currently, apart from Emergency Use Authorizations there are no fully approved treatments for COVID-19 in Europe or the United States, except for remdesivir that achieved full US FDA approval in October 2020. The lack of disease-directed therapeutic options has led to urgent interventions in anticipation of some potentially promising effects. Antivirals are currently under evaluation including favipirivir (AVIGAN) manufactured by Fujifilm in Japan and Kaletra® (lopinavir/ritonavir) commercially available for human immunodeficiency virus (HIV), among others. Although Kaletra did not show demonstrable efficacy in a recently reported study in China (39). While Regeneron's mAb cocktail casirivimab and imdevimab, Lilly's mAb bamlanivimab, and convalescent plasma have EUAs before licensure in the US, efficacy remains to be further defined. EUAs for mAbs are for use in the outpatient setting, and neither are indicated for hospitalized patients. The EUA for convalescent plasma indicates hospitalized patients with COVID-19.

Remdesivir has a full indication in the US for hospitalized COVID-19 patients. The NIAID Adaptive COVID-19 Treatment Trial, showed that subjects receiving remdesivir had a shorter median time to recovery compared with those receiving placebo (11 vs 15 days; $p<0.001$) with a trend toward a survival benefit, and mortality rate of 8.0% vs 11.6% by day 29 ($p=0.06$) (6). These results were affirmed in the final report for ACTT-1 published by Beigel and colleagues (40). A smaller randomized study from China did not show a significant benefit for remdesivir in a similar hospitalized population (hazard ratio for time to clinical improvement 1.23 [95% CI 0.87–1.75]); however, that trial was stopped early due to slow enrolment and power was substantially less than planned (58% instead of 80%) (7).

Additionally, dexamethasone has been shown to decrease mortality (25.7% in the usual care group vs. 22.9% in the dexamethasone group; $P<0.001$), with the largest benefit seen among patients receiving invasive mechanical ventilation (41). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) (41).

To date there are few specific disease modifying agents. Therefore, the potential therapeutic benefit conveyed by a hyperimmune IgG product that can be easily administered in an outpatient setting warrants clinical investigation. This is particularly true given the urgency and extent of the COVID-19 pandemic.

3 STUDY OBJECTIVES AND PURPOSE

3.1 Efficacy Objectives

3.1.1 Primary Efficacy Objective

- To compare C19-IG 20% (2 doses) versus Placebo with regard to proportion of asymptomatic subjects who remain asymptomatic, ie who do not develop symptomatic 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)

3.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives include:

- 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 an 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 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 the NEWS and ordinal clinical status scale through Day 29

- To compare C19-IG 20% (2 doses) versus Placebo with regard to frequency of requirement for hospital-level medical care (ie, 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 (eg, 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).

3.1.3 Exploratory Efficacy Objectives

The exploratory objectives of this 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 symptom severity on Day 7 and Day 29

3.2 Safety Objectives

- 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: ALT; LDH; absolute lymphocyte count; creatinine through Day 14.

4 STUDY DESIGN

4.1 Primary Endpoints and Secondary Endpoints

4.1.1 Primary Efficacy Endpoint

- Proportion of asymptomatic subjects who remain asymptomatic, ie who <u>do not develop symptomatic COVID-19</u> 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)*

  <u>OR</u>

Experiencing at least ONE of the following respiratory signs/symptoms: new or worsening shortness of breath or difficulty breathing,

OR

Experiencing an 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)

4.1.2 Secondary Efficacy Endpoints

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 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]). https://www.mdcalc.com/national-early-warning-score-news (Appendix 2)

- 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 (eg, 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 intensive care unit (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.
  [*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]
- 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

4.1.3 Exploratory Efficacy Endpoints

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 symptom severity on Day 7 and Day 29

  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)

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.

4.1.4 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

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.

4.2 Study Design and Plan

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 test 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. 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.

Participants randomized to C19-IG 20% will receive a blinded SC infusion on Day 1 at a dose of either 1 gram or 2 grams, according to the randomized dose assigned. Participants 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%).

C19-IG 20% is a human immune globulin preparation for SC administration, manufactured by essentially the same process as Gamunex-C, which has been commercially available as an IV IgG product since 2003 and is essentially the same manufacturing method as for Gamunex, licensed in Spain and most of the European countries with >15 years in the market without safety issues. C19-IG 20% is a more concentrated form containing a 200 mg/mL concentration of immunoglobulin in order to reduce administration volume which is made from the plasma of convalescent donors who have recovered from COVID-19. The conventional commercial form of Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is currently approved in the United States and Canada for SC administration in the treatment of PI for IgG replacement and is under evaluation by the European regulatory authorities for this indication.

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.

As described above, 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 also be evaluated at Healthcare Provider Visits on Day 3, Day 7, Day 14, and Day 29. If hospitalized, assessments required for Day 3, Day 7, Day 14, and Day 29 will be performed in hospital.

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.

Subjects will also be assessed as outpatients by Phone Check on Day 5, and Days 9 and 11. Phone Check surveillance is specifically targeted to detecting development of symptomatic COVID-19, to determine presence of sentinel alarm symptoms or symptoms that may indicate worsening (eg, 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. Details are provided in Appendix 1 (Schedule of Study Procedures) and elaborated further below.

Approximately 801 subjects (267 per arm) will be randomized (1:1:1). An independent Data Safety Monitoring Board 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).

An interim futility analysis will be conducted to assess whether the trial will be terminated due to lack of efficacy (futility) in the December 2021 timeframe based on all available data assessable for the primary endpoint and key secondary efficacy endpoints.

Asymptomatic ambulatory outpatients with COVID-19 will be evaluated at the Healthcare Provider Visit on Day 1 for Screening/Baseline assessments and if eligible will be randomized on Day 1. Subjects randomized to C19-IG 20% will receive either 1 gram or 2 grams blinded C19-IG 20% (according to randomization assignment) via SC infusion on Day 1. 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 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%).

As described above 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).

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.

Subjects will also 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 (eg, dyspnea) and to record the patient's daily entries for SpO2 and body temperature.

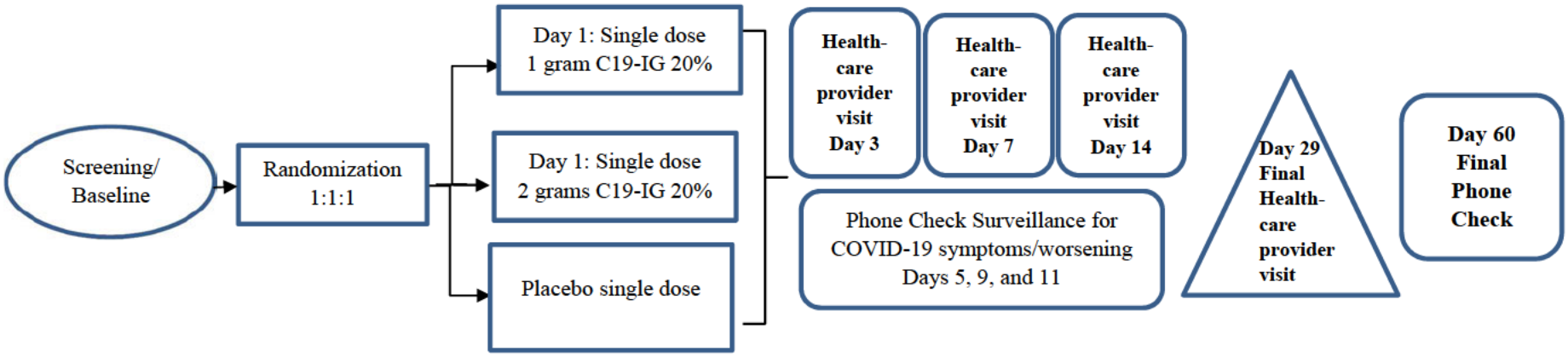
Following the Day 29 assessment time point, one more final Phone Check will be performed at Day 60 for vital status (living or deceased), any hospital admissions, ICU admissions, requirement for invasive mechanical ventilation, need for oxygen supplementation, or serious/non-serious adverse events after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

The Ordinal Scale and NEWS will be assessed at Screening/Baseline, and at Day 3, Day 7, Day 14, and Day 29 visits. The NEWS calculation is delineated in Appendix 2 and can be calculated using the on-line web tool at https://www.mdcalc.com/national-early-warning-score-news.

Basic chemistry analytes (creatinine, albumin, ALT, total bilirubin, LDH) will be assessed on Day 1 prior to blinded IP infusion, and on Day 7 and Day 14 (± 1 day). Hematology (hemoglobin, hematocrit, platelet count, absolute neutrophil & lymphocyte count, leukocyte count with differential) will be assessed on Day 1 prior to blinded IP infusion, and on Day 7 and Day 14 (± 1 day). Samples will be drawn for D-dimer, CRP, and ferritin prior to blinded IP infusion, and on Day 7 and Day 14 (± 1 day). Serum samples will be obtained on Day 1 prior to blinded IP infusion and at Day 7 and Day 14 (±1 day) (which may be stored at -70° C) for later analysis at a reference laboratory for the following parameters: IL-6; interferon γ; autoantibodies against type 1 interferons; and quantitative measurement of IgM and IgG antibodies to SARS-CoV-2. A sample for possible additional quantitative neutralizing antibody versus SARS-CoV-2 will also be obtained at these time points (serum sample reserved for neutralizing antibody testing if such testing becomes feasible stored frozen at -70°C for later analysis at an external lab).

Respiratory samples for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab) will be obtained for central laboratory analysis on Day 1 prior to blinded IP infusion, and on Day 3, Day 7, Day 14, and Day 29 (± 1 day).

The overall study schema is shown in Figure 4-1.



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.

Figure 4-1 Overall Study Schema

4.3 Measures Taken to Minimize/Avoid Bias

4.3.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (3 digits, assigned by the sponsor) followed consecutively with a unique number for each subject (4 digits, including leading zeros). For example, if the investigator's center number is 301, subject number will be 3010001, 3010002, 3010003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

4.3.2 Randomization

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.

4.3.3 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 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%).

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. The placebo is sterile 0.9% sodium chloride injection United States Pharmacopeia (0.9% NaCl, USP) or equivalent.

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.

4.4 Study Treatments

4.4.1 Treatments to Be Administered

Anti-COVID-19 Immune Globulin (Human) 20% (C19-IG 20%) is a sterile liquid formulation of immunoglobulin that has been purified from donors with high-titer anti-SARS-CoV-2 antibodies. Specifically, to qualify for product manufacture the convalescent plasma units must have anti-SARS-Cov-2 antibody titer ≥7.0 using the Architect-Abbott method or ≥10.0 using the Vitros-Ortho method.

The human plasma is purified via a multi-step process. C19-IG 20% is manufactured using the same process as for IGIV-C 10% (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified [IGIV-C]) and is further concentrated by ultrafiltration to a higher IgG concentration (20%). Concentration employs the same procedures as Grifols commercially available SC product, XEMBIFY® (IGSC 20%) which is approved in the US and Canada for PI.

C19-IG 20% is a sterile liquid formulation of 20% human immune globulin formulated in 0.16 to 0.26 M glycine and 10 to 40 µg/mL Polysorbate 80 (PS80) at pH 4.1 to 4.8. It will be supplied in 5 mL and 10 mL vial sizes containing a 20% solution of immunoglobulin (ie, a concentration of 20 g/100 mL [200 mg/mL]).

C19-IG 20% must be inspected visually before being administered. The solution must not be used if the solution is cloudy or turbid. Solution that has been frozen should not be used. The investigator, or designee, is responsible for immediately reporting any issues noted with C19-IG 20% to the study monitor.

For placebo, sterile 0.9% sodium chloride injection United States Pharmacopeia (0.9% NaCl, USP) or equivalent will be used as a placebo to maintain the blind.

Detailed IP administration instructions are provided in Section 6.

4.4.1.1 C19-IG 20%

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 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%).

Since the immunoglobulin concentration is 200 mg/mL subjects randomized to receive 1 gram of C19-IG 20% will be administered 5 mL via SC infusion. Subjects randomized to receive 2 grams of C19-IG 20% will be administered 10 mL via SC infusion (administered as described above to maintain the blind).

These doses are selected with the aim of providing at least the same neutralizing antibody capacity as transfusion of 1 unit of Convalescent plasma donated by people fully recovered from COVID-19.

All C19-IG 20%/Placebo administrations will be undertaken by a trained medical professional under the supervision of a healthcare provider.

C19-IG 20%/Placebo will be administered into the SC fat by direct push via syringe in a residence/clinic/healthcare setting and will be supervised by a healthcare professional. A 10-mL Luer lock syringe is recommended for ease in manual push administration due to viscosity, and SC infusion lines specifically designed for SC infusion should be used to facilitate manual push infusion. SC infusion lines have perpendicular needles that are easily inserted perpendicularly into the SC fat and are designed with very little dead space (minimizing product loss within the lines); they are designed with easily secured tabs for stable placement during the SC push administration. SC infusion sets with 24-gauge needle size are recommended and needle length is dependent upon SC fat layer (either 9 mm or 12 mm in most adults).

SC infusion is a slow push administration. It may take approximately 1-2 minutes for each mL of C19-IG 20% to infuse. Ancillary supplies (for example, SC infusion lines with 24-gauge perpendicular needles of 9 mm and 12 mm length or appropriate alternatives) will be supplied by the Sponsor.

There is extensive experience with conventional IGSC 20% based on considerations of tolerability in patients with SC administration of SCIG for PI. Experience with conventional IGSC 20% (XEMBIFY) in phase 3 study GTI1502 provides useful metrics for tolerability of SC infusions in PI patients. In the adult population, defined in GTI1502 as > 16 years, the mean dose per infusion was 179.5 mg/kg, the median number of SC sites utilized per infusion was 4 sites, and the mean volume per site was 21.7 mL/site. Participants in study GTI1502 tolerated SC infusions of IGSC 20% very well. In the current study, a dose of 1 or 2 grams of C19-IG 20% is selected. This translates, to a volume of 5 or 10 mL (blinded C19-IG 20%), thus providing a margin and buffer with regard to the weekly metrics from the pivotal study described above. This approach is anticipated to translate into good tolerability.

4.4.1.2 Placebo

Sterile 0.9% sodium chloride injection, United States Pharmacopeia (0.9% NaCl, USP) or equivalent will be used as placebo to maintain the blind. The infusion solution will be a total of 10 mL in volume (given in 2 syringes each containing 5 mL) and indistinguishable to maintain the blind. It will be prepared by the unblinded nurse or designee.

Sterile 0.9% sodium chloride injection United States Pharmacopeia (0.9% NaCl, USP) or equivalent will be supplied to the unblinded nurse using commercially available saline at the study center.

4.4.2 Labeling of Investigational Product

Investigational product will be labeled according to the requirements of local law and legislation.

4.4.3 Packaging of Investigational Product

The sponsor will be responsible for ensuring that the IP is manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

4.4.4 Storage of Investigational product

C19-IG 20% must be stored in a secure area accessible to study personnel authorized by the investigator, such as the study staff responsible for the preparation and dispensing of IP.

C19-IG 20% must be stored at temperatures of 2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze or partially freeze. Investigators, or designees, are responsible for maintaining storage temperature records and for immediately reporting deviations in temperature to the study monitor.

Details for the storage are located in the Pharmacy Manual provided to each site.

All partially used vials should be discarded as no preservative is present. Do not use after expiration date.

The pharmacist must keep IP accountability by means of an accountability log.

4.5 Expected Duration of Subject Participation in the Study

Subjects will receive one blinded 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.

4.6 Discontinuation Criteria for Individual Subjects and Study

4.6.1 Discontinuation Criteria for Individual Subjects

See Section 5.3 Subject Withdrawal Criteria

4.6.2 Premature Termination of Study/Closure of Center

The sponsor, Institutional Review Board/Ethics Committee (IRB/EC), and/or regulatory authorities have the right to close this study or a study center, and the investigator/sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The IRB/EC must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at the site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

The reasons a study center may be closed include, but are not limited to, the following:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with ICH GCP

4.7 Accountability Procedures for Investigational Product

Investigational product is to be used only for the study in accordance with the directions given in this protocol. The investigator, or designee such as the study pharmacist or specifically designated unblinded nurse, is responsible for handling of the IP in accordance with directions given in the protocol.

The investigator is responsible for maintaining accurate records of the IP for his/her site. Investigational product inventory/dispensing documentation verifying the receipt, dispensing, destruction, or return must be maintained and kept current by the investigator, or designee. The inventory must be made available for inspection by the monitor. Investigational product supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to IP return or destruction. Written documentation of any used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols.

4.8 Maintenance of Treatment Randomization Codes

Randomization codes will be generated and access to the actual randomization schedules or codes must be strictly controlled during the course of the study. This study is double-blind so there is blinding of treatment assignment.

4.9 Data to Be Recorded

All information contained in the medical history and complementary exploration reports including laboratory test will be considered as clinical trial source data.

Any data recorded in the Case Report Form should have written or electronic record in the subject's medical records. These written or electronic records will be considered source data and should be dated and signed by the investigator or by the qualified delegated person (eg, results of vital signs testing, or the IP administration procedure).

For every subject enrolled, the investigator will write into his/her medical history that he/she has been enrolled in a clinical trial, specifying its title, study number, and sponsor (Grifols Therapeutics LLC), as well as the date of informed consent form (ICF) provision.

The investigator is responsible for maintaining complete and adequate case histories in source records of each subject. All study-specific data necessary to be recorded that cannot be found in subjects' past medical records (such as medical history, past medications, etc) should be recorded by the investigator or their designee in subjects' medical files, dating and signing all new entries.

Source data must be preserved for the maximum period of time as required per local and international regulations and made available by the investigator in the cases described above.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Ambulatory male or female outpatients ≥ 18 years of age who have laboratory-confirmed SARS-CoV-2 infection as determined by qualitative PCR (RT-PCR), or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19 (inclusive of SARS-CoV-2 antigen testing or other approved rapid testing platforms) in any specimen ≤ 5 days prior to randomized treatment. (Note: ≤ 5 days is the post-sampling timeframe from date specimen obtained to administration of blinded study drug).

   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.
2. Asymptomatic with no constitutional COVID-19 illness (evident symptoms), specifically no fever, cough, shortness of breath, fatigue, anorexia, vomiting/diarrhea, headache that is unrelated to pre-existing conditions (eg, migraine), sore throat that is unrelated to other pre-existing medical conditions (eg, allergies, gastroesophageal reflux disease), myalgias,

olfactory disorders unrelated with previous medical condition, or evidence of pneumonia at Screening.

3. Pulse oximetry SpO2 (oxygen saturation) on room air > 94% (ie, 95% to 100%) at Screening.
4. National Early Warning Score (NEWS) ≤ 2 points (Appendix 2) at Screening.
5. Subject provides informed consent (ICF) prior to initiation of any study procedures.

5.2 Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Subjects who are admitted to hospital or for whom hospital admission is being planned at the time of Screening.
2. Subjects requiring any form of oxygen supplementation at Screening.
3. Concurrent or planned treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 including remdesivir.
4. Prior, concurrent or planned treatment with mAbs against SARS-CoV-2
5. Have participated in a previous SARS-CoV-2 vaccine study OR outside of a study have received any SARS-CoV-2 vaccine of any kind.
6. Have a history of convalescent COVID-19 plasma treatment at Screening.
7. Fever (temperature ≥38.0° C [≥100.4° F]) measured orally, requirement for antipyretics to reduce temperature (administered for fever), and/or respiratory symptoms (cough, dyspnea) at Screening.
8. Clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may place the subject at undue medical risk for study treatment.
9. The subject has had a known (documented) history of serious anaphylactic reaction to blood, any blood-derived plasma product or commercial immunoglobulin, or has known selective IgA deficiency with anti-IgA antibodies.
10. Decompensated congestive heart failure or renal failure with fluid overload. This includes currently uncontrolled congestive heart failure New York Heart Association Class III or IV stage heart failure.
11. Subjects for whom there is limitation of therapeutic effort such as “Do not resuscitate” status.
12. Currently participating in another interventional clinical trial with investigational medical product or device.
13. Subjects with known (documented) thrombotic complications to polyclonal IVIG therapy in the past.
14. Subject has medical condition (other than COVID-19) that is projected to limit lifespan to ≤ 1 year.

15. Subject has history of drug or alcohol abuse within the past 12 months.
16. Subject is unwilling to commit to follow-up visits.
17. Women who are pregnant or breastfeeding, or if of childbearing potential, unwilling to practice a highly effective method of contraception (oral, injectable, or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom, or occlusive cap with spermicidal foam/gel/cream/suppository, male sterilization, or true abstinence*) throughout the study.

    * True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

    Note: Women who are > 55 years and with absence of menses in the last 12 months are considered Not to be of childbearing potential. Female subjects of child-bearing potential must have a negative test for pregnancy blood or urine human chorionic gonadotropin (HCG)-based assay at Screening/Baseline Visit.

5.3 Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason, either before or after the infusion of the IP. The investigator can withdraw a subject from the clinical trial at any time.

The investigator will document the reason(s) for withdrawal of each subject in source documents and study record. All data gathered on the subject prior to termination will be made available to the sponsor.

5.3.1 Screen Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment. Subjects who fail to meet eligibility criteria during screening evaluations will be considered screen failures and will not participate in the study. Outcomes of screening evaluations will be documented in subject's source documents (e.g. medical history) - including compliance with each individual inclusion/exclusion criterion- and in study records as well.

5.3.2 Removal of Subjects

Subjects may withdraw or be withdrawn from the study for the following reasons:

1. At their own request or at the request of their legally acceptable representative.
2. If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
3. At the specific request of the sponsor.

Also, subjects may be withdrawn for the following reasons:

1. The subject is not able to adhere to the main protocol requirements (major protocol violations).
2. The occurrence of an adverse event (AE) which in the investigator's opinion requires the withdrawal of the subject from the clinical trial.
3. The subject is lost to follow-up.
4. Subject's death.
5. Any event which in the opinion of the investigator impedes the subject's participation in the study.

In all cases, the reason for withdrawal must be recorded in the study record and in the subject's records.

5.3.3 Subject Replacement

Subjects who are withdrawn from the study after being randomized will not be replaced.

5.3.4 Follow-up of Subjects Withdrawn from Study

For subjects administered any amount of blinded IP who discontinue the clinical trial details for follow-up are delineated below.

For subjects who withdraw from the clinical trial (excluding screen failures), study procedures and assessments scheduled for the Day 14 Visit will be performed at the time of withdrawal, during an unscheduled visit at the time of withdrawal. In addition, to assure major clinical outcomes are adequately captured as a measure of overall safety, these subjects will be asked to attend their chronological Day 29 Healthcare Provider Visit (ie, 28 days after Day 1 baseline), unless the unscheduled visit is within 4 days of their chronological Day 29 visit, and provided that they or their legally acceptable representative have not withdrawn consent. At the chronological Day 29 Healthcare Provider Visit, all assessments will be performed. These subjects will also have a Phone Checks on Day 60 as follow-up after the Day 29 Final Healthcare Provider Visit.

5.3.5 Definition of the End of Study

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 Healthcare Provider Visit performed at the scheduled on-study timeframe.

6 TREATMENT OF SUBJECTS

See Section 4.4 for the treatment to be administered, including the name of the IP, the dose, and the route/mode of administration.

6.1 Administration and Timing of Investigational Product for Each Subject

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 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%)

Since the immunoglobulin concentration is 200 mg/mL subjects randomized to receive 1 gram of C19-IG 20% will be administered 5 mL via SC infusion. Subjects randomized to receive 2 grams of C19-IG 20% will be administered 10 mL via SC infusion (administered as described above to maintain the blind).

These doses are selected with the aim of providing at least the same neutralizing antibody capacity as transfusion of 1 unit of Convalescent plasma donated by people fully recovered from COVID-19.

Subjects randomized to placebo will receive sterile 0.9% sodium chloride injection United States Pharmacopeia (0.9% NaCl, USP) or equivalent to maintain the blind. The infusion solution will be at a total volume of 10 mL administered in 2 syringes each containing 5 mL in order to maintain the blind. It will be prepared by the unblinded nurse.

All blinded C19-IG 20% administrations will be undertaken by a trained medical professional under the supervision of a healthcare provider.

C19-IG 20%/Placebo will be administered into the SC fat by direct push via syringe in a residence/clinic/healthcare setting and will be supervised by a healthcare professional. A 10-mL Luer lock syringe is recommended for ease in manual push administration due to viscosity, and SC infusion lines specifically designed for SC infusion should be used to facilitate manual push infusion. SC infusion lines have perpendicular needles that are easily inserted perpendicularly into the SC fat and are designed with very little dead space (minimizing product loss within the lines); they are designed with easily secured tabs for stable placement during the SC push administration. SC infusion sets with 24-gauge needle size are recommended and needle length is dependent upon SC fat layer (either 9 mm or 12 mm in most adults).

SC infusion is a slow push administration. It may take approximately 1-2 minutes for each mL of C19-IG 20% to infuse. Ancillary supplies (for example, SC infusion lines with 24-

gauge perpendicular needles of 9 mm and 12 mm length or appropriate alternatives) will be supplied by the Sponsor.

There is extensive experience with conventional Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) based on considerations of tolerability in patients with SC administration of SCIG for PI. Experience with conventional IGSC 20% in phase 3 study GTI1502 provides useful metrics for tolerability of SC infusions in PI patients. In the adult population, defined in GTI1502 as > 16 years, the mean dose per infusion was 179.5 mg/kg, the median number of SC sites utilized per infusion was 4 sites, and the mean volume per site was 21.7 mL/site. Participants in study GTI1502 tolerated SC infusions of IGSC 20% very well. In the current study, a dose of 1 or 2 grams of C19-IG 20% is selected. This translates, to a volume of 5 or 10 mL (blinded C19-IG 20%), thus providing a margin and buffer with regard to the weekly metrics from the pivotal study described above. This approach is anticipated to translate into good tolerability.

6.2 Prior and Concomitant Therapy

Concomitant medications must be recorded in the medical notes and in the case report form (CRF), including the trade and generic names of the medication, the dose, the route of administration, and the duration of the medication (frequency).

6.2.1 Prohibited Medications Prior to Study Participation

The following medications are prohibited prior to study participation:

- Concurrent or planned treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 including remdesivir .
- Prior, concurrent or planned treatment with mAbs against SARS-CoV-2.
- Participation in a previous SARS-CoV-2 vaccine study OR outside of a study receipt of any SARS-CoV-2 vaccine of any kind.
- Have received convalescent COVID-19 plasma treatment for COVID-19.

Additionally, study participants cannot be participating in another interventional clinical trial with investigational medical product or device.

6.2.2 Prohibited Concomitant Medications during the Study

The following medications are prohibited during study participation:

- Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 including remdesivir.
- Treatment with mAbs against SARS-CoV-2.
- Receipt of any SARS-CoV-2 vaccine of any kind during study. It is recommended that vaccination for participants in Study GC2010 be deferred for 90 days after receipt of blinded study drug. This is in accordance with available guidance from the Center for

Disease Control (CDC) to avoid potential interference of the antibody therapy with vaccine-induced immune responses.

- Convalescent COVID-19 plasma treatment for COVID-19.

Additionally, study participants cannot be participating in another interventional clinical trial with investigational medical product or device concurrently while participating in this study.

If the patient has worsening clinical symptoms and manifestations of COVID-19 requiring hospital admission (or hospital level care), then the above prohibitions will not apply, because the welfare and wellbeing of the patient is of paramount importance, and the Principal Investigator's considerations regarding best medical management of the individual patient will supersede protocol restrictions.

6.2.3 Restricted Concomitant Medications during the Study

There are no other restricted concomitant medications. Monitoring and recording in the case report form of administration of all medications and specifically any potential COVID-19 disease modifying drugs is necessary, particularly given the ongoing pandemic emergency.

6.3 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of the blinded 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.

7 ASSESSMENT OF EFFICACY

7.1 Efficacy Variables

7.1.1 Primary Efficacy Variable

- Proportion of asymptomatic subjects who remain asymptomatic, ie who <u>do not develop symptomatic COVID-19</u> 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)*

  <u>OR</u>

  Experiencing at least ONE of the following respiratory signs/symptoms: new or worsening shortness of breath or difficulty breathing,

  <u>OR</u>

  Experiencing an 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)

7.1.2 Secondary Efficacy Variables

The secondary efficacy variables include:

- 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 an 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]). https://www.mdcalc.com/national-early-warning-score-news (Appendix 2).
- 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 (eg, 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).
- 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.

7.1.3 [*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].Exploratory Efficacy Variables

The exploratory efficacy variables 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 symptom severity on Day 7 and Day 29

  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)

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.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Efficacy Parameters

7.2.1 Observations and Measurements

Before any study-specific screening/baseline procedures are performed, and after completely understanding the nature of the clinical trial, informed consent must be obtained. This means that the potential subject, provides oral or written informed consent prior to initiation of any study procedures.

The consent will be provided orally. This will be recorded in the medical history with the following paragraph "I have explained to the patient the characteristics and objectives of the study, its risks and potential benefits. I have been able to answer their questions and I confirm that this patient has given oral informed consent".

Subsequently, and when possible, the subject's written informed consent will be obtained (the approved information sheet by the Ethics Committee (EC) or IRB approved version, which will be signed by the investigator and the subject).

The procedure for obtaining the initial oral informed consent does not require the presence of a witness or the physical use of the information sheet (this prevents the investigator from having to double-record the act of oral consent [medical records and information sheet], minimizing infection risk).

The following is a description of the procedures/assessments to take place at each study visit. See the Schedules of Study Procedures in Appendix 1.

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.

Please note: Whilst at home, subjects are to record SpO2 using a pulse oximeter (self-monitoring at home daily) from Day 1 when they receive their pulse oximeter through the Healthcare Provider Visit on Day 14. Likewise, subjects are to measure and record body temperature (non-axillary) and whether any antipyretic was taken on each day (ie, self-monitoring at home daily) throughout this same period.

7.2.2 Screening/Baseline and Randomized Treatment (Day 1)

All required screening and baseline (pre-IP Day 1) procedures/assessments will be performed prior to administration of the blinded IP.

Briefly the following will occur: 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.

Detailed Assessments include the following:

- Informed consent
- Inclusion/exclusion criteria
- Record demography (age [year of birth], age at screening [years], gender [if female, fertility status], race, and ethnicity), disease characteristics (date of exposure, date of onset in terms of date of first potential contact with virus and date of PCR [RT-PCR], or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19)
- Ordinal Scale assessment
- NEWS (Appendix 2)
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Measure Body Weight and Height. Calculate Body Mass Index (BMI)
- Record result of historical SARS-CoV-2 PCR (qualitative RT-PCR) or other commercial or public health assay approved by regulatory authorities as a diagnostic test for COVID-19 in any specimen ≤ 5days prior to Screening (eligibility criterion)
- Record oxygen saturation
- Medical History
- Record presence or absence of any of the following specific conditions which may increase risk of severe COVID-19 disease: Cancer; Chronic kidney disease; COPD (chronic obstructive pulmonary disease); 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/m2) or higher; Diabetes mellitus

- Respiratory sample for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab)
- Sample for quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 by enzyme linked immunosorbent assay (ELISA), indirect fluorescent antibody (IFA), or another assay methodology (store *serum* samples frozen at -70°C for later analysis at an external lab)
- Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)
- Hematology: absolute neutrophil & lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)
- Sample for IL-6, interferon γ, and possibly autoantibodies against type 1 interferons. Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.
- 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).
- Pregnancy test for females of child-bearing potential (human chorionic gonadotropin [hCG] based assay [urine matrix also valid])
- Record SAEs and TEAEs
- Record concomitant medications
- Provide subjects with pulse oximeter for home use and SpO_2 monitoring on room air (train subjects in use of pulse oximeter).
    - Please note: Whilst at home, subjects are to record SpO2 using a pulse oximeter (self-monitoring at home daily) from Day 1 when they receive their pulse oximeter through the Healthcare Provider Visit on Day 14. Likewise, subjects are to measure and record body temperature (non-axillary) and whether any antipyretic was taken on each day (ie, self-monitoring at home daily) throughout this same period.

After all Screen/Baseline assessments are complete subjects may be randomized.

Subjects randomized to one of the two active treatment arms will receive a blinded single dose of C19-IG 20% (either 1 gram or 2 grams based on randomized treatment assignment) on Screen/Baseline and Randomized Treatment visit (Day 1) if eligibility criteria are met, and all pre-IP assessments are performed.

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 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%).

7.2.3 Day 3 Healthcare Provider Visit

Assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Surveillance for COVID-19 symptoms (detailed checklist) including: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record any Medically Attended Visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting, specifying type (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)
- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates
- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Respiratory sample for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab)
- Record SAEs and TEAEs
- Record concomitant medications

7.2.4 Day 5 Phone Check Surveillance for COVID-19 Symptoms/Worsening

Assessments include the following:

- Subjects record SpO_2 at home using pulse oximeter
- Subjects record body temperature (non-axillary) with a thermometer and record whether any antipyretic was taken
- Medically trained site personnel contact subject via phone and perform Phone Check Surveillance for COVID-19 symptoms (detailed checklist) including: fever, cough, shortness of breath, fatigue, myalgia etc.
- Medically trained site personnel contact subject via phone and record as part of Phone Check: (a) subject's SpO_2 measurement on room air from pulse oximeter, (b) the subject's measured temperature obtained with a thermometer (specifying route), (c) whether (or not) an antipyretic was taken (type, dose, frequency) specifically for fever.
- Medically trained site personnel contact subject via phone and record as part of Phone Check any Medically Attended Visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting, specifying type (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)
- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates
- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Record SAEs and TEAEs
- Record concomitant medications

7.2.5 Day 7 Healthcare Provider Visit

Assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Surveillance for COVID-19 symptoms (detailed checklist) including: fever, cough, shortness of breath, fatigue, myalgia etc.

- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record any Medically Attended Visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting, specifying type (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)
- Overall assessment of COVID-19 symptom severity 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)
  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
- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates
- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Respiratory sample for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab)
- Sample for quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 by ELISA, IFA, or another assay methodology (store serum samples frozen at -70°C for later analysis at an external lab)
- Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)
- Hematology: absolute neutrophil & lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)

- Sample for IL-6, interferon γ, and possibly autoantibodies against type 1 interferons. Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.
- 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).
- Record SAEs and TEAEs
- Record concomitant medications

7.2.6 Day 9 and Day 11 Phone Check Surveillance for COVID-19 Symptoms/Worsening

Assessments include the following:

- Subjects record SpO_2 at home using pulse oximeter
- Subjects record body temperature (non-axillary) with a thermometer and record whether any antipyretic was taken
- Medically trained site personnel contact subject via phone and perform Phone Check Surveillance for COVID-19 symptoms (detailed checklist) including: fever, cough, shortness of breath, fatigue, myalgia etc.
- Medically trained site personnel contact subject via phone and record as part of Phone Check: (a) subject's SpO_2 measurement on room air from pulse oximeter, (b) the subject's measured temperature obtained with a thermometer (specifying route), (c) whether (or not) an antipyretic was taken (type, dose, frequency) specifically for fever.
- Medically trained site personnel contact subject via phone and record as part of Phone Check any Medically Attended Visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting, specifying type (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)
- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates
- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Record SAEs and TEAEs
- Record concomitant medications

7.2.7 Day 14±1 day Healthcare Provider Visit

Assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Surveillance for COVID-19 symptoms (detailed checklist) including: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record any Medically Attended Visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting, specifying type (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)
- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates
- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Respiratory sample for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab)
- Sample for quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 by ELISA, IFA, or another assay methodology (store serum samples frozen at -70°C for later analysis at an external lab)
- Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)
- Hematology: absolute neutrophil & lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)
- Sample for IL-6, interferon γ, and possibly autoantibodies against type 1 interferons. Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.
- 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).

- Record SAEs and TEAEs
- Record concomitant medications

7.2.8 Day 29±1 day Final Healthcare Provider Visit

Assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Surveillance for COVID-19 symptoms (detailed checklist) including: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record any Medically Attended Visit(s) for management/treatment of COVID-19 (other than routine study-directed visits) in any setting, specifying type (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)
- Overall assessment of COVID-19 symptom severity 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)
  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.

- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates

- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Respiratory sample for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) (obtained via nasopharyngeal swab)
- Record SAEs and TEAEs
- Record concomitant medications

7.2.9 Day 60±2 days Final Phone Check

Assessments include the following in order to ascertain the final outcomes for participating subjects:

- If subject requires supplemental oxygen post randomization: Record any supplemental oxygen administration (type, %, flow start/end date/time)
- If subject requires hospital admission post randomization: Record hospital admission and discharge dates
- If subject requires ICU admission post randomization: Record ICU admission and discharge dates
- If subject requires invasive mechanical ventilation post randomization: Record details of invasive mechanical ventilation parameters (start/end date/time)
- Record SAEs and TEAEs
- Record concomitant medications

7.2.10 Description of Laboratory Tests and Procedures

Table 7-1 provides a summary of the laboratory tests conducted for this study.

Table 7-1 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel[a]	Description	Location
Hematology	Absolute lymphocyte and neutrophil count; Basic hematology: Hemoglobin, hematocrit, platelet count, white blood cell (WBC) count with differential	Central
Chemistry	Creatinine, albumin, alanine aminotransferase (ALT), total bilirubin, lactate dehydrogenase (LDH)	Central
Markers of inflammation	C-reactive protein (CRP), D-dimer, ferritin	Central
Pregnancy test	Pregnancy test (hCG-based assay for women of childbearing potential [urine matrix is also valid])	Local
Specialty biomarkers	*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).	Central
Quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (RT-PCR)	Quantitative NAT or PCR (real-time RT-PCR) in respiratory samples (obtained via nasopharyngeal swab)	Central
Quantitative measurement of IgM and IgG antibodies to SARS-CoV-2	Quantitative IgM and IgG antibody levels by ELISA, IFA, or other assay methodology (store serum samples frozen at -70°C for later analysis at an external lab)	Central
Sample for possible additional quantitative neutralizing antibody versus SARS-CoV-2	Sample reserved for neutralizing antibody testing if such testing becomes feasible (store serum samples frozen at -70°C for later analysis at an external lab)	Central

8 ASSESSMENT OF SAFETY

8.1 Safety Parameters

The safety and tolerability of C19-IG 20% in subjects with COVID-19 will be evaluated in this study. Safety variables will include:

- Cumulative incidence of treatment-emergent SAEs and potentially related SAEs through Day 60 Phone Check
- Cumulative incidence of Grade 3-5 TEAEs and potentially related severe TEAEs through Day 29 as defined in the CTCAE, US Department of Health and Human Services, NIH, and 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

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.

8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The Schedule of Study Procedures is located in Appendix 1.

TEAEs will be recorded in source documents and on Grifols form for recording of TEAEs.

8.3 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Event and Intercurrent Illnesses

8.3.1 Warnings/Precautions

C19-IG 20% should not be administered to patients with known (documented) history of serious anaphylactic reaction to blood, any blood-derived plasma product or commercial immunoglobulin, or with known selective IgA deficiency with anti-IgA antibodies.

Because IGSC 20% is a biological product, it may carry a risk of transmitting infectious agents (eg, viruses and, theoretically, the vCJD and CJD agents). The risk that C19-IG 20% can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and by the inclusion of steps in the manufacturing process with the demonstrated capacity to inactivate and/or remove pathogenic agents. Despite these measures, a risk of transmitting infectious agents cannot be entirely ruled out.

C19-IG 20% must only be administered as directed in this protocol. C19-IG 20% CANNOT be administered intravenously.

Further details are available in the Investigator's Brochure.

8.3.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs particularly in terms of their seriousness, severity, and causal relationship to the IP.

8.3.3 Adverse Event Definitions

8.3.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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.

8.3.3.2 Suspected Adverse Drug Reactions/Adverse Reactions

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs (ie, potentially drug related AEs). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility.

In the framework of this study, a suspected ADR for which there is a reason to conclude that the drug caused the event will be labeled as an AR; thus, ARs are a subset of suspected ADRs.

8.3.4 Assessment of Causality of Adverse Event

The investigator is required to provide a causality assessment for each AE reported to the sponsor. The assessment of the causal relationship of an AE to the administration of blinded IP must be a clinical decision based on all available information at the time of the completion of the CRF and/or SAE Report Form. The sponsor will consider the investigator's causality assessment and also provide its own assessment.

Causal relationship to the blinded IP will be established according to medical judgment on whether there is a **reasonable possibility of a causal relationship between the AE and the IP administration.**

The investigator must determine and classify the AE causality according to the following categories:

Unrelated/Not related: there is not a reasonable possibility of causal relationship between the AE and the IP.

Possibly related: there is evidence to suggest a causal relationship between the IP and the AE.

Definitely related: there is a reason to conclude that the IP caused the AE.

Criteria to assess the causal relationship should take into account of the following conditions: 1) a plausible temporal sequence from the IP administration to the AE onset; 2) whether the event follows a known response pattern to the suspected treatment; 3) whether the AE could be reasonably explained by the subject's clinical state, comorbidities, or concomitant medications, as well as 4) the occurrence of improvement on stopping/reducing the treatment

(positive dechallenge) and/or reappearance of the event on repeated exposure (positive rechallenge).

For expedited safety reporting purposes, AEs assessed as either "definitely related" or "possibly related" will be considered POTENTIALLY RELATED or just RELATED.

Any AE reported prior to the first administration of the IP will be considered a non-treatment-emergent AEs and causal relationship will always be "Unrelated/Not related."

8.3.5 Severity of Adverse Event or Suspected Adverse Drug Reaction

Adverse events and suspected ADRs (ie, potentially drug related AEs) will be classified depending on their severity according to the following definitions:

Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.

Moderate: an AE that interferes with the subject's normal activities.

Severe: an AE that prevents the subject from performing their normal activities.
This category is further subdivided into Grade 3-5 AEs defined according to CTCAE criteria, US Department of Health and Human Services, NIH, and NCI.

Adverse events and suspected ADR severity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate or severe but not necessarily serious in all these cases.

The investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account current criteria included in this section.

8.3.6 Expectedness of Adverse Event or Suspected Adverse Drug Reaction (Reference Safety Information)

An AE or suspected ADR (ie, potentially drug related AE) is considered "unexpected" if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information, which is the C19-IG 20% Investigator's Brochure. The expectedness shall be determined by the sponsor for any serious ADRs (potentially related SAEs) according to the reference document for expedited safety reporting purposes.

8.3.7 Seriousness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR (ie, potentially drug related AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death

- Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization*
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above).

*Hospitalization is to be considered only hospital admission (including emergency room stay) for equal or more than 24 hours. The following hospitalizations should not be reported as SAEs:

- Hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol or as part of a routine procedure followed by the center.
- Admissions not associated with an AE (eg, social hospitalization for the purpose of respite care, survey visits, or annual physicals).
- Elective or pre-planned hospitalizations for a pre-existing condition that had not worsened from baseline (eg, elective or scheduled surgery arranged prior to start of the study).

This definition permits either the sponsor or the investigator to decide whether an event is "serious". If either the sponsor or the investigator believes that the event is serious, the event must be considered "serious" and evaluated by the sponsor for expedited reporting.

8.3.8 Adverse Event Documentation

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 CRF, and SAE report 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.

It is the responsibility of the investigator to ensure that AEs are appropriately recorded.

AEs will be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded:

- The verbatim term (a diagnosis is preferred)
- Date/time of onset
- Date/time of resolution
- Severity (mild, moderate, severe [Grade 3 to Grade 5])
- Causality (unrelated, possibly related, definitely related)*
- Seriousness (yes, no)
- Action taken (with regard to IP)
- Other action (to treat the event)
- Outcome and sequel (follow-up on AE)

*Causality assessment will be made only when the AE occurs after the subject has initiated at least one infusion of the IP. An AE occurring before subject's exposure to IP will be always labeled as "unrelated".

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured.

In addition to the investigator's own description of the AE, each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For example, a laboratory test abnormality considered clinically significant, eg, causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged clinically significant in the context of the subject's medical history by the investigator, should be reported as an AE.

Each event must be described in detail along with start and stop dates, severity, relationship to IP, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

8.3.9 Reporting of Serious Adverse Events

Any SAE (see Section 8.3.7) that occurs after informed consent on Day 1 through the Day 29 (±1 day)/Final Healthcare Provider Visit and any SAE recorded at the time of the Day 60 (±2 days) Phone Check must be fully recorded in the subject's medical record, CRF and SAE Report form. SAEs must be expeditiously reported whether or not considered attributable to the IP.

Serious adverse events will be reported using the designated SAE Report Form. When the investigator becomes aware of an SAE, she/he must submit a completed, signed and dated SAE Report Form (in English) **within 24 hours** to the sponsor by email/fax. The date of this

SAE discovery by the site staff should be documented in the source documents (ie, medical records).

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow-up, and for the outcome, must also be supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the SAE Report Form. In addition, the sponsor may request additional information and/or reports.

All SAE Report Forms must be reported to Grifols via email or fax as follows:

Grifols Global Pharmacovigilance

Email: [redacted]

FAX (back-up only): [redacted] (International)

Pharmacovigilance in Sant Cugat Spain FAX number: [redacted]

When required, and according to local law and regulations, SAEs must be reported to the IRB/EC and regulatory authorities. Copies of the investigator's reports must be sent to the sponsor.

8.4 Type and Duration of the Follow-Up of Subjects after Adverse Events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected, and the investigator decides that no further follow-up is necessary.

9 STATISTICS

9.1 Statistical Methods

Descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data. All statistical tests will be 2-sided at a significance level of 0.05.

An interim futility analysis will be conducted to assess whether the trial will be terminated due to lack of efficacy (futility) in the December 2021 timeframe based on all available data assessable for the primary endpoint and key secondary efficacy endpoints.

There will be 4 analysis populations in this study; 3 populations for efficacy assessments and 1 population for safety evaluation.

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

The modified intention 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 population is defined as subjects who receive at least any amount of blinded C19-IG 20%/Placebo. Safety analyses will be based on the Safety population.

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 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). Primary efficacy endpoint of proportion of asymptomatic subjects who remain asymptomatic will be compared between 2 doses of C19-IG 20% and Placebo by Fisher's exact test or Chi-square test. Sensitivity analysis stratified by age group will be performed using Cochran-Mantel-Haenszel (CMH) test. The first secondary efficacy endpoint of change in SARS-CoV-2 viral load (log_{10} copies/mL) from Baseline (Day 1) to Day 7 and to Day 14 will be analyzed by ANCOVA with treatment and randomization strata as fixed effects and baseline value as covariate. Other secondary and exploratory efficacy analyses will be analyzed by means of Kaplan-Meier survival estimates and curves and compared between treatment groups by means of the Log-rank test for time to event variables, analysis of covariance (ANCOVA) or Student's t test for normally-distributed variables or Wilcoxon rank-sum test for non-normally-distributed variables, Fisher's exact test or Chi-square test or CMH as appropriate for proportion variables.

Subgroup analysis based on the presence of comorbidities associated with increased risk of serious COVID-19 will be performed to explore the impact on the study outcomes. 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/m^2) or higher; Diabetes mellitus.

Detailed data handling and evaluation procedures will be described in the Statistical Analysis Plan (SAP).

9.2 Determination of Sample Size

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.

Assumptions for the purposes of sample size estimation in this setting are difficult.

For overall context, one may reference the mAb data for casirivimab and imdevimab (Regeneron cocktail) in support of their 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). The reduction in MAVs in patients given mAb was substantial (at least half), and in higher risk individuals this was even more pronounced, though the overall rate of MAVs was low in all arms including control (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization). Among other caveats, a different population of patients was evaluated (albeit non-hospitalized outpatients) who already had mild/moderate COVID-19 symptomatology; additionally, the endpoint was need for a higher threshold intervention (MAVs), and not maintenance of an asymptomatic state. However, this does provide a benchmark and context for subsequent sample size extrapolations.

If it is assumed that 80% of patients in the Placebo control arm will remain asymptomatic at Day 14 (42 [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 9-1). 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 9-1 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 (42, 43). 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 (44). 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.

9.3 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).

[*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]

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 outcome will be analyzed according to Section 9.1.

9.4 Criteria for Termination of the Study

The sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the principal investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) and/or ethics committee(ies) when required.

9.5 Procedure for Accounting for Missing, Unused, and Spurious Data

Handling of missing, unused and spurious data will be described in the SAP. All available efficacy and safety data will be included in data listings.

9.6 Reporting Deviations from the Statistical Analysis Plan

The detailed statistical analysis methodologies will be documented in the SAP. If there are any deviations from the originally planned analyses in the SAP, they will be fully described and justified in the protocol amendment(s) and/or final Clinical Study Report.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data will be recorded and kept current in the medical notes, and in the CRF by the study site personnel directly responsible for the information. Grifols personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the investigator's source documentation in order to verify the data recorded for consistency and to verify adherence to the protocol, and the completeness, consistency, and accuracy of data entered. "Source documentation" includes individual subject files, separate from the study forms, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, IP logs, and other notes as appropriate. The investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved. If access to source documentation is restricted due to COVID-19 emergency, source data verification will occur at the earliest practicable time when the monitor can have safe and direct access to the documentation. No remote source data verification will be carried out.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with ICH GCP guidelines. Each center will be visited by a monitor (or evaluated

by remote monitoring) to ensure compliance with the study protocol, ICH GCP and legal aspects according to the clinical monitoring plan. If access to the study center is restricted due to COVID-19 emergency, only remote monitoring will occur until restrictions are lifted. On-site visits will occur as soon as it is possible to safely access the site and have direct access to the documentation. No remote source data verification will be carried out.

Representatives of regulatory authorities or of Grifols may conduct audits or inspections of the investigator study site. If the investigator is notified of an audit or inspection by a regulatory authority, the investigator agrees to notify the Grifols Representative (eg, Clinical Assessment Monitor/Medical Monitor, Program Manager, Program Leader) immediately. The investigator agrees to provide to representatives of a Regulatory Agency or Grifols access to records, facilities, and personnel for the effective conduct of an audit or inspection.

12 ETHICS

12.1 Institutional Review Board/Ethics Committee

Documented approval from appropriate IRBs/ECs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRBs/ECs approval must be obtained and also forwarded to the sponsor. The IRBs/ECs must supply to the sponsor, upon request, a list of the IRBs/ECs members involved in the vote and a statement to confirm that the IRBs/ECs is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

12.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the sponsor representatives and/or an inspection by regulatory authority representatives at any time. The investigator must agree to the audit or inspection of study-related records by the sponsor representatives and/or regulatory authority representatives and must allow direct access to source documents to the sponsor and/or regulatory authority representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/EC/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/EC/sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

No medical waivers for protocol inclusion/exclusion criteria will be allowed by the sponsor. If there is a need for changes to the protocol inclusion/exclusion criteria is identified, the protocol will be amended to include such changes. The protocol amendment will be

submitted to the competent regulatory authority and/or IRB/EC as applicable per regulations, which allows implementation of the revised inclusion/exclusion criteria in the study.

12.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

12.4 Subject Information and Consent

Subject information and ICF will be provided to investigator sites. Prior to the beginning of the study, the investigator must have the IRB/EC written approval/favorable opinion of the ICF and any other information to be provided to subjects. The written approval of the IRB/EC together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to sponsor by the investigator site.

Informed consent must be obtained before any study specific procedure takes place and after completely understanding the nature of the clinical trial, potential subjects must give oral or written informed consent. Participation in the study and date of ICF discussion with subject should be documented appropriately in the subject's files.

The consent will be obtained orally. This will be recorded in the medical history with the following paragraph "I have explained to the patient the characteristics and objectives of the study, its risks and potential benefits. I have been able to answer their questions and I confirm that this patient has given oral informed consent".

Subsequently, and when possible, the subject's written informed consent will be obtained (the approved information sheet by the Ethics Committee will be signed by the investigator and the patient or IRB/EC approved version, which will be signed by the investigator and the patient).

The procedure for obtaining the initial oral informed consent does not require the presence of a witness or the physical use of the information sheet (this prevents the investigator from having to double-record the act of oral consent [medical records and information sheet], minimizing the risk of infection).

12.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names or other personal data or identifiers will not be supplied to the sponsor. Only the subject code number will be recorded in the study records, and if the subject's name or other personal data identifiers appear on any other document (eg, pathologist report), it must be redacted before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be

informed in writing that representatives of the sponsor, IRB/EC, or regulatory authorities may inspect their medical records and personal health information to verify the information collected, and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Handling

The study data will be recorded and kept current in the study records by the site study personnel directly responsible for the information. Entries made in the study records must be verifiable against source documents. The data in the study records will be monitored (on site or remotely) by Grifols representatives at regular intervals. Data will be reviewed for completeness and compared with the source documents at site level or data will be evaluated by remote monitoring. Remote source data verification will not be carried out. Examples of acceptable source documents include individual subject medical records, prospective information gathered on source documentation worksheets, lab reports and other diagnostics pertinent to this study which are separate from the study records. The listing of types of source documents which will be defined in the source data agreement will be filed in the trial master file.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE Report Form. The SAE Report Form must be kept in site records with a copy provided to the designated person as detailed in the study file.

13.2 Record Retention

At study completion, all study data will be transferred to Grifols according to ICH GCP guidelines, local laws, regulations, and Grifols requirements. The study file and all source data should be retained until notification is given by the sponsor for destruction.

An investigator is required by ICH GCP guidelines to retain the study files for a minimum of 25 years. If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (eg, other investigator). Grifols must be notified in writing of the person responsible for record retention and the notification will be retained in the sponsor study file and the investigator site file.

14 FINANCING AND INSURANCE

In the event of subject injury as a direct result of either administration of investigational product or any non-standard of care study procedure, sponsor will pay for the costs of treatment, provided the subject has followed the instructions given by the study doctor and

the illness or injury is not due to the natural progression of any conditions existing before the subject participated in the study. Financial compensation for such things as lost wages, disability, or discomfort due to any research-related injury is not available.

Sponsor shall maintain comprehensive general liability insurance or self-insurance in amounts adequate to cover any damage, demand, claim, loss or liability caused or incurred by sponsor, or as otherwise required by applicable laws and/or regulations.

15 PUBLICATION POLICY

Institution and the investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all appropriates sites. If such a multi-center publication is not submitted within 18 months after conclusion of the study at all sites or after Grifols confirms there will be no joint, multi-center publication, then institution and/or investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or investigator shall furnish Grifols with a copy of any proposed publication at least thirty (30) days in advance of the date of submission for publication.
- Within said thirty (30) day period, Grifols shall:
  - Review such proposed publication for Confidential Information (other than Study results) and for subject information subject to the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and other applicable privacy laws;
  - Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
  - By written notice to the investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains Confidential Information, protected subject information, or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and
  - By written request, Grifols may delay proposed publications up to sixty (60) days to allow Grifols to protect its interests in Grifols Inventions described in such publications.
- Institution and/or investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

16 REFERENCES

1. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Interim guidance. 13 March 2020 https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 19 March 2020)

2. Team NCPERE. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. China CDC Weekly. 2020;2(8):113-22.

3. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Epub 2020/02/28. doi: 10.1016/S2213-2600(20)30079-5. PubMed PMID: 32105632.

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. Epub 2020/01/28. doi: 10.1016/S0140-6736(20)30183-5. PubMed PMID:31986264.

5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective study. Lancet, 2020. doi: 1016/S0140-6736(20)30566-3.

6. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Remdesivir (GS-5734) 1 May 2020.

7. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial. Lancet 2020 doi.org/10.1016/S0140-6736(20)31022-9.

8. FDA product labeling Veklury® (remdesivir) for injection for intravenous use. Oct 2020.

9. FDA Emergency Use Authorization of Bamlanivimab Fact Sheet for Health Care Providers. Eli Lilly and Company; 13.0-BAM-0003-EUA HCP-20201211 (Updated December 2020) (https://www.fda.gov/media/143603/download). Accessed 24 December 2020.

10. FDA Emergency Use Authorization of Casirivimab and Imdevimab Fact Sheet for Health Care Providers. Regeneron (Updated December 2020) (https://www.fda.gov/media/143892/download). Accessed 24 December 2020.

11. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020; 117(17):9490-9496.

12. Liu STH, Lin H, Baine M, et al. Convalescent plasma treatment of severe COVID-19: A matched control study. medRxiv preprint. 2020 doi:https://doi.org/10.1101/2020.05.20.20102236

13. Salazar E, Christensen PA, Graviss EA, et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased Mortality. The American Journal of Pathology 2020; doi: https://doi.org/10.1016/j.ajpath.2020.08.001.

14. FDA Emergency Use Authorization for Convalescent Plasma in COVID-19 (Updated Evidence August 2020) (https://www.fda.gov/media/142386/download). Accessed 11 October 2020.

15. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. medRxiv. 2020:2020.08.12.20169359. doi: 10.1101/2020.08.12.20169359. Preprint.

16. Libster R, Perez Marc G, Wappner D, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. The New England Journal of Medicine. January 7, 2020. DOI: 10.1056/NEJMoa2033700.

17. Reed EC, Bowden RA, Dandliker PS, et al. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med 1988; 109:783.

18. Koduri PR, Kumapley R, Valladares J, et al. Chronic pure red cell aplasia caused by parvovirus B19 in acquired immunodeficiency syndrome (AIDS): use of intravenous immunoglobulin--a report of eight patients. Am J Hematol 1999; 61:16.

19. Whimbley E, Champlin RE, Englund JA, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in bone transplant recipients. Bone Marrow Transplant 1995; 16: 393.

20. Kluge T. Gamma globulin in the prevention of viral hepatitis. A study on the effect of medium size doses. Rev Int Serv Sante Amees 1963; 36 Suppl: 59.

21. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993; 329:1842.

22. MMWR Recomm Rep. Human Rabies Prevention - United States, 1999 Recommendations of the Advisory Committee on Immunization Practices (ACIP); 1990; 48(RR-1):1.

23. Grifols. GAMUNEX®-C - Immune Globulin (Human) Injection product label. US prescribing information, 2020.

24. Davey RT Jr, Fernández-Cruz E, Markowitz N, et al. INSIGHT FLU-IVIG Study Group. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. Lancet Respir Med. 2019;7(11):951-963. doi: 10.1016/S2213-2600(19)30253-X.

25. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005; 24(1):44-46.

26. Soo Y, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high dose methyl prednisolone treatment in SARS patients. Clin Microbiol Infect 2004; 10:657-658.

27. Ho J, Wu A, Lam B, et al. Pentaglobin in steroid-resistant severe acute respiratory syndrome. Int J Tuberc Lung Dis. 2004; 8:1173.

28. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLOS Medicine 3(9): e343. https://doi.org/10.1371/journal.pmed.0030343..

29. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020; doi:10.1001/jama.2020.4783.

30. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28. doi: 10.1056/NEJMoa2002032.

31. Maiztegui JI, Fernandez NJ, de Damilano AJ. Efficacy of immune plasma in treatment of Argentine hemorrhagic fever and association between treatment and a late neurological syndrome. Lancet 1979; 2 (8154), 1216–1217.

32. Hung IFN, To KKW2 Lee CK, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest. 2013 Aug;144(2):464-473. doi: 10.1378/chest.12-2907.

33. Makhoul B, Braun E, Herskovitz M, et al. Hyperimmune gammaglobulin for the treatment of West Nile virus encephalitis. Isr Med Assoc J. 2009;11(3):151-153.

34. Boyle ML, Scalchunes C. Impact of intravenous immunoglobulin (IVIG) treatment among patients with Primary Immunodeficiency diseases. Pharm Pol Law. 2008;10:133–146.

35. Ochs H, Gupta S, Kiessling P, et al, the Subcutaneous IgG Study Group. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol. 2006;26(3):265-273.

36. Wan Y, Shang J, Sun S, et al. Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. J Virol. 2020;94(5). pii: e02015-19. doi: 10.1128/JVI.02015-19.

37. Zhou G, Zhao Q. Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. International J of Biological Sciences 2020; 16(10): 1718-1723.

38. Yip MS, Leung HL, Li PH, et al. Antibody-Dependent Enhancement of Sars Coronavirus Infection and Its Role in the Pathogenesis of SARS. Hong Kong medical journal 2016;22(3 Supplement 4):25-31.

39. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19. N Engl J Med. 2020;382(19):1787-1799. doi: 10.1056/NEJMoa2001282.

40. Beigel JH, Tomashek KM, Dodd LE, et al. ACTT-1 Study Group Members. Remdesivir for the treatment of COVID-19 - Final Report. N Engl J Med. 2020:NEJMoa2007764. doi: 10.1056/NEJMoa2007764.

41. Horby P, Lim WS, Emberson JR, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. N Engl J Med. 2020: DOI: 10.1056/NEJMoa2021436.

42. Mitjà O, Corbacho□Monné M, Ubals M, et al. BCN-PEP-CoV2 Research Group. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. N Engl Med 2020; DOI: 10.1056/NEJMoa2021801.

43. To KK-WW, Tsang OT-YY, Leung W-SS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020; 20:565.

44. Mitjà O, Corbacho-Monné M, Ubals M, et al. BCN PEP-CoV-2 RESEARCH GROUP. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. Clin Infect Dis. 2020:ciaa1009. doi: 10.1093/cid/ciaa1009.

45. Emergency Use Authorization (EUA) casirivimab and imdevimab; Regeneron; November 2020; https://www.fda.gov/media/143892/download and https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization (accessed 21 Nov 2020).

17 APPENDICES

Appendix 1 Schedule of Study Procedures

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	

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									

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									

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
<u>C19-IG 20% or Placebo:</u> 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

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		

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)

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.

Appendix 2 National Early Warning Score (NEWS)

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]). To calculate you may access https://www.mdcalc.com/national-early-warning-score-news

Details are also provided below.

Formula: Addition of the selected points; points assigned below:

Criteria	Point Value
Respiratory Rate (breaths per minute)	
≤8	+3
9-11	+1
12-20	0
21-24	+2
≥25	+3
Oxygen Saturation (%)	
≤91	+3
92-93	+2
94-95	+1
≥96	0
Any Supplemental Oxygen	
Yes	+2
No	0
Temperature in °C (°F)	
≤35.0 (95)	+3
35.1-36.0 (95.1-96.8)	+1
36.1-38.0 (96.9-100.4)	0
38.1-39.0 (100.5-102.2)	+1
≥39.1 (≥102.3)	+2

Systolic BP	
≤90	+3
91-100	+2
101-110	+1
111-219	0
≥220	+3
Heart Rate (beats per minute)	
≤40	+3
41-50	+1
51-90	0
91-110	+1
111-130	+2
≥131	+3
AVPU	
A	0
V, P, or U	+3

AVPU, Alert, Voice, Pain, Unresponsive.

Interpretation;

1. A low score (NEWS 1–4) should prompt assessment by a competent registered nurse who should decide if a change to frequency of clinical monitoring or an escalation of clinical care is required.
2. A medium score (ie NEWS of 5–6 or a RED score) should prompt an urgent review by a clinician skilled with competencies in the assessment of acute illness – usually a ward-based doctor or acute team nurse, who should consider whether escalation of care to a team with critical-care skills is required (ie critical care outreach team). ◦A RED score refers to an extreme variation in a single physiological parameter (i.e., a score of 3 on the NEWS chart in any one physiological parameter, colored RED to aid identification; e.g., heart rate
3. A high score (NEWS ≥7) should prompt emergency assessment by a clinical team/critical care outreach team with critical-care competencies and usually transfer of the patient to a higher dependency care area.

Evidence Appraisal

The six physiological parameters that were proposed to form the basis standardized National Early Warning Score were derived from this study. It retrospectively analyzed data from 35,585 medical admissions.

Original/Primary Reference

Research Paper Royal College of Physicians. National Early Warning Score (NEWS) Standardising the assessment of acute-illness severity in the NHS. Report of a working party. London: RCP, 2012.

Validation

Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013 Apr;84(4):465-470. doi: 10.1016/j.resuscitation.2012.12.016. Epub 2013 Jan 4.

Other References

Prytherch D, Smith GB, Schmidt PE, Featherstone PI. ViEWS – towards a national Early Warning Score for detecting adult inpatient deterioration. Resuscitation 2010;81:932–937.