Official Title:	**A Multicenter, Randomized, Open-label Parallel Group Pilot Study to Evaluate Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) Plus Standard Medical Treatment (SMT) Versus SMT Alone in Subjects With COVID-19 Requiring Admission to the Intensive Care Unit**
NCT Number:	NCT04480424
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Clinical Study Protocol

Protocol Title:	A Multicenter, Randomized, Open-label Parallel Group Pilot Study to Evaluate Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) plus Standard Medical Treatment (SMT) versus SMT alone in Subjects with COVID-19 Requiring Admission to the Intensive Care Unit
Investigational Product:	Gamunex®-C
Sponsor's Name and Address:	Grifols Therapeutics LLC 79 TW Alexander Drive Research Triangle Park, NC 27709
Study Number/Protocol Version Number:	GC2007/Version 4.0
Additional Identifier	Gamunex®-C High Dose in COVID-19
IND Number:	IND22687
Development Phase:	2
Sponsor Signatory:	[redacted] Grifols Therapeutics, LLC. email address: [redacted] Phone: [redacted] [redacted] Grifols Bioscience Industrial Group Email address: [redacted] Telephone number: [redacted] See Sponsor Signatures on the cover page of the protocol

Protocol Version History

Protocol Version	Date of Approval/Effective Date
4.0 Amendment 3 + Integrated Protocol	See Left Margin
3 Amendment 2 + Integrated Protocol	30 Oct 2020
2 Amendment 1 + Integrated Protocol	02 Jul 2020
1.0 Original	21 May 2020

Amendment 3

The protocol for GC2007 (Version 3.0, dated 30 Oct 2020) has been amended as Protocol Amendment 3, Version 4.0. See Appendix 5 for a summary of changes for Protocol Amendment 3.

PROTOCOL SYNOPSIS

Title of Study: A Multicenter, Randomized, Open-label Parallel Group Pilot Study to Evaluate Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) plus Standard Medical Treatment (SMT) versus SMT alone in Subjects with COVID-19 Requiring Admission to the Intensive Care Unit

Study to Evaluate the Safety and Efficacy of High Dose IVIG in Subjects in ICU with Coronavirus Disease (COVID-19)

Study Number: GC2007

Phase: 2

Study Objectives:

Primary Efficacy Objective

To determine if high dose Intravenous Immune Globulin (IVIG) plus Standard Medical Treatment (SMT) can reduce all-cause mortality versus SMT alone in hospitalized subjects with COVID-19 requiring admission to the intensive care unit (ICU) through Day 29.

Secondary Efficacy Objective(s)

To compare high dose IVIG plus SMT versus SMT alone with regard to clinical efficacy as assessed by clinical severity, duration of hospital and ICU stay, dependency on oxygen and ventilatory support, and clinical response criteria including National Early Warning Score (NEWS), clinical status scale, and Sequential Organ Failure Assessment Score (SOFA) through Day 29 in hospitalized subjects ill with COVID-19 requiring admission to the ICU.

Exploratory Efficacy Objectives

To evaluate the effect of high dose IVIG plus SMT versus SMT alone with regard to quantitative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and anti-SARS-CoV-2 antibodies in hospitalized subjects with COVID-19.

To evaluate whether high dose IVIG plus SMT versus SMT alone reduces the frequency of hyperinflammation based on a pre-specified biochemical definition through Day 29.

To evaluate cytokine profile changes from baseline for high dose IVIG plus SMT versus SMT alone through Day 29.

Safety Objective

To determine the safety and tolerability profile through Day 29 of high dose IVIG plus SMT versus SMT alone in hospitalized subjects with COVID-19.

Overall Study Design and Description:

This is a prospective, multi-center, randomized (1:1), open-label, pilot study of high dose IVIG plus SMT versus SMT alone in subjects with COVID-19 who are hospitalized and require ICU admission. Symptomatic subjects with positive polymerase chain reaction

(PCR; reverse transcriptase [RT]-PCR) or other FDA-approved or regulatory-authority approved diagnostic assay for SARS-CoV-2 in any specimen during the current hospital admission prior to randomization will receive SMT or SMT plus a net total dose of IVIG (Gamunex®-C [Immune Globulin (Human), 10% Caprylate/Chromatography Purified]) of 2 g/kg (body weight) administered in divided doses over 4 to 5 consecutive days at the Principal Investigator's discretion. The maximum dose will be capped at 160 g (equivalent to body weight of 80 kg).

Specifically, subjects randomized to combination high dose IVIG will receive the first IV infusion of Gamunex-C on Day 1. The total net dose of 2 g/kg body (capped at a maximum of 160 g for subjects weighing more than 80 kg) will be administered in divided doses over consecutive days. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days.

Subjects will be assessed daily while hospitalized. Discharged subjects will be evaluated on Days 15 and 29. Days 15±1 and 29±1 may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. Phone Checks will occur at Day 60 and Day 90 for vital status (living or deceased), any hospital re-admissions, or serious/non-serious adverse events after the Day 29 Final Clinic Visit. Details are provided in Appendix 1 (Schedule of Study Procedures).

The first 6 subjects randomized will be staggered with an interval of no less than 1 week between subjects. If there are no definitely related serious adverse events (SAEs) reported 1 week after the randomization of the 6th subject, competitive enrollment would ensue thereafter. If a definitely related SAE were to be reported among these 6 subjects, the Study-Independent Safety Review Committee (SISRC) would carefully review and evaluate the case and make appropriate recommendations with regard to study status.

Number of Subjects Planned:

Approximately 100 subjects will be randomized (1:1) with an interim analysis after 50 subjects (approximately 25 per group). Due to the exploratory nature of this phase 2 study, the multiplicity adjustments will not be considered; full details will be described in the statistical analysis plan. These interim evaluations are part of Sponsor safety due diligence.

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. Hospitalized male or female subjects of ≥ 18 years of age at time of Screening who are being treated in the ICU for COVID-19 for not longer than 48 hours or for whom a decision has been made that COVID-19 disease severity warrants ICU admission.

2. Has laboratory-confirmed novel coronavirus (SARS-CoV-2) infection as determined by qualitative PCR (reverse transcriptase [RT]-PCR), or other FDA-approved or regulatory-authority approved diagnostic assay for COVID-19 in any specimen during the current hospital admission prior to randomization.
3. Illness (symptoms of COVID-19 of any duration requiring ICU level care), and the following:
   a) Radiographic infiltrates by imaging (chest X-Ray, CT scan, etc.), AND
   b) Requiring mechanical ventilation and/or supplemental oxygen.

   Note: ICU level care is defined as the medical need for intensive or invasive monitoring; immediate or impending need for supportive care of the airway, breathing, or circulation; and/or stabilization of acute severe or life-threatening complications of COVID-19.
4. Any one of the following related to COVID-19: i. Ferritin > 400ng/mL, ii. LDH > 300 U/L, iii. D-Dimers > reference range, or iv. C-reactive protein (CRP) > 40 mg/L.
5. Subject provides informed consent prior to initiation of any study procedures.

Diagnosis and Main Criteria for Eligibility:

Exclusion Criteria

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

1. Clinical evidence of any significant acute or chronic disease or pathophysiologic manifestations (eg, complications of COVID-19 standard medical treatments) that, in the opinion of the investigator, may place the subject at undue medical risk.
2. The subject has had a known (documented) serious anaphylactic reaction to blood, any blood-derived or plasma product or a past history of any hypersensitivity reactions to commercial immunoglobulin.
3. A medical condition in which the infusion of additional fluid is contraindicated (e.g., decompensated congestive heart failure [New York Heart Association Class III or IV stage heart failure] or renal failure with fluid overload).
4. Shock that is unresponsive to fluid challenge and/or multiple vasopressors and accompanied by multiorgan failure considered by the Principal Investigator not able to be reversed.
5. Subjects with known (documented) thrombotic complications to polyclonal IVIG therapy in the past.
6. Subjects with current or prior myocardial infarction, stroke, deep vein thrombosis, or thromboembolic event (within the past 12 months) or who have a history of thromboembolic events of unknown etiology.
7. Subjects with limitations of therapeutic effort (e.g., 'do not resuscitate' status).

Note: If the decision is made not to apply treatments or therapeutic procedures that will provide little benefit for the suffering or agony the subject is experiencing, such a subject would not be appropriate for participation in this study and should be excluded.

8. Female subjects who are pregnant or of child-bearing potential with a positive test for pregnancy blood or urine human chorionic gonadotropin (HCG)-based assay at Screening/Baseline.
9. Subjects participating in another interventional clinical trial with investigational medical product or device.
10. Known history of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome.
11. Presence of malignancy (either new diagnosis of malignancy or known residual disease) within the past 12 months (note: exceptions for non-melanoma skin cancer and carcinoma in situ of cervix are allowed)
12. Creatinine at Screening is $\geq$ 4 mg/dL (or subject is dependent on dialysis/renal replacement therapy)
13. Known Immunoglobulin A (IgA) deficiency with anti-IgA serum antibodies
14. Uncontrolled hypertension at the time of Screening (systolic blood pressure > 200 mm Hg) or refractory severe hypotension with sustained systolic blood pressure < 90 mm Hg unresponsive to vasopressors.

Investigational Product, Dose and Mode of Administration:

Gamunex-C is a ready-to-use sterile solution of human IgG protein for IV administration. Gamunex-C is a licensed IVIG product. Gamunex-C vials may be supplied in the vial sizes of 10, 25, 50, 100, and 200 mL. In this study, administration of Gamunex-C will be via the IV route only.

Subjects randomized to combination IVIG plus SMT will receive the first IV infusion of Gamunex-C on Day 1. The total net dose of 2 g/kg body is capped to a maximum of 160 g for subjects weighing more than 80 kg. The dose of 2g/kg will be administered in divided doses over consecutive days. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days.

To calculate the dose for each infusion, multiply the weight of the subject (kg) by the dose in mg/kg. For example, a 70 kg individual dosed for 5 days at 400 mg/kg per infusion will receive 28 g per day. For Gamunex-C 10%, multiply the number of grams for the subject's infusion by 10 mL/gram to obtain the number of milliliters (mL) of Gamunex-C to be infused IV each day (in this example the amount is 280 mL daily for 5 days).

Gamunex-C should be infused using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The Gamunex-C infusion

line can be flushed with 5% dextrose in water or 0.9% sodium chloride for injection. Do Not flush with heparin.

Gamunex-C should be administered with careful monitoring of the subject for any acute reactions. Gamunex-C infusion should commence at an infusion rate of 0.5 mg/kg/minute (0.005 mL/kg/min) for approximately 30 minutes. If the infusion is well tolerated, the rate of administration may be increased to a maximum of 4 mg/kg/minute (0.04 mL/kg/minute) as follows: the rate may be increased by doubling the infusion rate after intervals of not less than 15-30 minutes, so long as the infusion remains well tolerated.

Duration of Treatment:

If randomized to combination with SMT, subjects will receive Gamunex-C starting on Day 1 and a net total dose of 2 g/kg will be administered in divided doses over 4 or 5 consecutive days according to the Principal Investigator's medical judgement; for all subjects SMT alone will be continued throughout the subject's hospitalization. Subject participation (from Screening Visit to the Final Visit) will be approximately 30 days. After the Day 29 Final Clinic Visit, Phone Checks will occur at Day 60 and Day 90 for follow-up of vital status (living or deceased), any hospital re-admissions, or serious/non-serious adverse events after the Day 29 Final Clinic Visit.

Reference Therapy, Dose and Mode of Administration:

Standard medical treatment for COVID-19

Key Study Variables:

The primary efficacy variable is all-cause mortality rate through Day 29.

The secondary efficacy variables include:

- Time to actual ICU discharge: defined as duration of ICU stay from Day 1 through Day 29
    - Additionally, time to a medical equivalence of ICU discharge will be recorded and analyzed (defined as the time point when the patient no longer requires ICU level care, i.e., not requiring invasive mechanical ventilation, or intensive monitoring such as arterial line or central line placement, administration of IV vasopressors to support blood pressure, or O2 supplementation greater than that delivered by nasal cannula)
- Duration of mechanical ventilation from Day 1 through Day 29
- Time to actual hospital discharge: defined as duration of hospitalization from Day 1 through Day 29
    - Additionally, time to a medical equivalence of hospital discharge will be recorded and analyzed (defined as the time point when the patient no longer requires supplemental oxygen and no longer requires ongoing medical care [yet may not be discharged from hospital for social or quarantine reasons])

- Duration of any oxygen use from Day 1 through Day 29
- Absolute value and mean change from baseline in the Ordinal scale Day 1 through Day 29

  The Ordinal scale is as follows:

  1) Death;

  2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

  3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;

  4) Hospitalized, requiring supplemental oxygen;

  5) Hospitalized, not requiring supplemental oxygen;

  6) Not hospitalized, limitation on activities;

  7) Not hospitalized, no limitations on activities.
- Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29
- Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS) overall and distribution by severity through Day 29 (Appendix 3)
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 5, Day 15, and Day 29 (Appendix 4)
- Assessment of Clinical Severity: Change in NEWS from baseline (Day 1 through Day 29)

  The NEWS has demonstrated an ability to discriminate subjects 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)
- Time to clinical response: NEWS ≤ 2 maintained for 24 hours, Day 1 through Day 29

The exploratory efficacy variables include:

- Change from baseline in quantitative SARS-CoV-2 viral load by nucleic acid amplification technology (NAT) or PCR (real-time RT-PCR) to Days 5, 15, and 29
- Change from baseline in quantitative anti-SARS-CoV-2 IgM and IgG antibodies to Days 5, 15, and 29
- Proportion of subjects with evidence of hyperinflammation on Day 1, Day 5, Day 15, and Day 29 defined as:
  - Lymphocyte counts <1000 cells/µL, AND
  - Two of the following 4 criteria:
    - Ferritin > 500 ng/mL,

- LDH > 300 U/L,
- D-Dimers > 1000 ng/mL (fibrinogen equivalent units [FEU]) or > 2 times upper normal limit,
- C-reactive protein (CRP) > 70 mg/L

- Change from baseline in cytokine profile (IL-1β, IL-10, IL-6, IL-8 IL-2, interferon γ, and tumor necrosis factor-α [TNF-α]) to Days 5, 15, and 29

The safety variables include:

- Cumulative incidence of treatment-emergent serious adverse events (SAEs) and potentially related SAEs through Day 90 Phone Check
- Cumulative incidence of Grade 3-5 treatment-emergent adverse events (TEAEs) and potentially related 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)
- Cumulative incidence of all TEAEs and potentially related TEAEs through Day 29

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 Gamunex-C and the TEAE.

Study Assessments and Procedures:

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

Clinical status will be evaluated for all hospitalized subjects daily with vital signs, Ordinal Scale, and NEWS at Screening/Baseline and during IVIG plus SMT or SMT alone treatment and during Follow-up. 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

All subjects will be followed daily through Day 10. After Day 10, if subjects are discharged from the hospital, evaluations at Day 15 and 29 are required. Berlin criteria for ARDS and SOFA score (Appendix 3 and Appendix 4) will be assessed on Day 1, 5, 15, and 29. Subjects remaining hospitalized will be followed daily through Day 29. Days 15±1 and 29±1 may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. If an in-person visit is unable to be conducted for Day 15 or Day 29, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications). Phone Checks will occur at Day

60 and Day 90 for vital status (living or deceased), any hospital re-admissions or serious/non-serious adverse events after the Day 29 Final Clinic Visit.

For subjects in the combination arm (IVIG plus SMT) all laboratory samples must be drawn *prior to* infusion of IVIG, if laboratory assessments are required for a day in which IVIG is being infused.

Respiratory Samples for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) will be obtained on Day 1, and subsequently on Day 4-6 (ie, Day 5± 1 day), Day 15± 1 day and Day 29 ± 1 day (obtained via nasopharyngeal swab). *The results of these samples are not necessary for continuing on study.* Similarly, *blood samples for* quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 via enzyme linked immunosorbent assay (ELISA), Indirect Fluorescent Antibody (IFA) or other assay methodology will be drawn at the same time points: Day 1, and subsequently on Day 4-6 (ie, Day 5± 1 day), Day 15± 1 day, and Day 29 ± 1 day. *The results of these samples are not necessary for continuing on study.*

Ferritin, D-dimer, CRP and Basic chemistry analytes (creatinine, albumin, alanine aminotransferase [ALT], total bilirubin, lactate dehydrogenase [LDH]) will be assessed on Day 1 and on Day 5± 1 day, Day 15± 1 day, and Day 29± 1 day. Hematology (hemoglobin, hematocrit, platelet count, absolute lymphocyte count, leukocyte count with differential) will be assessed on Day 1, on Day 5 ± 1 day, Day 15± 1 day, and Day 29± 1 day. Direct antiglobulin test (DAT) will be performed on Day 1, and on Day 4-6 (i.e., Day 5± 1 day), Day 15 ± 1 day, and Day 29 ± 1 day. All routine laboratory tests will be assessed locally at the hospital/site's laboratory. A cytokine panel will be performed at the same time points. Cytokine panel includes IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and tumor necrosis factor- α (TNF-α). Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.

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 analysis will be conducted after 50 subjects (25 per group) for safety variables. Due to the exploratory nature of this phase 2 study, the multiplicity adjustments will not be considered; full details will be described in the statistical analysis plan. This interim evaluation simply represents Sponsor safety due diligence

Grifols will analyze use of COVID-19 specific, potentially disease modifying treatments between arms and this will be fully detailed in the SAP since medical understanding of COVID-19 interventions is rapidly evolving and for ethical reasons (apart from participation in another clinical trial) there are no restrictions on what are perceived to be potentially life-saving therapies.

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 pilot study is commensurate with other Phase 2 investigations ongoing during the COVID-19 pandemic. Approximately 100 subjects are allowed to be randomized as part of a humanitarian effort against COVID-19.

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
ALI	acute lung injury
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
ARDS	acute respiratory disease syndrome
ARMA	Acute Respiratory Management of ARDS (database)
AMS	aseptic meningitis syndrome
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CoVs	coronaviruses
COVID-19	Coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DVT	deep vein thrombosis
EDTA	ethylenediaminetetraacetic acid
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
EUA	Emergency Use Authorization
FcR	Fc receptors
FDA	US Food and Drug Administration
FEU	fibrinogen equivalent units
FiO_2	inspired oxygen concentration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCoVs	highly pathogenic CoVs
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
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
IgG	immunoglobulin G
IGIV-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IL-1β	interleukin-1β

IL-6	interleukin-6
IP	investigational product
IQR	interquartile range
IRB/EC	Institutional Review Board/Ethics Committee
ITP	primary immune thrombocytopenia
ITT	intention to treat
IV	intravenous
IVIG	intravenous immune globulin
MABP	mean arterial blood pressure
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MMN	multifocal motor neuropathy
NAT	nucleic acid amplification technology
NCI	National Cancer Institute
NEWS	National Early Warning Score
NF-κB	Nuclear Factor-kappaB
NIH	National Institutes of Health
p38	mitogen-activated protein kinase
PCR	polymerase chain reaction
PE	pulmonary embolism
PEEP	positive end-expiratory pressure
PI	primary immunodeficiency
PICs	pro-inflammatory cytokines
PP	Per Protocol
RR	respiratory rate
RT-PCR	reverse transcriptase PCR
SAE	serious adverse event
SaO_2	arterial oxygen saturation
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SISRC	Study-Independent Safety Review Committee
SMT	standard medical treatment
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral oxygen saturation by pulse oximetry
T	Temperature
TEAE	treatment-emergent adverse event
TGF-β1	transforming growth factor β 1
Th17	T helper 17 cells
TNF-α	tumor necrosis factor-α
TRALI	transfusion-related acute lung injury

US	United States
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 (WHO Interim guidance 13 March 2020). Genetic sequencing of the virus suggests that SARS-CoV-2 is a betacoronavirus closely linked to the severe acute respiratory syndrome (SARS) virus (Team NCPERE 2020). 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 (Team NCPERE 2020). 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 (Yang et al., 2020). 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 (Huang et al., 2020; Zhou et al., 2020).

Currently there are no approved treatments for COVID-19 and no approved prophylactic, post-exposure, or therapeutic treatment modalities exist for SARS-CoV-2. While both remdesivir and chloroquine phosphate/hydroxychloroquine sulfate have emergency use authorizations (EUA) before licensure, efficacy remains to be further defined. Initial results for remdesivir are most 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 ($p=0.06$) (Fact Sheet Remdesivir EUA 1 May 2020). 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%) (Wang, Zhang et al., 2020).

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

with COVID-19 requiring intensive care unit (ICU) hospital admission, and it is considered that high-dose intravenous immune globulin (IVIG) may provide therapeutic benefit via its immunomodulatory properties in this critical situation when given in addition to standard medical treatment (SMT).

With regard to the current COVID-19 epidemic in China, there is a study of high dose IVIG based on the idea of leveraging the potential immunomodulatory effect of immunoglobulin (NCT04261426). This trial is utilizing high doses of conventional commercial IVIG product for its immunomodulatory properties (Lin et al., 2020). In the previous SARS epidemic (2003), based on retrospective subgroup analysis, high dose IVIG 400 mg/kg for 3 days for immunomodulation purposes combined with intravenous pulsed methylprednisolone appeared to show some benefit in critically ill patients with ARDS (Lew et al., 2003). Further data reported by Wang and colleagues suggested a beneficial effect in a subgroup of the 76 patients in their series hospitalized with SARS pneumonia; the dosage of IVIG was 1 g/kg/day for 2 days (Wang et al., 2004). Additionally, during the current COVID-19 epidemic in China there are small case series which demonstrate satisfactory recovery in critically ill individuals receiving high dose conventional IVIG at doses of ~2 g/kg body weight in divided doses over 5 days; although the series was small (3 patients). The inflection point in recovery was temporally correlated with IVIG administration (Cao et al., 2020).

In Israel, Makhoul and colleagues also employed a dose of 400 mg/kg for 5 days (net total dose 2 g/kg) given to a small group of 8 patients with worsening West Nile encephalopathy with apparent benefit; the IVIG used contained high West Nile virus antibodies. The study was uncontrolled, and the net cumulative dose was high (2 g/kg) (Makhoul et al., 2009).

The IVIG doses described in these studies of viral pathogens are high, and similar to those used for myasthenia gravis exacerbations, Kawasaki disease, Guillain-Barré syndrome, and as the initial loading dose for chronic inflammatory demyelinating polyneuropathy. The immunomodulatory effects of IVIG are multifactorial and incompletely understood. The mechanism by which IVIG suppresses harmful inflammation has not been definitively identified. It is believed to involve blocking Fc receptors, which are associated with tolerance to self and severity of the inflammatory state. This strategy has been used in the treatment of viral-induced cytokine storm and was confirmed to have improved the outcome in infections, such as SARS and the 2009 H1N1 pandemic influenza (Liu et al., 2016).

The severity of COVID-19 in vulnerable individuals in the setting of the ongoing pandemic warrants investigation regarding whether high dose IVIG (in the present study, Gamunex®-C [Immune Globulin (Human), 10% Caprylate/Chromatography Purified]), may provide therapeutic benefit and impact illness severity and mortality. While the majority of infected patients will recover, a significant number require hospitalization; and morbidity and sequelae can be severe (Guan et al., 2020).

In addition to the information provided here and below, please also refer to the full Gamunex-C Prescribing Information, 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 Gamunex-C (Immune Globulin [Human], 10% Caprylate/Chromatography Purified [IGIV-C]), a preparation of purified human immunoglobulin manufactured by Grifols Therapeutics LLC. It is licensed in numerous countries under different trade names for intravenous (IV) administration in the treatment of a number of immune system disorders (e.g., primary immunodeficiency [PI], idiopathic thrombocytopenic purpura [ITP] and chronic inflammatory demyelinating polyneuropathy [CIDP]). In the United States the product is known as Gamunex-C.

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

Table 2-1 Investigational products

Investigational Products	
Test: **Gamunex-C**	Vials containing sterile liquid preparation of Intravenous Immune Globulin (human) 10% (1 gram per 10 mL; 100 mg/mL) in single use vials

Gamunex-C will be the investigational product being tested in combination with SMT versus SMT alone in subjects with COVID-19.

Gamunex-C is a sterile, preservative free, and pyrogen-free preparation with a total protein content of 9.0 to 11.0%, a glycine content of 0.16 to 0.24 M and a pH of 4.0 to 4.5. The osmolality is close to the physiologic range with an average of 258 mOsmol/kg. The molecular composition of IGIV-C is demonstrated via electrophoresis to be predominantly gamma globulin, and predominantly monomeric IgG through testing of its molecular weight distribution by size exclusion chromatography.

Gamunex-C is approved by United States (US) Food and Drug Administration (FDA) and in the European Economic Area (EEA) countries and is available as commercial product.

Gamunex-C is a highly purified, ready-to-use unmodified human IgG solution for infusion prepared from human plasma pools. The authorized indications of Gamunex-C depend on the country. However, it can be considered that, in general, the product is indicated for replacement therapy in PI syndromes, ITP, and CIDP. In addition, the product is also indicated for immunomodulation in certain geographies for Guillain-Barré syndrome and Kawasaki disease.

2.2 Relevant Findings from Nonclinical and Clinical Trials

In toxicology studies there were no IGIV-C related treatment effects following single dose (8,000 mg/kg) or repeated dosing (2,000 mg/kg/day for 5 consecutive days) in rodents or guinea pigs, respectively. Therefore, a sufficient margin of safety has been demonstrated for acute and repeated dosing of IGIV-C. The maximum tolerated single dose was determined for both male and female mice and rats and was >8,000 mg/kg.

Gamunex-C is immediately and completely bioavailable in the recipient's circulation after IV administration. Clinical evaluations of the efficacy of IGIV-C were conducted between 1998 and 2000 in indications for IgG replacement therapy and high dose immunomodulatory therapy, PI and ITP, respectively. A clinical study was conducted between 2004 and 2006 to evaluate the effectiveness of IGIV-C in treating CIDP. Clinical studies evaluating efficacy of IGIV-C in myasthenia gravis have also been conducted, as well as a retrospective study conducted between 2014 and 2015 to assess the effectiveness of IGIV-C in pediatric and adult subjects with Guillain-Barré syndrome.

IGIV-C is approved in 57 countries worldwide under different trade names (eg, GAMUNEX, GAMUNEX-C, IGIVnex). IGIV-C was initially approved in 2003 in the United States and its safety profile is well established with a total number of more than 8,159,628 estimated infusions.

Adverse reactions (ARs) associated with IVIG administration such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain may occur occasionally. Rarely IVIG may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the subject has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis, isolated cases of reversible hemolytic anemia/hemolysis, and rare cases of transient cutaneous reactions have been observed with IVIG. Increase in serum creatinine level and/or acute renal failure have also been observed. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism (PE), and deep vein thrombosis (DVT) have been reported (Katz et al., 2007).

Important nonclinical and clinical data related to efficacy and safety of Gamunex-C is summarized in the Gamunex-C prescribing information and IB.

2.3 Known and Potential Risks and Benefits to Human Subjects

2.3.1 Benefits

Besides its role in immunodeficiency, IVIG products may trigger immunomodulatory and anti-inflammatory effects in different diseases. The mechanisms involved in the immunomodulatory effects of the IVIG infusions are dependent upon the interaction between the Fc portion of infused IgG with the Fcγ receptors on the surface of target cells (macrophages, B cells, natural killer cells, plasma cells, eosinophils, neutrophils and platelets) or with the variable regions of antibodies in the preparation (Fernandez-Cruz et al., 2009). Immunoglobulins can also modulate the inflammatory response by preventing

complement-mediated tissue damage or the deposition of immune complexes containing C3b (Murakami et al., 2012), or by modulating the induction of anti-inflammatory cytokines and cytokine antagonists such as interleukin (IL)-1b, IL-1 receptor antagonist and TNF-α (Fernández-Cruz et al. 2009 and references therein).

To date, a number of possible mechanisms for the immunomodulatory and anti-inflammatory effects of IVIG therapy have been described (Kazatchkine and Kaveri, 2001; Wu et al., 2006), including anti-complement effects (Farbu et al., 2007), anti-idiotypic neutralization of pathogenic autoantibodies (Fernandez-Cruz et al., 2009), immune regulation via an inhibitory Fc receptor (Jordan et al., 2009; Ballow et al., 2011), enhancement of regulatory T cells (Andrew et al., 2011) and inhibition of T helper 17 cells (Th17) differentiation (Akio Matsuda et al., 2012). Thus, IVIG can mediate a wide variety of biological and immunomodulatory effects via various types of blood cells (Akio Matsuda et al., 2012). As such, high dose IVIG may provide therapeutic benefit in the current COVID-19 pandemic.

Fu and colleagues 2020 indicated that potential therapeutic tools to reduce SARS-CoV-2-induced inflammatory responses include various methods to block Fc receptors (FcR) activation. In the absence of a proven clinical FcR blocker, the use of IVIG to block FcR activation may be a viable option for the urgent treatment of pulmonary inflammation to prevent severe lung injury (Fu et al., 2020).

Given the previous experience with high dose conventional IVIG in the previous SARS epidemic reported by Lew and colleagues, Wang and colleagues, and current case series from the COVID-19 epidemic, it appears that high dose IVIG may be potentially beneficial (Lew et al., 2003; Wang et al., 2004; Cao et al., 2020). This may possibly be due to immunomodulatory effects, best evidenced clinically at higher doses, such as those employed for ITP, CIDP, and Guillain-Barré syndrome.

Decreasing morbidity and mortality remain the theoretical benefit and aim of administration of high dose IVIG in patients with COVID-19. In this study, therapeutically high doses of IVIG will be administered to those patients hospitalized with COVID-19 requiring ICU admission in an effort to improve outcomes by leveraging the immunomodulatory effects of IVIG described above. The Gamunex-C dose is commensurate with the labeled indications for Gamunex-C (eg, 2 g/kg dose for ITP). The efficacy of this approach in COVID-19 cannot be inferred from historical precedents without carrying out a controlled clinical trial. Although retrospective series, such as the cohort reported by Shao and colleagues of 305 patients with COVID-19 suggest benefit in critical patients (Shao et al., 2020).

2.3.2 Risks

Full details regarding tolerability and safety of Gamunex-C are provided in the prescribing information and the IB. The main risks of Gamunex-C are summarized below:

- Gamunex-C is contraindicated in subjects with a known history of anaphylactic or severe systemic reaction to human immunoglobulins, especially in subjects with antibodies against IgA.

- Certain adverse events may be related to the rate of infusion. Subjects must be closely monitored and carefully observed for any symptoms throughout the infusion period.
- There is clinical evidence of an association between IVIG administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), PE, and DVT that is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk subjects. In subjects at risk for thromboembolic ARs, IVIG products should be administered at the minimum rate of infusion and dose practicable.
- Cases of acute renal failure have been reported in subjects receiving IVIG therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products, or age over 65. In subjects at risk for acute renal failure, IVIG products should be administered at the minimum rate of infusion and dose practicable.
- Aseptic meningitis syndrome (AMS) has been reported to occur in association with IVIG treatment. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.
- Gamunex-C may contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs test) and, rarely, hemolysis. Hemolytic anemia can develop subsequent to IVIG therapy due to enhanced red blood cells sequestration. IVIG recipients should be monitored for clinical signs and symptoms of hemolysis. If these are present after IVIG infusion, perform appropriate confirmatory laboratory testing.
- Transfusion-related acute lung injury has been reported with IVIG products as a class effect (non-cardiogenic pulmonary edema).

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 (Wan et al., 2020). It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for MERS (Wan et al., 2020).

Structural and functional analysis of the SARS-CoV-2 shows that the SARS-CoV-2 S protein binds the Angiotensin-converting enzyme 2 (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 (Zhou and Zhao, 2020).

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) (Wan et al., 2020). 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 (Wan et al., 2020). Thus, sub neutralizing antibodies (or non-neutralizing antibodies in some cases) are responsible for ADE of these viruses (Wan et al., 2020).

Additionally, Yip and colleagues discuss experiments which suggest for SARS that in vitro potential ADE resulted in abortive infection in vitro (Yip et al. 2016). 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 (Yip et al. 2016). 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 (Yip et al. 2016).

While the possibility of ADE from administration of high dose conventional IVIG cannot be entirely ruled out. The available data from the earlier SARS epidemic, and currently early case series of COVID-19 from China suggest that the over-riding effect of high dose IVIG (2 g/kg) is immunomodulatory and salutary in cases where the immune inflammatory response may be producing harmful collateral damage. Therefore, the premise of the current study is that high dose IVIG (2 g/kg total in divided doses) may produce therapeutic benefit for serious COVID-19 requiring hospitalization and ICU admission; the aim is to intervene and modulate the inflammatory cascade in order to reduce mortality.

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 randomized to the combination arm of IVIG plus standard medical treatment, will receive IV Gamunex-C. Gamunex-C will be administered intravenously (peripheral or central vein) through a separate infusion line. It is recommended that Gamunex-C infusion should commence at an infusion rate of 0.5 mg/kg/minute (0.005 mL/kg/min) for approximately 30 minutes. If the infusion is well tolerated, the rate of administration may be increased to a maximum of 4 mg/kg/minute (0.04 mL/kg/minute) as follows: the rate may be increased by doubling the infusion rate after intervals of not less than 15-30 minutes, so long as the infusion remains well tolerated. For subjects judged to be at risk for renal dysfunction

or thrombosis, Gamunex-C infusion should be at the minimum infusion rate practicable. If adverse events (AEs) occur, the rate may be reduced or the infusion interrupted until symptoms subside. Lack of tolerance at any given rate must be recorded as an AE at that rate. The infusion may then be resumed at the rate that is tolerable for the subject.

The total net dose of 2 g/kg body is capped to a maximum of 160 g for subjects weighing more than 80 kg. The dose of 2g/kg will be administered in divided doses over consecutive days. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days.

To calculate the dose for each infusion, multiply the weight of the subject (kg) by the dose in mg/kg. For example, a 70 kg individual dosed for 5 days at 400 mg/kg per infusion will receive 28 g per day. For Gamunex-C 10%, multiply the number of grams for the subject's infusion by 10 mL/gram to obtain the number of milliliters (mL) of Gamunex-C to be infused IV each day (in this example the amount is 280 mL daily for 5 days).

Gamunex-C should be infused using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The Gamunex-C infusion line can be flushed with 5% dextrose in water or 0.9% sodium chloride for injection. Do Not flush with heparin.

Subjects in the SMT alone arm will receive all standard of care interventions required.

2.4.2 Justification for Selection of Doses/Timing of Investigational Product

The dose of Gamunex-C selected for this study is commensurate with that employed to abrogate autoimmune phenomena and attenuate symptoms of neurological disorders. Gamunex-C dosages for various medical conditions for which high doses are prescribed are summarized in Table 2-2 across the 57 countries wherein IGIV-C is approved.

Table 2-2 Immunomodulatory Doses of IGIV-C Worldwide (Development Safety Update Report 2019)

Indication	Administration
*Primary immune thrombocytopenia (ITP)	Total dose of 2 g/kg divided in 2 doses of 1 g/kg for 2 consecutive days or into 5 doses (400 mg/kg) for 5 consecutive days
Guillain Barré syndrome	400 mg/kg on 3 to 7 consecutive days
Kawasaki disease	1.6- 2 g/kg as a single infusion or divided doses over 2 to 5 days
*Chronic inflammatory demyelinating polyneuropathy (CIDP)	Loading dose: 2 g/kg in divided doses over 2 to 4 days Maintenance dose: 1 g/kg over 1 day or in 2 divided doses over 2 consecutive days, every 3 weeks

Multifocal motor neuropathy (MMN)	Starting dose: Total of 2 g/kg in divided doses for 2 to 5 days Maintenance dose: 1 to 2 g/kg every 2 to 6 weeks

*Indicates FDA approved indications.
Reference: Development Safety Update Report IGIV-C (version 8; July 2019).

Subjects randomized to the combination arm of IVIG plus SMT will receive a total dose of 2 g/kg of Gamunex-C administered in divided doses over 4 or 5 days.

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 high dose IVIG plus SMT can reduce the proportion of subjects dying through Day 29 versus SMT alone in hospitalized subjects with COVID-19 requiring ICU admission.

Approximately 100 subjects will be randomized (1:1) with an interim analysis after 50 subjects (approximately 25 per group). There will be no interruption in study conduct during the interim analysis as this simply represents sponsor safety due diligence.

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.

Several studies demonstrate that cells infected by SARS-CoV produce elevated levels of pro-inflammatory cytokines (PICs) in order to combat the invading viruses. However, the overproduced PICs (including monocyte chemoattractant protein-1 [MCP-1], transforming growth factor β 1 [TGF-β1], tumor necrosis factor-α [TNF-α], interleukins- 1β and -6 [IL-1β, and IL-6]), may cause immuno-mediated damage to the lungs and other organs, resulting in acute lung injury (ALI) and ARDS (He et al., 2006; DeDiego et al., 2014).

The elevated levels of PICs in blood released from the SARS-CoV-infected cells and the uninfected cells stimulated by viral antigens or some PIC-regulatory factors, eg Nuclear Factor-kappaB (NF-κB) and p38 (a mitogen-activated protein kinase) (He et al., 2006; DeDiego et al., 2014), may damage the cells in the lungs and other organs. In addition, blood hypo-oxygenation due to ARDS and disseminated intravascular coagulation resulting from

impairment of microvessel endothelial cells may further damage the structure and function of different organs in SARS patients, resulting in multi-organ dysfunction.

The ACE2 expressing cells are the primary targets for SARS-CoV infection in humans initiating a massive cascade of pro-inflammatory cytokines via macrophages over-activation causing ARDS. High levels of PICs are expressed in the SARS-CoV-infected ACE2+ cells, but not in the uninfected cells (He et al., 2006).

Therefore, application of PIC antagonists may reduce the severity and mortality of SARS and may potentially reduce other pathogenic human coronaviruses (He et al., 2006; DeDiego et al., 2014; Tse et al., 2004). In the current study, it is considered that the immunomodulatory properties of high dose IVIG (Gamunex-C) may attenuate the deleterious effects of cytokine release syndrome engendered in COVID-19.

Currently, there are no approved treatments for COVID-19 in Europe or the United States. The lack of disease-directed therapeutic options has led to urgent interventions in anticipation of some potentially promising effects. Some antivirals are currently under evaluation. These include favipirivir (AVIGAN) manufactured by Fujifilm in Japan, Gilead's remdesivir, and Kaletra® (lopinavir/ritonavir) commercially available for human immunodeficiency virus (HIV). Although Kaletra did not show demonstrable efficacy in a recently reported study in China (Cao et al., 2020), additional trials are underway. There are also investigations of chloroquine and hydroxychloroquine as treatment modalities and potential applications for post-exposure prophylaxis according to Clinicaltrials.gov and other clinical trial registries. While both remdesivir and chloroquine phosphate/hydroxychloroquine sulfate have EUAs before licensure in the United States, efficacy remains to be further defined. Initial results for remdesivir are most 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 ($p=0.06$) (Fact Sheet Remdesivir EUA 1 May 2020). 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%) (Wang, Zhang et al., 2020).

To date there are still no confirmed specific disease modifying agents. Therefore, the potential therapeutic benefit conveyed by the immunomodulatory effects of high dose IVIG 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 determine if high dose IVIG plus SMT can reduce all-cause mortality versus SMT alone in hospitalized subjects with COVID-19 requiring admission to the ICU through Day 29.

3.1.2 Secondary Efficacy Objectives

The secondary efficacy objective includes:

- To compare high dose IVIG plus SMT versus SMT alone with regard to clinical efficacy as assessed by clinical severity, duration of hospital and ICU stay, dependency on oxygen and ventilatory support, and clinical response criteria including National Early Warning Score (NEWS), clinical status scale, and Sequential Organ Failure Assessment Score (SOFA) through Day 29 in hospitalized subjects ill with COVID-19 requiring admission to the ICU.

3.1.3 Exploratory Efficacy Objectives

The exploratory objectives of this study are:

- To evaluate the effect of high dose IVIG plus SMT versus SMT alone with regard to quantitative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and anti-SARS-CoV-2 antibodies in hospitalized subjects with COVID-19.
- To evaluate whether high dose IVIG plus SMT versus SMT alone reduces the frequency of hyperinflammation based on a pre-specified biochemical definition through Day 29.
- To evaluate cytokine profile changes from baseline for high dose IVIG plus SMT versus SMT alone through Day 29.

3.2 Safety Objective

To determine the safety and tolerability profile through Day 29 of high dose IVIG plus SMT versus SMT alone in hospitalized subjects with COVID-19.

4 STUDY DESIGN

4.1 Primary Endpoint and Secondary Endpoints

4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is all cause mortality rate through Day 29.

4.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Time to actual ICU discharge: defined as duration of ICU stay from Day 1 through Day 29
    - Additionally, time to a medical equivalence of ICU discharge will be recorded and analyzed (defined as the time point when the patient no longer requires ICU level care, i.e., not requiring invasive mechanical ventilation, or intensive monitoring such as arterial line or central line placement, administration of IV vasopressors to support blood pressure, or O2 supplementation greater than that delivered by nasal cannula)
- Duration of mechanical ventilation from Day 1 through Day 29
- Time to actual hospital discharge: defined as duration of hospitalization from Day 1 through Day 29
    - Additionally, time to a medical equivalence of hospital discharge will be recorded and analyzed (defined as the time point when the patient no longer requires supplemental oxygen and no longer requires ongoing medical care [yet may not be discharged from hospital for social or quarantine reasons])
- Duration of any oxygen use from Day 1 through Day 29
- Absolute value and mean change from baseline in the Ordinal scale Day 1 through Day 29

  The Ordinal scale is as follows:

  1) Death;

  2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

  3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;

  4) Hospitalized, requiring supplemental oxygen;

  5) Hospitalized, not requiring supplemental oxygen;

  6) Not hospitalized, limitation on activities;

  7) Not hospitalized, no limitations on activities.
- Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29
- Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS) overall and distribution by severity through Day 29 (Appendix 3)
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 5, Day 15, and Day 29 (Appendix 4)

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

  The NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness [Alert, Voice, Pain, Unresponsive]). https://www.mdcalc.com/national-early-warning-score-news (Appendix 2)

- Time to clinical response: NEWS ≤ 2 maintained for 24 hours, Day 1 through Day 29

4.1.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Change from baseline in quantitative SARS-CoV-2 viral load by nucleic acid amplification technology (NAT) or PCR (real-time RT-PCR) to Days 5, 15, and 29
- Change from baseline in quantitative anti-SARS-CoV-2 IgM and IgG antibodies to Days 5, 15, and 29
- Proportion of subjects with evidence of hyperinflammation on Day 1, Day 5, Day 15, and Day 29 defined as:
  - Lymphocyte counts <1000 cells/µL, AND
  - Two of the following 4 criteria:
    - Ferritin > 500 ng/mL,
    - LDH > 300 U/L,
    - D-Dimers > 1000 ng/mL (fibrinogen equivalent units [FEU]) or > 2 times upper normal limit,
    - C-reactive protein (CRP) > 70 mg/L
- Change from baseline in cytokine profile (IL-1β, IL-10, IL-6, IL-8 IL-2, interferon γ, and tumor necrosis factor-α [TNF-α]) to Days 5, 15, and 29

4.1.4 Safety Endpoints

The safety endpoints include:

- Cumulative incidence of treatment-emergent serious adverse events (SAEs) and potentially related SAEs through Day 90 Phone Check
- Cumulative incidence of Grade 3-5 treatment-emergent adverse events (TEAEs) and potentially related 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)
- Cumulative incidence of all TEAEs and potentially related TEAEs through Day 29

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 IVIG and the TEAE.

4.2 Study Design and Plan

This is a prospective, multi-center, randomized (1:1), open-label, pilot study of high dose IVIG plus SMT versus SMT alone in subjects with COVID-19 who are hospitalized and require ICU admission. The first 6 subjects randomized will be staggered with an interval of no less than 1 week between subjects. If there are no definitely related serious adverse events (SAEs) reported 1 week after the randomization of the 6th subject, competitive enrollment would ensue thereafter. If a definitely related SAE were to be reported among these 6 subjects, the Study-Independent Safety Review Committee (SISRC) would carefully review and evaluate the case and make appropriate recommendations with regard to study status.

In this study, symptomatic subjects with positive polymerase chain reaction (PCR; reverse transcriptase [RT]-PCR) or other FDA-approved or regulatory-authority-approved diagnostic assay for SARS-CoV-2 in any specimen during the current hospital admission prior to randomization will receive SMT or SMT plus a net total dose of IVIG of 2 g/kg (body weight) administered in divided doses over 4 to 5 consecutive days at the Principal Investigator's discretion. The maximum dose will be capped at 160 g (equivalent to body weight of 80 kg).

Specifically, subjects randomized to combination high dose IVIG will receive the first IV infusion of IVIG on Day 1. The total net dose of 2 g/kg body (capped at a maximum of 160 g for subjects weighing more than 80 kg) will be administered in divided doses over consecutive days. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days.

Approximately 100 subjects will be randomized (1:1) with an interim analysis after 50 subjects (approximately 25 per group). There will be no interruption in study conduct during interim analysis as this simply represents sponsor safety due diligence.

All subjects will be followed daily through Day 10. After Day 10, if subjects are discharged from the hospital, evaluations at Day 15 and 29 are required. Berlin criteria for ARDS (Appendix 3) and SOFA score (Appendix 4) will be assessed on Day 1, 5, 15, and 29. Subjects remaining hospitalized will be followed daily through Day 29. Days 15±1 and 29±1 may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. If an in-person visit is unable to be conducted for Day 15 or

Day 29, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications). Phone Checks will occur at Day 60 and Day 90 for vital status (living or deceased), any hospital re-admissions or serious/non-serious adverse events after the Day 29 Final Clinic Visit. Details are provided in Appendix 1 (Schedule of Study Procedures). Clinical status will be evaluated for all hospitalized subjects daily with vital signs, Ordinal Scale (7 categories analogous to Cao et al. 2020), and NEWS at Screening/Baseline and during IVIG plus SMT or SMT alone treatment and during Follow-up. 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 .

For subjects in the combination arm (IVIG plus SMT) all laboratory samples must be drawn prior to infusion of IVIG, if laboratory assessments are required for a day in which IVIG is being infused.

Respiratory samples for quantitative measurement of SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) will be obtained on Day 1, and subsequently on Day 5± 1 day, Day 15± 1 day and Day 29 ± 1 day (obtained via nasopharyngeal swab). The results of these samples are not necessary for continuing on study. Similarly, blood samples for quantitative measurement of IgM and IgG antibodies to SARS-CoV-2 via enzyme linked immunosorbent assay (ELISA), Indirect Fluorescent Antibody (IFA) or other assay methodology will be drawn at the same time points: Day 1, and subsequently on Day 5± 1 day, Day 15± 1 day, and Day 29 ± 1 day. The results of these samples are not necessary for continuing on study.

Ferritin, D-dimer, CRP and Basic chemistry analytes (creatinine, albumin, alanine aminotransferase [ALT], total bilirubin, lactate dehydrogenase [LDH]) will be assessed on Day 1 and on Day 5± 1 day, Day 15± 1 day, and Day 29 ± 1 day. Hematology (hemoglobin, hematocrit, platelet count, absolute lymphocyte count, leukocyte count with differential) will be assessed Day 5± 1 day, Day 15± 1 day, and Day 29± 1 day. Direct antiglobulin test (DAT) will be performed on Day 1, and on Day 5± 1 day, Day 15 ± 1 day, and Day 29 ± 1 day. All routine laboratory tests will be assessed locally at the hospital/site's laboratory. A cytokine panel will be performed at the same time points. Cytokine panel includes IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and TNF-α. Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.

This clinical trial will consist of the following phases:

- Screening/Baseline (Day 1) during which eligibility criteria are reviewed. Once all eligibility criteria are met and all pre-infusion assessments are completed, IVIG administration can begin for those subjects randomized to the combination plus SMT arm as expeditiously as feasible.
- SMT, Observations, and Follow-up (Days 2 to Day 29): SMT will be provided to all subjects with daily assessments while hospitalized and follow-up from Day 2 through Day 29±1 day (inclusive).

- Phone Checks will occur at Day 60 and Day 90 for vital status (living or deceased), any hospital re-admissions or serious/non-serious adverse events after the Day 29 Final Clinic Visit.

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

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

Subjects will be randomized 1:1 to receive either combination treatment with IVIG plus SMT or SMT alone. A central randomization will be used for this study. A randomization list containing the randomization numbers and the corresponding randomized treatment assignments will be generated by using a SAS program and be stored in a secured area that is only accessible to the randomization team. Once a subject has met eligibility criteria, a site personnel will email a randomization request to the randomization center. A randomization center operator will randomize the subject by selecting the next available randomization slot in the randomization list, starting at the top of the list and moving toward the bottom of the list, and reply to the email with the randomization number and corresponding randomized treatment assignment included. The personnel will communicate the randomization number, date/time, and treatment assigned to the site study staff, so that the information can be entered in the case report form.

4.3.3 Blinding

Not applicable. This is an open-label study.

4.4 Study Treatments

4.4.1 Treatments to Be Administered

Gamunex-C is a ready-to-use sterile solution of human IgG protein for IV administration. Gamunex-C is a licensed product. Gamunex-C vials may be supplied in the vial sizes of 10, 25, 50, 100, and 200 mL. In this study, administration of Gamunex-C will be via the IV route only.

Gamunex-C consists of 9 to 11% IgG in 0.16 to 0.24 M glycine. The buffering capacity of Gamunex-C is 35.0 mEq/L (0.35 mEq/g protein). A dose of 1 g/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45 to 50 mEq/L of blood, or 3.6 mEq/kg body weight. Thus, the acid load delivered with a dose of 1 g/kg of Gamunex-C would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously.

During this clinical trial, subjects randomized to receive combination IVIG plus SMT will receive a total dose of 2 g/kg in divided doses at the discretion of the Principal Investigator over 4 or 5 days. The first IV Infusion will be on Day 1 (see Section 6.1).

4.4.1.1 Gamunex-C

Subjects randomized to combination IVIG plus SMT will receive the first IV infusion of Gamunex-C on Day 1. The total net dose of 2 g/kg body is capped to a maximum of 160 g for subjects weighing more than 80 kg. The dose of 2g/kg will be administered in divided doses over consecutive days. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days.

To calculate the dose for each infusion, multiply the weight of the subject (kg) by the dose in mg/kg. For example, a 70 kg individual dosed for 5 days at 400 mg/kg per infusion will receive 28 g per day. For Gamunex-C 10%, multiply the number of grams for the subject's infusion by 10 mL/gram to obtain the number of milliliters (mL) of Gamunex-C to be infused IV each day (in this example the amount is 280 mL daily for 5 days).

Gamunex-C should be infused using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The Gamunex-C infusion line can be flushed with 5% dextrose in water or 0.9% sodium chloride for injection. Do Not flush with heparin.

Gamunex-C should be administered with careful monitoring of the subject for any acute reactions. Gamunex-C infusion should commence at an infusion rate of 0.5 mg/kg/minute (0.005 mL/kg/min) for approximately 30 minutes. If the infusion is well tolerated, the rate of administration may be increased to a maximum of 4 mg/kg/minute (0.04 mL/kg/minute) as follows: the rate may be increased by doubling the infusion rate after intervals of not less than 15-30 minutes, so long as the infusion remains well tolerated.

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

Gamunex-C may be stored for 36 months at 2-8°C (36-46°F) from the date of manufacture, and while product may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months anytime during the 36 month shelf life, after which the product must be immediately used or discarded, for the purposes of this study Gamunex-C is to be stored at 2-8°C (36-46°F). Do not freeze. All partially used vials should be discarded as no preservative is

present. Do not use after expiration date. Investigators, or designees, are responsible for maintaining storage temperature logs and for immediately reporting deviations in temperature to the monitor.

Keep Gamunex-C in its original carton to protect it from light.

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

4.5 Expected Duration of Subject Participation in the Study

The total estimated maximum duration of a subject's participation in terms of actual Clinic Visits will be up to 30 days. Additionally, Phone Checks will occur at Day 60 and Day 90 for vital status (living or deceased), any hospital re-admissions or serious/non-serious adverse events after the Day 29 Final Clinic Visit.

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, 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 open-label so there is no 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 (e.g., 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 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. Hospitalized male or female subjects of ≥ 18 years of age at time of Screening who are being treated in the ICU for COVID-19 for not longer than 48 hours or for whom a decision has been made that COVID-19 disease severity warrants ICU admission.
2. Has laboratory-confirmed novel coronavirus (SARS-CoV-2) infection as determined by qualitative PCR (reverse transcriptase [RT]-PCR), or other FDA-approved-or regulatory-

authority-approved diagnostic assay for COVID-19 in any specimen during the current hospital admission prior to randomization.

3. Illness (symptoms of COVID-19 of any duration requiring ICU level care), and the following:
   a) Radiographic infiltrates by imaging (chest X-Ray, CT scan, etc.), AND
   b) Requiring mechanical ventilation and/or supplemental oxygen.

   Note: ICU level care is defined as the medical need for intensive or invasive monitoring; immediate or impending need for supportive care of the airway, breathing, or circulation; and/or stabilization of acute severe or life-threatening complications of COVID-19.
4. Any one of the following related to COVID-19: i. Ferritin > 400ng/mL, ii. LDH > 300 U/L, iii. D-Dimers > reference range, or iv. C-reactive protein (CRP) > 40 mg/L.
5. Subject provides informed consent 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. Clinical evidence of any significant acute or chronic disease or pathophysiologic manifestations (eg, complications of COVID-19 standard medical treatments) that, in the opinion of the investigator, may place the subject at undue medical risk.
2. The subject has had a known (documented) serious anaphylactic reaction to blood, any blood-derived or plasma product or a past history of any hypersensitivity reactions to commercial immunoglobulin.
3. A medical condition in which the infusion of additional fluid is contraindicated (eg, decompensated congestive heart failure [New York Heart Association Class III or IV stage heart failure (Mann et al, 2008)] or renal failure with fluid overload).
4. Shock that is unresponsive to fluid challenge and/or multiple vasopressors and accompanied by multiorgan failure considered by the Principal Investigator not able to be reversed.
5. Subjects with known (documented) thrombotic complications to polyclonal IVIG therapy in the past.
6. Subjects with current or prior myocardial infarction, stroke, deep vein thrombosis, or thromboembolic event (within the past 12 months) or who have a history of thromboembolic events of unknown etiology.
7. Subjects with limitations of therapeutic effort (e.g., 'do not resuscitate' status).

   Note: If the decision is made not to apply treatments or therapeutic procedures that will provide little benefit for the suffering or agony the subject is experiencing, such a subject would not be appropriate for participation in this study and should be excluded.

8. Female subjects who are pregnant or of child-bearing potential with a positive test for pregnancy blood or urine human chorionic gonadotropin (HCG)-based assay at Screening/Baseline.
9. Subjects participating in another interventional clinical trial with investigational medical product or device.
10. Known history of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome.
11. Presence of malignancy (either new diagnosis of malignancy or known residual disease) within the past 12 months (note: exceptions for non-melanoma skin cancer and carcinoma in situ of cervix are allowed)
12. Creatinine at Screening is ≥ 4 mg/dL (or subject is dependent on dialysis/renal replacement therapy)
13. Known Immunoglobulin A (IgA) deficiency with anti-IgA serum antibodies
14. Uncontrolled hypertension at the time of Screening (systolic blood pressure > 200 mm Hg) or refractory severe hypotension with sustained systolic blood pressure < 90 mm Hg unresponsive to vasopressors.

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 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.

With regard to individual subject criteria for discontinuation of Gamunex-C IV infusions, discontinuation of study drug treatment will occur if the subject develops any of the following:

- Evidence of hypersensitivity/anaphylaxis to Gamunex-C
- Occurrence of thromboembolic complication (e.g., pulmonary embolism) whether or not related to COVID-19
- Hypertensive emergency with sustained systolic blood pressure > 200 mm Hg unresponsive to intervention or refractory severe hypotension with sustained systolic blood pressure < 90 mm Hg unresponsive to vasopressors
- Development of renal failure with creatinine ≥ 4 mg/dL (or subject becomes dependent on dialysis/renal replacement therapy)

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 IP (infusion) who discontinue the clinical trial, and for subjects randomized to SMT alone, 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 15 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 return for their chronological Day 29 Clinic 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 Clinic Visit, all assessments will be performed *except for* central laboratory testing: cytokine panel, respiratory sample for quantitative measurement of SARS-

CoV-2 viral load (obtained via nasopharyngeal swab), and quantitative measurement of IgM and IgG antibodies, which are not required for these subjects at chronological Day 29 for premature withdrawals. These subjects will also have Phone Checks at Day 60 and Day 90 for vital status (living or deceased), and any hospital re-admissions or serious/non-serious adverse events after the Day 29 Final Clinic 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 Clinic 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 combination IVIG plus SMT will receive the first IV infusion of Gamunex-C on Day 1. The total net dose of 2 g/kg body is capped to a maximum of 160 g for subjects weighing more than 80 kg. The dose of 2g/kg will be administered in divided doses over consecutive days. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days. All Gamunex-C infusions must be administered in the hospital or in a professional healthcare setting with emergency equipment available.

To calculate the dose for each infusion, multiply the weight of the subject (kg) by the dose in mg/kg. For example, a 70 kg individual dosed for 5 days at 400 mg/kg per infusion will receive 28 g per day. For Gamunex-C 10%, multiply the number of grams for the subject's infusion by 10 mL/gram to obtain the number of milliliters (mL) of Gamunex-C to be infused IV each day (in this example the amount is 280 mL daily for 5 days).

Gamunex-C should be infused using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The Gamunex-C infusion line can be flushed with 5% dextrose in water or 0.9% sodium chloride for injection. Do Not flush with heparin.

Gamunex-C infusion should commence at an infusion rate of 0.5 mg/kg/minute (0.005 mL/kg/min) for approximately 30 minutes. If the infusion is well tolerated, the rate of administration may be increased to a maximum of 4 mg/kg/minute (0.04 mL/kg/minute) as follows: the rate may be increased by doubling the infusion rate after intervals of not less than 15-30 minutes, so long as the infusion remains well tolerated.

An infusion may be stopped at the discretion of the medical personnel according to normal practice, for instance if there is extravasation at the IV site, and then restarted using a new IV site. However, if a hypersensitivity reaction occurs, such as anaphylaxis, the infusion of IV Gamunex-C will be stopped permanently, and no further Gamunex-C infusions will be given. During infusion vital signs will be measured and the patient carefully observed. Early signs and symptoms of hypersensitivity reactions may include pruritus; generalized urticaria; flushing; swollen lips, tongue, or uvula; wheezing; tightness of the chest; dyspnea; hypotension; and syncope. If hypersensitivity symptoms occur, promptly stop study drug infusion and begin appropriate therapy. Such patients who discontinue infusion will be monitored according to standard of care until hypersensitivity/anaphylaxis resolves and will not receive any further IP.

Additionally, if there is a high clinical suspicion of fluid overload the infusion of Gamunex-C should be slowed or stopped. If Gamunex-C is stopped, the Principal Investigator should consider restarting Gamunex-C infusion when clinical signs of fluid overload have resolved, or the patient has shown adequate response to therapy.

Furthermore, vital signs will be measured within 1 hour prior to the start of Gamunex-C infusion, 30 minutes after the start of infusion, and hourly through the end of Gamunex-C infusion. If the systolic blood pressure measured within 1 hour prior to the start of Gamunex-C infusion is > 160 mm Hg, then measures to lower blood pressure below this threshold should be administered and documented prior to commencing Gamunex-C infusion. To commence the Gamunex-C infusion, the systolic blood pressure must be < 160 mm Hg.

6.2 Prior and Concomitant Therapy

Concomitant medications must be recorded in the medical notes and in CRF, including the trade and generic names of the medication, the dose, the route of administration, and the duration of the medication (frequency). Concomitant prophylaxis for potential venous thrombosis or thromboembolism in hospitalized subjects with COVID-19 is supported within this study according to institutional standard practices.

6.2.1 Prohibited Medications Prior to Study Participation

There are no prohibited medications.

6.2.2 Prohibited Concomitant Medications during the Study

Administration of other commercial IVIG products during study is not allowed.

6.2.3 Restricted Concomitant Medications during the Study

There are no restricted concomitant medications. Monitoring and recording in the case report form of administration of azithromycin, tocilizumab, remdesivir and other potential COVID-19 disease modifying drugs in recognition of their potential immunomodulatory and anti-inflammatory effects 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 IP dose must be recorded in the subject's medical records.

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

7 ASSESSMENT OF EFFICACY

7.1 Efficacy Variables

7.1.1 Primary Efficacy Variable

The primary efficacy variable is all-cause mortality rate through Day 29.

7.1.2 Secondary Efficacy Variables

The secondary efficacy variables include:

- Time to actual ICU discharge: defined as duration of ICU stay from Day 1 through Day 29
    - Additionally, time to a medical equivalence of ICU discharge will be recorded and analyzed (defined as the time point when the patient no longer requires ICU level care, i.e., not requiring invasive mechanical ventilation, or intensive monitoring such as arterial line or central line placement, administration of IV vasopressors to support blood pressure, or O2 supplementation greater than that delivered by nasal cannula)
- Duration of mechanical ventilation from Day 1 through Day 29
- Time to actual hospital discharge: defined as duration of hospitalization from Day 1 through Day 29
    - Additionally, time to a medical equivalence of hospital discharge will be recorded and analyzed (defined as the time point when the patient no longer requires supplemental oxygen and no longer requires ongoing medical care [yet may not be discharged from hospital for social or quarantine reasons])
- Duration of any oxygen use from Day 1 through Day 29
- Absolute value and mean change from baseline in the Ordinal scale Day 1 through Day 29

  The Ordinal scale is as follows:

  1) Death;

  2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;

4) Hospitalized, requiring supplemental oxygen;

5) Hospitalized, not requiring supplemental oxygen;

6) Not hospitalized, limitation on activities;

7) Not hospitalized, no limitations on activities.

- Proportion (percentage) of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29
- Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS) overall and distribution by severity through Day 29 (Appendix 3)
- Change from baseline in Sequential Organ Failure Assessment (SOFA) score at Day 5, Day 15, and Day 29 (Appendix 4)
- Assessment of Clinical Severity: Change in NEWS from baseline (Day 1 through Day 29)

  The NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes. This score is based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness [Alert, Voice, Pain, Unresponsive]). https://www.mdcalc.com/national-early-warning-score-news (Appendix 2)
- Time to clinical response: NEWS ≤ 2 maintained for 24 hours, Day 1 through Day 29

7.1.3 Exploratory Efficacy Variables

The exploratory efficacy variables include:

- Change from baseline in quantitative SARS-CoV-2 viral load by NAT or PCR (real-time RT-PCR) to Days 5, 15, and 29
- Change from baseline in quantitative anti-SARS-CoV-2 IgM and IgG antibodies to Days 5, 15, and 29
- Proportion of subjects with evidence of hyperinflammation on Day 1, Day 5, Day 15, and Day 29 defined as:
  - Lymphocyte counts <1000 cells/µL, AND
  - Two of the following 4 criteria:
    - Ferritin > 500 ng/mL,
    - LDH > 300 U/L,
    - D-Dimers > 1000 ng/mL (fibrinogen equivalent units [FEU]) or > 2 times upper normal limit,
    - C-reactive protein (CRP) > 70 mg/L
- Change from baseline in cytokine profile (IL-1β, IL-10, IL-6, IL-8 IL-2, interferon γ, and tumor necrosis factor-α [TNF-α]) to Days 5, 15, and 29

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 (or a legal representative or a nearest relative or relative by marriage, as appropriate), provides oral or written informed consent prior to initiation of any study procedures.

If the subject is not be able to consent for himself/herself prior to initiation of any study procedures, a legal representative or a nearest relative or relative by marriage will provide oral informed consent on behalf of the subject. If the legal representative or a nearest relative or relative by marriage is quarantined because of Covid-19 emergency, informed consent will be provided orally by a phone call and documented in the subject's medical notes.

This will be recorded in the medical history with the following paragraph "I have explained to the subject [representative] the characteristics and objective of the study, its risks and potential benefits. I have been able to answer their questions and I affirm that this subject [representative] has given oral informed consent".

Subsequently, and when possible, the subject's written informed consent will be obtained (IRB approved version, which will be signed by the researcher and the subject).

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.

7.2.2 Screening/Baseline and Randomized Treatment (Day 1)

All required screening and baseline (pre-infusion Day 1) procedures/assessments will be performed prior to administration of the IP (for subjects randomized to the combination arm).

Assessments include the following:

- Informed consent
- Inclusion/exclusion criteria
- Pregnancy test for females of child-bearing potential
- 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)
- Ordinal Scale assessment
- National Early Warning Score (NEWS) (Appendix 2)

- Record clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Initial Body Weight (this weight is to be used to calculate all IVIG doses if randomized to combination arm with Gamunex-C)
- Record result of historical SARS-CoV-2 PCR (qualitative RT-PCR) or other FDA-approved or regulatory-authority-approved diagnostic assay in any specimen during the current hospital admission prior to randomization (eligibility criterion)
- Record hospital admission date
- Record ICU admission date
- Record supplemental oxygen administration (type, %, flow start/end date/time)
- Record details of mechanical ventilation parameters (start/end date/time)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Assessment of ARDS (Berlin Criteria) (Appendix 3)
- SOFA score (Appendix 4)
- 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, alanine aminotransferase [ALT], total bilirubin, lactate dehydrogenase [LDH])
- Hematology: absolute lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)
- Direct antiglobulin test (DAT)
- Cytokine panel (IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and TNF-α). Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.
- Record daily 24-hour fluid balance (intake and output)
- Record body weight a second time for assessing fluid balance on Day 1 (at least 8 hours should separate the time from the first recorded weight)
- Record SAEs and TEAEs
- Record standard care concomitant medications

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

Subjects in the combination arm may receive the first infusion of Gamunex-C on Screen/Baseline and Randomized Treatment visit (Day 1) if eligibility criteria are met, and all pre-infusion assessments are performed. Subjects in the combination arm will receive a total of 2 g/kg Gamunex-C in divided doses. At the prerogative of the Principal Investigator the 2 g/kg dose may be divided into 4 days (500 mg/kg/day) or 5 consecutive days (400 mg/kg/day).

Vital signs will be monitored during Gamunex-C infusion. Vital signs will be measured within 1 hour prior to the start of Gamunex-C infusion, 30 minutes after the start of infusion, and hourly through the end of Gamunex-C infusion. If the systolic blood pressure measured within 1 hour prior to the start of Gamunex-C infusion is > 160 mm Hg, then measures to lower blood pressure below this threshold should be administered and documented prior to commencing Gamunex-C infusion. To commence the Gamunex-C infusion, the systolic blood pressure must be < 160 mm Hg.

7.2.3 SMT, Randomized IVIG Treatment, Daily Evaluations (Days 2 through 10 inclusive) and Additional Day 5±1 Day Assessments

All subjects receive continued SMT. Subjects randomized to IVIG plus SMT will receive the remainder of the net 2 g/kg dose in divided doses at the Principal Investigator's prerogative on consecutive days through Day 4 (500 mg/kg/day) or through Day 5 (400 mg/kg/day) to achieve the total dose of 2 g/kg body weight. Subjects receiving Gamunex-C infusions will have vital signs measured within 1 hour prior to the start of each Gamunex-C infusion, 30 minutes after the start of infusion, and hourly through the end of Gamunex-C infusion. If the systolic blood pressure measured within 1 hour prior to the start of Gamunex-C infusion is > 160 mm Hg, then measures to lower blood pressure below this threshold should be administered and documented prior to commencing Gamunex-C infusion. To commence the Gamunex-C infusion, the systolic blood pressure must be < 160 mm Hg.

Daily assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record any supplemental oxygen administration (type, %, flow start/end date/time)
- Record details of mechanical ventilation parameters (start/end date/time)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record daily 24-hour fluid balance (intake and output) while in hospital
- Record body weight for assessing fluid balance twice daily on Days 1 through 5 inclusive (at least 8 hours should separate the time from the first recorded weight)

- Record SAEs and TEAEs
- Record standard care concomitant medications

All laboratory tests and serum and plasma samples are required for all study subjects, regardless of treatment assignment. For subjects randomized to IVIG plus SMT all laboratory samples must be obtained prior to the Gamunex-C infusion on the designated day.

On Day 5 ± 1 day the following *additional* assessments will be performed:

- Assessment of ARDS (Berlin Criteria) (Appendix 3)
- SOFA score (Appendix 4)
- 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 (store serum samples frozen at -70°C for later analysis at an external lab)
- Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)
- Hematology: absolute lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- DAT
- Cytokine panel (IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and TNF-α). Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.

7.2.4 Day 11-14 for Subjects Still Hospitalized: SMT and Daily Evaluations

All subjects receive continued SMT.

Daily assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record any supplemental oxygen administration (type, %, flow start/end date/time)
- Record details of mechanical ventilation parameters (start/end date/time)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record SAEs and TEAEs
- Record standard care concomitant medications

7.2.5 Day 15±1 day – All Subjects

Day 15±1 day may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. If an in-person visit is unable to be conducted for Day 15, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications).

Assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record any supplemental oxygen administration (type, %, flow start/end date/time)
- Record details of mechanical ventilation parameters (start/end date/time)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Assessment of ARDS (Berlin Criteria) (Appendix 3)
- SOFA score (Appendix 4)
- 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 (store serum samples frozen at -70°C for later analysis at an external lab)
- Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)
- Hematology absolute lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- DAT
- Cytokine panel (IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and TNF-α). Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.
- Record SAEs and TEAEs
- Record standard care concomitant medications

7.2.6 Day 16-28 for Subjects Still Hospitalized: SMT and Daily Evaluations

All subjects receive continued SMT.

Daily assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record any supplemental oxygen administration (type, %, flow start/end date/time)
- Record details of mechanical ventilation parameters (start/end date/time)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record SAEs and TEAEs
- Record standard care concomitant medications

7.2.7 Day 29±1 day – All Subjects

Day 29±1 day may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. If an in-person visit is unable to be conducted for Day 29, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications).

Assessments include the following:

- Ordinal Scale assessment
- NEWS (Appendix 2)
- Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.
- Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)
- Record any supplemental oxygen administration (type, %, flow start/end date/time)
- Record details of mechanical ventilation parameters (start/end date/time)
- Record oxygen saturation (specify on or off oxygen supplementation)
- Record hospital discharge date
- Record ICU discharge date
- Assessment of ARDS (Berlin Criteria) (Appendix 3)
- SOFA score (Appendix 4)

- 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 (store serum samples frozen at -70°C for later analysis at an external lab)
- Serum Chemistry (creatinine, albumin, ALT, total bilirubin, LDH)
- Ferritin (serum), D-dimer (plasma, sodium citrate tube), CRP (serum)
- Hematology: absolute lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)
- DAT
- Cytokine panel (IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and TNF-α). Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.
- Record SAEs and TEAEs
- Record standard care concomitant medications

7.2.8 Day 60±2 days and Day 90±2 days Phone Checks – All Subjects

Phone Checks will be performed on Day 60 and Day 90:

- To confirm the subject's vital status (living or deceased)
- To record any hospital re-admissions
- To record any SAEs/non-serious AEs after the Day 29 final clinic visit

7.2.9 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 count; Basic hematology: Hemoglobin, hematocrit, platelets, white blood cell (WBC) count with differential	Local
Chemistry	Creatinine, albumin, alanine aminotransferase (ALT), total bilirubin, lactate dehydrogenase (LDH)	Local
Markers of inflammation	C-reactive protein (CRP), D-dimer, ferritin	Local
Direct Coombs	direct antiglobulin test (DAT)	Local
Cytokine panel	Cytokine panel includes IL-1β, IL-10, IL-6, IL-8, IL-2, interferon γ, and tumor necrosis factor-α (TNF-α). Note: serum samples must be stored at -70°C for later analysis at a reference laboratory.	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

8 ASSESSMENT OF SAFETY

8.1 Safety Parameters

The safety and tolerability of Gamunex-C in subjects with COVID-19 will be evaluated in this study. Safety endpoints will include:

- Cumulative incidence of treatment-emergent SAEs and potentially related SAEs through Day 90 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
- Cumulative incidence of all TEAEs and potentially related TEAEs through Day 29

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 IVIG 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

True hypersensitivity reactions from IVIG administration are rare. They can occur in subjects with anti-IgA antibodies. Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in subjects who had tolerated previous treatment with human normal immunoglobulin.

There is clinical evidence of an association between IVIG administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), PE, and DVT that is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk subjects. In subjects at risk for thromboembolic adverse reactions, IVIG products should be administered at the minimum rate of infusion and dose practicable.

Cases of acute renal failure have been reported in subjects receiving IVIG therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products, or age over 65. In case of renal impairment, IVIG discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIG products containing various excipients such as sucrose, glucose, and maltose, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. In subjects at risk, the use of IVIG products that do not contain these excipients may be considered. Gamunex-C *does not* contain sucrose, maltose, or glucose.

AMS has been reported to occur in association with IVIG treatment. The syndrome usually begins within several hours to 2 days following IVIG treatment.

Gamunex-C may contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive DAT and, rarely, hemolysis. Hemolytic anemia can develop subsequent to IVIG therapy due to enhanced red blood cells sequestration. IVIG recipients should be monitored for clinical signs and symptoms of hemolysis. If these are present after IVIG infusion, perform appropriate confirmatory laboratory testing.

In subjects receiving IVIG, there have been some reports of acute non-cardiogenic pulmonary oedema (Transfusion Related Acute Lung Injury [TRALI)]). TRALI is characterized by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A and parvovirus B19 viruses. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to viral safety. It is strongly recommended that every time that Gamunex-C is administered to a subject, the batch number of the product is recorded in order to maintain a link between the subject and the batch of the product.

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 IVIG 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 (i.e., 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 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 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 (i.e., 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 Gamunex-C prescribing information and the IB. 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 (e.g., 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 (e.g., 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 form (if serious).

At the time of the Day 60 (±2 days) and Day 90 (±2 days) Phone Checks 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, e.g., 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 Clinic Visit and any SAE recorded at the time of the Day 60 (±2 days) or Day 90 (±2 days) Phone Checks 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)

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.

8.5 Study-Independent Safety Review Committee (SISRC) and Stopping Rules

Grifols will utilize a Study-Independent Safety Review Committee (SISRC) whose members (from Grifols) will be impartial and independent of the clinical trial team, and will consist of a statistician, global pharmacovigilance representative, and medical director. The SISRC will review relevant safety information from the study as outlined in the SISRC Charter. At a minimum, after the first 20 subjects are enrolled and have completed treatment, the SISRC will conduct an initial safety review. The SISRC will perform a causality review of all TEAEs and SAEs. The SISRC will be notified of relevant SAEs inasmuch as feasible within 24 hours, but no later than 3 days.

Stopping criteria for temporary suspension of further study enrollment/recruitment pending full safety investigation by the SISRC are detailed below.

The SISRC will conduct a safety evaluation and study enrollment/recruitment will be temporarily suspended while the safety investigation is undertaken if any one of the following occur:

- 1 death considered related to Gamunex-C
- 1 Grade 4 treatment-emergent AE occurs in any of the first 3 randomized subjects considered potentially related to Gamunex-C
- 1 subject develops a Grade 3 hypersensitivity reaction or serious anaphylactic reaction at any time attributable to Gamunex-C
- 10 subjects given Gamunex-C develop treatment-emergent AEs in the same system organ class that are ≥ Grade 2 severity (CTCAE grading criteria)
- 2 subjects given Gamunex-C develop treatment-emergent Grade 4 serious AEs of the same kind in the first 10 subjects randomized to Gamunex-C
- 5 subjects develop Grade 3 or 4 treatment-emergent AEs that are at least possibly related to Gamunex-C at any time during the study
- 3 or more subjects per 10 subjects enrolled and dosed with Gamunex-C develop definitely related treatment-emergent serious AEs of the same kind (same or related verbatim terms). This stopping criterion will be applied after at least 10 subjects are randomized and treated with Gamunex-C.

- An unanticipated safety signal is detected by the SISRC that was unexpected and of sufficient magnitude to warrant concern

Further details are outlined in the SISRC Charter.

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 analysis will be conducted after 50 subjects (approximately 25 per group) for safety variables through Day 29. Due to the exploratory nature of this phase 2 study, the multiplicity adjustments will not be considered; full details will be described in the statistical analysis plan. This interim evaluation simply represents Sponsor safety due diligence.

There will be 3 analysis populations in this study; 2 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 ITT population will be used for all efficacy analyses.

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

The Safety population is defined as the subset of subjects who receive at least any amount of IVIG plus SMT or SMT alone. Safety analyses will be based on the Safety population.

The primary efficacy analysis will be carried out on the ITT population and repeated on the PP population (if different from the ITT population) by Fisher's exact test or Chi-square test. 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. Detailed data handling and evaluation procedures and details of the interim reviews will be described in the Statistical Analysis Plan (SAP). The SAP may include exploratory analyses of various aspects of SMT inclusive of different interventional strategies and evolving treatment modalities.

Grifols will analyze use of COVID-19 specific, potentially disease modifying treatments between arms and this will be fully detailed in the SAP since medical understanding of COVID-19 interventions is rapidly evolving and for ethical reasons (apart from participation

in another clinical trial) there are no restrictions on what are perceived to be potentially life-saving therapies. Additionally, a sensitivity analysis evaluating potential effects of fluid balance will be included in the 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 pilot study is commensurate with other Phase 2 investigations ongoing during the COVID-19 pandemic. Approximately 100 subjects are allowed to be randomized as part of a humanitarian effort against COVID-19.

9.3 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.

9.4 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.

9.5 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.

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.

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 (e.g., 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 (or a legal representative or a nearest relative or a relative by marriage, as appropriate). 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 (or a legal representative or a nearest relative or a relative by marriage, as appropriate) must give oral or written informed consent. Participation in the study and date of ICF discussion with subject (or a legal representative or a nearest relative or a relative by marriage, as appropriate) should be documented appropriately in the subject's files.

If the subject is not be able to consent for himself/herself prior to initiation of any study procedures, a legal representative or a nearest relative or relative by marriage will provide oral informed consent on behalf of the subject. If the legal representative or a nearest relative or relative by marriage is quarantined because of Covid-19 emergency, informed consent will be provided orally by a phone call and documented in the subject's medical notes.

This will be recorded in the medical history with the following paragraph "I have explained to the subject [representative] the characteristics and objective of the study, its risks and potential benefits. I have been able to answer their questions and I affirm that this subject [representative] has given oral informed consent".

Subsequently, and when possible, the subject's written informed consent will be obtained (IRB approved version, which will be signed by the researcher and the subject).

A copy of the subject ICF will be provided to the subject or subject's legal representative or a nearest relative or a relative by marriage, as appropriate.

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 (e.g., 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 be allowed when appropriate and feasible to ensure data integrity, quality, safety of the participants and the patients' confidentiality date is not compromised. 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 (e.g., 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.

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17 APPENDICES

Appendix 1 Schedule of Study Procedures

Study Period	Screen/ Baseline	1st IP	SMT and Daily Evaluations									Follow-Up	Follow-Up Clinic Visit Day			Phone Checks	
Study Day																	
Procedures/assessments	1		2	3	4	5±1 day	6	7	8	9	10	11-14 **Daily** if in hospital	15±1 [e] day	16-28 **Daily** if in hospital	29[e,f] ± 1 day	Day 60 ± 2 days	Day 90 ± 2 days
Informed consent	X																
Inclusion/exclusion criteria	X																
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[a])	X																
Pregnancy test[b]	X																
Ordinal Scale (at the 1st assessment of a given day)[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
National Early Warning Score (NEWS) Appendix 2	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical features key symptoms: fever, cough, shortness of breath, fatigue, myalgia etc.	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs (temperature, systolic and diastolic blood pressure, pulse, respiratory rate)	X	X[k]	X[k]	X[k]	X[k]	X[k]	X	X	X	X	X	X	X	X	X		
Initial Body Weight for determining all IVIG doses if randomized to combination arm	X																
Body weight for assessing fluid balance twice daily (at least 8 hours		X	X	X	X	X											

Study Period	**Screen/ Baseline**	**1st IP**	**SMT and Daily Evaluations**									**Follow-Up**	**Follow-Up Clinic Visit Day**			**Phone Checks**	
Study Day / **Procedures/assessments**	1		2	3	4	5±1 day	6	7	8	9	10	11-14 **Daily** if in hospital	15±1 [e] day	16-28 **Daily** if in hospital	29[e,f] ± 1 day	Day 60 ± 2 days	Day 90 ± 2 days
should separate the time from the first recorded weight)																	
Record result of *historical* SARS-CoV-2 PCR (qualitative RT-PCR) or other FDA-approved or regulatory-authority-approved diagnostic assay in any specimen during the current hospital admission prior to randomization (eligibility criterion)	X																
Record any supplemental oxygen administration (type, %, flow start/end date/time)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Record any mechanical ventilation (start/end date/time)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Record oxygen saturation (specify on or off oxygen supplementation)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization (after all Screen/Baseline assessments complete)	X																
Combination arm: Gamunex-C 2 g/kg (total) may be given either as 500 mg/kg in divided doses over 4 consecutive days OR 400 mg/kg in divided doses over 5 consecutive days		X[g]	X[g]	X[g]	X[g]	X[g]											

Study Period	**Screen/ Baseline**	**1st IP**	**SMT and Daily Evaluations**									**Follow-Up**	**Follow-Up Clinic Visit Day**			**Phone Checks**	
Study Day / **Procedures/assessments**	1		2	3	4	5±1 day	6	7	8	9	10	11-14 **Daily** if in hospital	15±1 [e] day	16-28 **Daily** if in hospital	29[e,f] ± 1 day	Day 60 ± 2 days	Day 90 ± 2 days
Record hospital admission and discharge dates	X														X[h]		
Record ICU admission & discharge dates	X														X[h]		
Sequential Organ Failure Assessment (SOFA) score (Appendix 4)	X					X							X		X		
Assessment of ARDS (Berlin Criteria) (Appendix 3)	X					X							X		X		
Daily 24-hour fluid balance (intake and output) while in hospital	X	X	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)	Pre randomized treatment [i]					X[i]							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)	Pre randomized treatment [i]					X[i]							X		X		
Serum Chemistry (creatinine, albumin, alanine aminotransferase [ALT], total bilirubin, lactate dehydrogenase [LDH])	Pre randomized treatment [i]					X[i]							X		X		

Study Period	**Screen/ Baseline**	**1st IP**	**SMT and Daily Evaluations**									**Follow-Up**	**Follow-Up Clinic Visit Day**			**Phone Checks**	
Study Day / **Procedures/assessments**	1		2	3	4	5±1 day	6	7	8	9	10	11-14 **Daily** if in hospital	15±1 [e] day	16-28 **Daily** if in hospital	29[e,f] ± 1 day	Day 60 ± 2 days	Day 90 ± 2 days
Ferritin, CRP, D-dimer	Pre randomized treatment [i]					X [i]							X		X		
Hematology: absolute lymphocyte count and standard hematology (hemoglobin, hematocrit, platelet count, leukocyte count with differential)	Pre randomized treatment [i]					X[i]							X		X		
Direct antiglobulin test (DAT)	Pre randomized treatment [i]					X[i]							X		X		
Cytokine panel[j]	Pre randomized treatment [i]					X[i]							X		X		
Record SAEs and TEAEs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Record standard care concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Phone Checks for Vital Status (living or deceased), any hospital re-admissions or SAEs/non-serious AEs after Day 29 Final Clinic Visit																X	X

a Date of first contact with the virus, date of first symptoms, date of PCR (RT-PCR)/other FDA approved- or regulatory-authority-approved diagnostic assay positive

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

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

d Grade 3-5 TEAEs 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 IVIG and the TEAE.

e Procedures/assessments for indicated visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. If an in-person visit is unable to be conducted for Day 15 or Day 29, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications).

f Final Clinic Visit, followed by Phone Checks.

g The total net dose is 2 g/kg body (maximum of 160 g for subjects weighing more than 80 kg). The first infusion is on Day 1. At the discretion of the Principal Investigator, the 2 g/kg net total dose may be divided either into (a) infusions of 500 mg/kg body weight over 4 days OR (b) 400 mg/kg body weight over 5 days.

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

i All laboratory tests and serum and plasma samples are required for all study subjects, regardless of treatment assignment. For subjects randomized to IVIG plus SMT all laboratory samples must be obtained prior to the Gamunex-C infusion on the designated day.

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

k During study infusions of Gamunex-C vital signs will be measured within 1 hour prior to the start of Gamunex-C infusion, 30 minutes after the start of infusion, and hourly through the end of Gamunex-C infusion.

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 (i.e. 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 (i.e. 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

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Other References

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Appendix 3 Acute Respiratory Distress Syndrome (ARDS) Berlin Definition

The Berlin Definition of Acute Respiratory Distress Syndrome is summarized in the table below. Timing is usually within 1 week of a known clinical insult or new or worsening respiratory symptoms.

Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b],	Mild 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2Oc
	Moderate 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O
	Severe PaO2/FIO2 ≤100 mm Hg with PEEP ≥ 5 cm H2O

Abbreviations: CPAP, continuous positive airway pressure; FIO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

a. Chest radiograph or computed tomography scan.

b If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO2/FIO2 X (barometric pressure/760)].

c This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

The following may be used for the Berlin criteria, **for patients who are Not on a ventilator and do not have a blood gas performed.** *Since the effect of positive end-expiratory pressure (PEEP) may modify the derivation of SaO_2 to SpO_2, please do Not use SpO_2 to apply Berlin criteria to patients while on a mechanical ventilator.*

Respiratory Thresholds Determined by Pulse Oximetry Measurement of O_2 Saturation (for patients Not on mechanical ventilation)

PaO_2/FiO_2	**Corresponding SpO_2/FiO_2 Threshold**
≥ 400	≥ 512
<400	<512
<300	<357

PaO_2/FiO_2	Corresponding SpO_2/FiO_2 Threshold
<200	<214
<100	<89

Derivation of SpO_2/FiO_2 values corresponding to PaO_2/FiO_2 ratios in the combined anesthesia and ARMA database* [*Data derived from 4728 matched SpO_2/FiO_2 and PaO_2/FiO_2 measurements from the combined anesthesia and ARMA database]

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Appendix 4 Sequential Organ Failure Assessment (SOFA) Score

SOFA Score

Variable Score (0-4)	0	1	2	3	4
PaO_2/FiO_2 mmHg	≥ 400	< 400	< 300	< 200	< 100
Platelets, x $10^3/\mu L$ (x $10^6/L$)	≥ 150 (> 150)	< 150 (< 150)	< 100 (< 100)	< 50 (< 50)	< 20 (< 20)
Bilirubin, mg/dL (µmol/L)	< 1.2 (< 20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 100)	6.0 - 11.9 (101 - 203)	≥ 12 (> 203)
Hypotension	None	MABP < 70 mmHg	Dop < 5	Dop 6 - 15 or Epi < 0.1 or Norepi < 0.1	Dop > 15 or Epi > 0.1 or Norepi > 0.1
Glasgow Coma Scale Score	15	13 - 14	10 - 12	6 - 9	< 6
Creatinine, mg/dL (µmol/L)	< 1.2 (< 106)	1.2 - 1.9 (106 - 168)	2.0 - 3.4 (169 - 300)	3.5 - 4.9 (301 - 433)	≥ 5 (> 434)
TOTAL (0 - 24):					

Dopamine [Dop], epinephrine [Epi], and norepinephrine [Norepi] doses in µg/kg/min (administered for at least one hour). MABP, mean arterial blood pressure; SI units in parentheses ( )

The following may be used to calculate the Respiratory item of the SOFA score, **for patients who are Not on a ventilator and do not have a blood gas performed.** *Since the effect of positive end-expiratory pressure (PEEP) may modify the derivation of SaO_2 to SpO_2, please do Not use SpO_2 in the SOFA calculation for patients while on a mechanical ventilator.*

SOFA Respiratory Score Determined by Pulse Oximetry Measurement of O_2 Saturation (for patients Not on mechanical ventilation)

SOFA Respiratory Item score	PaO_2/FiO_2	SpO_2/FiO_2 Threshold for scoring
0	≥ 400	≥ 512
1	<400	<512
2	<300	<357

SOFA Respiratory Item score	PaO_2/FiO_2	SpO_2/FiO_2 Threshold for scoring
3	<200	<214
4	<100	<89

Derivation of SpO_2/FiO_2 values corresponding to PaO_2/FiO_2 ratios in the combined anesthesia and ARMA database* [*Data derived from 4728 matched SpO_2/FiO_2 and PaO_2/FiO_2 measurements from the combined anesthesia and ARMA database]

Glasgow Coma Scale

Criteria	Score
Best Eye Response (1 – 4)	
No eye opening	1
Eye opens to painful stimulus	2
Eye opens to verbal command	3
Eyes open spontaneously	4
Best Verbal Response (1 – 5)	
No verbal response	1
Incomprehensible sounds	2
Inappropriate words	3
Confused	4
Oriented	5
Best Motor Response (1 – 6)	
No motor response	1
Extension to painful stimulus	2
Flexion to painful stimulus	3
Withdraws from painful stimulus	4
Localizes to painful stimulus	5
Obeys commands	6
Total Score (add three subscores, range from 3 to 15):	

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Appendix 5 Summary of Changes from Version 3.0 to Version 4.0

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

Sections	**Change From:** **(Version 3.0, dated 30 Oct 2020)** (Strikethrough is added to highlight deleted text)	**Change To:** **(Version 4.0)** (Underline is added to highlight new text)	**Rationale:**
Title Page	Not applicable	Study Number/Protocol Version Number: GC2007/Version 4.0	Added to identify the protocol and version number of this document.
Protocol Synopsis; Study Assessments and Procedures Section 4.2 Study Design and Plan Appendix 1 Schedule of Study Procedures; Footnote e	Not applicable	If an in-person visit is unable to be conducted for Day 15 or Day 29, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications).	Added to allow the flexibility in obtaining study related data.
Section 7.2.5 Day 15±1 day – All Subjects	Not applicable	If an in-person visit is unable to be conducted for Day 15, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications).	Added to allow the flexibility in obtaining study related data.

Sections	**Change From:** **(Version 3.0, dated 30 Oct 2020)** (Strikethrough is added to highlight deleted text)	**Change To:** **(Version 4.0)** (Underline is added to highlight new text)	**Rationale:**
Section 7.2.7 Day 29±1 day – All Subjects	Not applicable	If an in-person visit is unable to be conducted for Day 29, the study site will make a phone call to the subject to obtain as much information as possible remotely (e.g., Ordinal Scale, clinical features key symptoms, supplementation oxygen use, SAEs and TEAEs, concomitant medications).	Added to allow the flexibility in obtaining study related data.
Section 8.3.9.1 Reporting of Serious Adverse Events	Grifols Global Pharmacovigilance Email: [redacted] FAX (back-up only): [redacted] (US/Canada) [redacted] (International)	Grifols Global Pharmacovigilance Email [redacted] FAX (back-up only): [redacted] ~~(US/Canada)~~ [redacted] (International)	Updated to remove the US/Canada fax number and to keep only International fax number.
Section 10 Direct Access to Source Data/documents	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.	~~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.~~	Removed to allow remote Source Data Verification when appropriate and feasible to ensure data integrity, quality, and safety of the participants.
Section 11 Quality Control and Quality Assurance	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.	~~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.~~	Removed to allow remote Source Data Verification when appropriate and feasible to ensure data integrity, quality, and safety of the participants.

Sections	**Change From:** **(Version 3.0, dated 30 Oct 2020)** (Strikethrough is added to highlight deleted text)	**Change To:** **(Version 4.0)** (Underline is added to highlight new text)	**Rationale:**
Section 13.1 Data Handling	Remote source data verification will not be carried out.	Remote source data verification will ~~not be carried out~~ be allowed when appropriate and feasible to ensure data integrity, quality, safety of the participants and patients' confidentiality data is not compromised.	Updated to allow remote Source Data Verification when appropriate and feasible to ensure data integrity, quality, safety of the participants and patients' confidentiality data is not compromised.