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Supplementary appendix

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Supplemental Materials

Hyperimmune Immunoglobulin for Hospitalized Patients With COVID-19

The ITAC (INSIGHT 013) Study Group

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III: Supplemental Appendix C: Supplemental Methods

A. Study Design: Analysis Populations
According to version 1.0 of the data analysis plan the comparison of safety outcomes were to be analyzed by modified intention to treat (mITT, participants who received a complete or partial infusion), and the analysis of efficacy outcomes was to be by intention to treat (ITT, all randomized participants).

In version 2.0 the analysis plan was modified to carry out all analyses, including efficacy analyses, by mITT. This modification was made because 11 of the 12 participants who were not infused withdrew consent prior to the infusion and this plan allowed potential risks and benefits to be evaluated in the same analysis population.

B. Inclusion/Exclusion Criteria

The complete inclusion and exclusion criteria from the protocol are given below.

Inclusion criteria

1. SARS-CoV-2 infection documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection

2. Symptomatic COVID-19 disease

3. Duration of symptoms attributable to COVID-19 ≤ 12 days

4. Requiring inpatient hospital medical care for clinical manifestations of COVID-19 (admission for public health or quarantine only is not included)

5. Age ≥ 18 years

6. Willingness to abstain from participation in other COVID-19 treatment trials until after study Day 7

7. Provision of informed consent by participant or legally authorized representative

Exclusion Criteria

1. Prior receipt of SARS-CoV-2 hIVIG or convalescent plasma from a person who recovered from COVID-19 at any time

2. Prior receipt of standard IVIG (not hyperimmune to SARS-CoV-2) within 45 days

3. Prior receipt of any SARS-CoV-2 monoclonal antibody treatments at any time (24 November 2020 Letter of Amendment)

4. Current or predicted imminent (within 24 hours) requirement for any of the following:

    - Invasive ventilation
    - Non-invasive ventilation

- Extracorporeal membrane oxygenation
- Mechanical circulatory support
- Continuous vasopressor therapy

5. History of allergy to IVIG or plasma products

6. History of selective IgA deficiency with documented presence of anti-IgA antibodies

7. Any medical conditions for which receipt of the required volume of intravenous fluid may be dangerous to the patient

    - Includes New York Heart Association Class III or IV stage heart failure

8. Any of the following thrombotic or procoagulant disorders:
    - Acute coronary syndromes, cerebrovascular syndromes and pulmonary or deep venous thrombosis within 28 days of randomization
    - History of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome

9. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments

C. Measurement of Potency of Hyperimmune Products

Each lot was initially tested using an assay developed by a laboratory at the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID, NIH)[1]. The four participating manufacturers agreed to a range of potency for each lot and the dose of hIVIG to give each patient. The acceptable range was set as 50% to 200% of the average of 8 lots, 2 made by each manufacturer. The selected dose of 400 mg/kg is significantly higher than in a fixed dose of 400 mL of convalescent plasma (3.5-5 fold higher than the dose of plasma when administered to a 70-100 kg person). Thus, the dose selected provided an appreciable margin over that of convalescent plasma.

At the end of the trial, a sero-neutralization validated assay of SARS-CoV-2 that was calibrated against the World Health Organization International standard[2] was carried out by Texcell for each lot of hyperimmune intravenous immunoglobulin (hIVG) used in the trial. Results are reported in International Units (IU) per ml.

D. Outcomes

Primary Outcome

The primary objective is to compare the clinical status of participants in the hIVIG + standard of care (SOC) and placebo + SOC groups on Day 7 using an ordinal outcome with 7 mutually exclusive categories. On Day 7, the worst of the 7 categories the participant was in that day will constitute the primary outcome. The 7 categories are:

Ordinal Category	Categorical Description	Categorical Definition
7	Death	Death

6	End-organ failure	Currently requiring invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy
5	Life-threatening end-organ dysfunction	Currently requiring non-invasive assisted ventilation or high-flow oxygen or Extra-pulmonary: Symptoms and signs of an acute stroke (NIHSS > 14)
4	Serious end-organ dysfunction	Currently requiring supplemental oxygen (≥ 4 liters/min, or ≥ 4 liters/min above premorbid requirements**) but not high-flow oxygen or Any of symptoms or signs of the following extra-pulmonary conditions: Stroke (NIH Stroke Scale/Score [NIHSS] ≤ 14), meningitis, encephalitis, or myelitis, myocardial infarction, myocarditis, pericarditis, or New York Heart Association Class III or IV congestive heart failure, arterial or deep venous thrombosis including pulmonary embolism.
3	Moderate end-organ dysfunction	Requiring supplemental oxygen < 4 liters/min, or < 4 liters/min above premorbid requirements**
2	Limiting symptoms due to COVID-19	Symptomatic and currently unable to independently undertake usual activities
1	No limiting symptoms due to COVID-19	Can independently undertake usual activities with minimal or no symptoms

** Premorbid requirement refers to requirements prior to the development of COVID-19, for example in patients with chronic obstructive pulmonary disease, other chronic pulmonary diseases, or oxygen requirements related to altitude.

A key pre-specified secondary outcome includes only the pulmonary components of the 7-category ordinal outcome.

The 7 categories of the pulmonary only components of the primary endpoint are:

Ordinal Category	**Categorical Definition**
7	Death
6	Currently requiring invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy
5	Currently requiring non-invasive assisted ventilation or high-flow oxygen
4	Currently requiring supplemental oxygen (≥ 4 liters/min, or ≥ 4 liters/min above premorbid requirements**) but not high-flow
3	Requiring supplemental oxygen < 4 liters/min, or < 4 liters/min above premorbid requirements**
2	Symptomatic and currently unable to independently undertake usual activities
1	Can independently undertake usual activities with minimal or no symptoms

** Premorbid requirement refers to requirements prior to the development of COVID-19, for example in patients with chronic obstructive pulmonary disease, other chronic pulmonary diseases, or oxygen requirements related to altitude.

Other secondary efficacy outcomes are stated in the statistical analysis plan.

Composite Safety Outcomes

A composite safety endpoint that included grade 3 and 4 adverse events, SAEs, end organ dysfunction, serious infections, or death was collected through Day 7.

Grade 3 and 4 adverse events were not collected after day 7. Thus the composite safety outcome through Day 28 only includes SAEs, organ dysfunction, serious infections and death.

Adverse events were graded for severity using a toxicity table developed by the Division of AIDS, NIAID, NIH. For adverse events that were not in the table, a generic grading scheme was used. This scheme is given in the protocol on page 47. Adverse events were categorized according to codes in the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1.

End organ dysfunction and serious infection were defined as "protocol-specified exempt events". Those events were systematically reported during follow-up but not reported as a SAE unless they were considered related to study agent. These events are listed below for each of reference:

- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Acute delirium
- Disseminated intravascular coagulation
- Microbiologically-proven severe infection (not including SARS-CoV-2)

Other Safety Outcomes

Infusion related signs/symptoms of any grade that are new or have increased in grade compared to their pre-infusion level are reported for the hIVIG/placebo if they occur during or within 2 hours post infusion. Any infusion related reaction assessed as meeting SAE criteria will be reported as an SAE. Similarly, any grade 3 or 4 infusion related reaction will be reported as an AE.

On Day 0 prior to infusion and on Days 1, 3, 7 and 28 the prevalence of AEs of any grade severity that the participant reports that day will be collected. This information supplements the information on grade 3 and 4 events through Day 7 that is collected.

From the time of randomization on Day 0 through Day 7, clinical events reaching Grade 3 or 4 severity level will be reported as AEs unless they are a protocol-specified exempt event (see below).

Any medical condition of grade 1 and 2 that is present at Day 0 will be reported as an AE if it increases to Grade 3 or 4 by Day 7.

Isolated laboratory abnormalities will not be recorded on the eCRF for grade 3 and 4 events. However, as noted above, if an isolated laboratory result meets SAE criteria, it should be reported as an SAE.

Serum creatinine, ALT or AST, white blood cell count, hemoglobin, platelets, lymphocytes, and C-reactive protein were measured locally at baseline and day 7.

E. Centrally Determined Laboratory Measurements

SARS-CoV-2 RNA load in the nasal swab material collected at baseline was determined using extraction, master mix preparation, and RT-PCR as described in the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. The lower limit of quantification (LLoQ) for this measurement is 399 copies/mL. Viral RNA levels were determined centrally at Advanced Biomedical Laboratories which also served as the central specimen repository.

SARS-CoV-2 nucleocapsid antigen levels were determined in 90 µL plasma in duplicate using a Quanterix assay (Quanterix, Billerica, MA). The lower level of quantification was determined to be 3 ng/L. Results below that level are imputed as 2.9 ng/L. The antigen determinations were made centrally at the Frederick National Laboratory, blinded to treatment group.

Stored plasma specimens were used to measure total anti-SARS-CoV-2 antibody levels. Antibody levels were determined using the BioRad Platelia SARS-CoV-2 Total Ab assay (BioRad, Hercules, California) (anti-N antibodies). Results of this assay are reported as "specimen ratios". Specimen ratios are defined as the specimen optical density (OD) divided by the OD of the control R4(OD_MR4). Specimen ratios ≥ 1.0 are considered positive, those between 0.8 and 1.0 equivocal, and those < 0.8 negative. In this report, we refer to those with levels < 1.0 specimen ratios as having "negative" anti-N Abs and those with specimen ratios ≥ 1.0 as having positive anti-N Abs.

Levels of neutralizing antibodies (nAbs) directed against the SARS-CoV-2 receptor binding domain (RBD) were determined using the GenScript SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) assay (GenScript, Piscataway, NJ) (nAbs). nAbs are expressed as percent binding inhibition; levels ≥ 30% are considered positive for nAbs as recommended by the manufacturer, and those < 30% are considered negative for nAbs.

Antibody determinations were made centrally at the Frederick National Laboratory, blinded to treatment group.

F. Sample Size (extracted from protocol)

The planned sample size is 500 participants (250 per group).
The following assumptions were made in estimating the required sample size.

a. *The primary analysis will be modified intention-to-treat (mITT).*
b. A proportional odds model with indicators for the six cut-offs corresponding to using any of categories 1 to 6 as cut-offs for determining clinical improvement, treatment group (hIVIG versus placebo), baseline severity of illness as defined by the ordinal outcome, two-way interactions between baseline severity of illness and the six cut-offs, hIVIG product/matching placebo used, and two-way interactions between hIVIG product/matching placebo used and the six cut-offs will be used to estimate the odds ratio (OR).
c. Type 1 error = 0.05 (2-sided) and power = 0.80.
d. The clinical status of participants in the placebo group at Day 7 is assumed as shown in the third column in. Since both randomized treatment groups will receive remdesivir as SOC (unless contraindicated), these percentages were estimated using Day 7 data from the ACTT-1 trial for a subgroup of patients similar to ours (the subgroup of participants who entered ACTT-1 in categories 4 and 5 of their eight-category ordinal outcome for disease severity and were randomized to the remdesivir group).
e. We assumed an OR (hIVIG/placebo) of 1.61 for a more favorable outcome. This corresponds to the percentage of participants in the hIVIG group at Day 7 shown in each level of the ordinal scale given in the second column in Table 1 below. For example, the percentage of participants in the two most favorable categories would be increased to 65.4% in the hIVIG group from 54.0% in the placebo group (an 11.4 percentage point increase from the placebo group). Conversely, the percentage of participants in the four most severe categories would decrease to 19.4% from 28.1% in the placebo group. The same proportional improvement was assumed across the ordinal scale.
f. Sample size depends on a number of assumptions, including the hypothesized odds ratio, the number of categories in the ordinal outcome, and the distribution of responses for the placebo group.[3] Hypothesized odds ratios closer to 1.0 correspond to a smaller treatment effect and require a larger sample size to maintain 80% power. The final sample size was chosen after consideration of a range of odds ratios and of category percentages for the placebo group.
g. *Based on the category percentages in Table 1, the estimated sample size is 494. This was increased to 500 to allow for a small number of participants who may be randomized but not receive the study infusion or meet strict eligibility criteria. These participants will be excluded from the mITT analysis.*

HYPOTHESIZED PERCENTAGE OF PARTICIPANTS IN EACH CATEGORY ON DAY 7 IN THE HIVIG AND PLACEBO GROUPS BASED ON AFOREMENTIONED ASSUMPTIONS

Category	hIVIG + SOC Group	Placebo + SOC Group
7. Death	0.6	1.0
6. End-organ failure	4.0	6.3
5. Life-threatening end-organ dysfunction	4.2	6.3
4. Serious end-organ dysfunction	10.6	14.5
3. Moderate end-organ dysfunction.	15.1	17.9
2. Limiting symptoms due to COVID-19	57.6	49.0
1. No limiting symptoms due to COVID-19	7.8	5.0
Total	100.0	100.0

Following the DSMB meeting on January 5, 2021, the DSMB approved the provision of the pooled (both treatment groups combined) category proportions to blinded statisticians in order to re-estimate sample size. Using the observed pooled proportions, power was estimated to be 0.83 for the planned sample size of 500. Based on this, no change in sample size was recommended.

In January 2021, a decision was made to continue enrollment through February 10, 2021. This allowed an opportunity for sites that opened to enrollment late to contribute to the trial. It was recognized that with the rapid pace of enrollment, this decision could result in over-enrollment of the planned 500 participants. Thus, the central IRB was notified on February 3, 2021. This decision did not result from a review of unblinded data by the investigators or DSMB.

G. Monitoring Guidelines

The information below is taken from the protocol and version 1.0 of the statistical analysis plan.

The following guidelines were given to the DSMB for trial monitoring:

The DSMB is to consider a recommendation for stopping the trial early for efficacy only if there is clear and convincing evidence of superiority of the hIVIG versus the control group with respect to the primary outcome.

For monitoring superiority, the Lan-DeMets spending function analogue of the O'Brien-Fleming boundaries will be used, with a 1-sided 0.025 level of significance over multiple looks. The boundary for harm is asymmetric, requiring less evidence to stop for harm (described below) than for superiority. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the observed total number of participants with Day 7 ordinal outcome data divided by the planned number of participants.

It is important that each hIVIG product is well-represented in the number of participants enrolled at the time of a recommendation by the DSMB to stop early due to convincing evidence of efficacy. Thus, we recommend that early termination for efficacy not be considered until at least 250 participants have been enrolled and at the time such a decision is made the DSMB also consider the number assigned each product. As a guideline we recommend that at least 20% of the information (number with a Day 7 outcome), be from each hIVIG product.

A Haybittle-Peto boundary of 2.5 standard deviations (SD) for the first 100 participants enrolled and 2.0 SD afterwards will be used as a guideline for harm. The SD refers to the standard deviation of the test statistic (standardized estimate of the summary log OR). With this boundary, less evidence is needed for stopping a trial early due to harm compared with stopping for efficacy.

To assess futility, conditional power calculations based on an unadjusted model (as was done for the original power calculations) for the Day 7 ordinal outcome will be presented under a range of scenarios. In the primary futility analysis, it will be assumed that the treatment effect for the future, as yet unobserved follow-up, will be as hypothesized in the study design (adjusted OR = 1.61). As secondary analysis, the treatment effect for future follow-up will be assumed to be similar to the observed effect. Additional scenarios may be provided. Typical futility guidelines recommend stopping a trial when conditional power (assuming the originally hypothesized treatment effect for the future, as yet unobserved follow-up) is below 10%-20%.

As a guideline, futility will first be assessed after 50% of the planned number of participants have Day 7 ordinal outcome data, and a value of 20% will be suggested as a threshold for the conditional power. Conditional power will be computed using the test statistic for the treatment indicator in a cumulative logistic regression model.

Decisions to terminate the study for futility will include a broad assessment of the risk/benefit trade-off in addition to these guidelines.

H. Statistical Methods

Details of Analysis for Primary Efficacy Endpoint

A proportional odds model was used to compare the distribution of the primary ordinal outcome at day 7. The proportional odds model estimates a summary OR; that is, the ratio of the cumulative odds of being in a better category of the ordinal outcome for hIVIG versus placebo. A 7 category outcome can be dichotomized in 6 possible ways according to which cut-off is used. For each of the six dichotomized outcomes an odds ratio for the effect of treatment on the odds of being in the better of the two categories can be calculated. A proportional odds model makes the assumption that each of the six underlying odds ratios is the same and thus gives a single odds ratio estimate.

The model uses the cumulative probabilities of being in any of categories 1 up to a threshold (or cut-off) to define six cumulative odds corresponding to cut-offs at categories 1, 2,.., 6. The model included a single indicator for treatment, indicators for the participant's clinical state at entry (categories of ordinal outcome), and its two-way interactions with the six cut-offs for each of the six cumulative odds of improvement. The model also included indicators for which of the four study products was used by the site and their two-way interactions with the six cut-offs. That is, the baseline ordinal outcome and indicators for the four study products were allowed to have unequal slopes in the model.

Proportional odds models with the same covariates were also fit for the ordinal outcome at days 1-6, 14, and 28.

A test for the proportional odds assumption was made from a model that allows different effect estimates for the hIVIG versus placebo according to the cut-off of the ordinal scale (a partial proportional odds model).

Multiple Imputation

A multiple imputation strategy was developed prior to unblinding for the 7 participants with a missing Day 7 primary ordinal outcome. Six of these 7 participants were known to have been discharged. For these participants it was assumed that they are in one of the three most favorable categories (3 of the 6 discharged participants were on oxygen the day of discharge). For this imputation, for those discharged by Day 7, in addition to treatment group, the following baseline covariates were considered: age, clinical status based on the ordinal outcome at enrollment, duration of symptoms, presence of any comorbidity, and NEW score. In addition to the baseline covariates, the day of discharge after randomization, and oxygen status on the day of discharge was used in the imputation.

The participant for whom discharge from the hospital was unknown was transferred to another hospital on Day 2 and was known to be alive on Day 7 (this was established on Day 27 but there were no other intermediate contacts between Day 2 and Day 27). For this participant, the ordinal category on Day 2 was imputed for the Day 7 primary outcome.

We imputed ten data sets; parameter estimates (e.g., the summary odds ratio) from the 10 multiply imputed datasets were combined using Rubin's combining rules.

Sensitivity Analyses for the Primary Endpoint

Three sensitivity analyses were carried out to further characterize the summary OR for the primary endpoint and any any deviations from proportional odds (see Statistical Data Analysis Plan)

- The model was refitted excluding the 7 participants for whom the Day 7 outcome was missing.

- Categories 3 and 4 of the primary endpoint at Day 7 were combined to create a six-category ordinal outcome.
- Separate ORs were estimated for the six dichotomized definitions of improvement, e.g., category 1 vs 2-7, categories 1 and 2 versus 3-7,…, categories 1-6 vs 7.

Subgroup Analysis

Subgroup analyses for the primary seven-category ordinal outcome (primary efficacy outcome), as well as for the composite safety outcomes (Grade 3 and 4 adverse events, SAEs, end organ dysfunction, serious infections, or death through Day 7 and Day 28) (Grade 3 and 4 events are only collected through Day 7) are performed to determine whether and how the treatment effect (hIVIG versus placebo) differs qualitatively across various subgroups defined at baseline, and whether there are safety concerns in specific subgroups.

The protocol specified duration of symptoms at entry as a key subgrouping variable for the Day 7 ordinal outcome. It was hypothesized that those with shorter duration of symptoms would have a better outcome on hIVIG compared to placebo than those with longer duration of symptoms.

In addition, after the trial was completed stored specimens collected prior to randomization were analysed for viral RNA in mid-turbinate samples, plasma antigen level, and plasma antibody levels. Our *a priori* hypothesis was as follows: Patients with negative or lower positive antibody levels will benefit more from hIVIG compared to placebo than patients with higher antibody levels. Furthermore, those with lower antibody levels AND with higher antigen levels, will benefit more from hIVIG compared to placebo than other subgroups categorized by both antibody and antigen levels.

For other subgroups we had no *a priori* reason to believe the clinical efficacy or safety of hIVIG compared to placebo will be substantially different in relative terms in any of the subgroups considered.

Subgroup analyses for the primary efficacy endpoint use the adjusted (cumulative) logistic models described earlier. ORs with 95% CIs comparing the treatment group versus control are estimated for each subgroup. Global tests for heterogeneity of the treatment effect across subgroups is carried out by adding the interaction between the subgroup indicator and the treatment group indicator to the model. In case the subgroup is formed by categorizing a continuous variable, the interaction term is formed between the subgroup indicator and the continuous variable.

Subgroup analyses for the composite safety endpoints use logistic and proportional hazards regression models with the same approach.

Over 20 subgroups were pre-specified in version 2.0 of the data analysis plan. Thus, the results of the subgroup analyses should be interpreted with caution; a significant interaction could be due to chance, because there was no adjustment made to the type 1 error for the number of subgroups examined.

Data Management and Quality Assurance

Case reports forms were completed by trained staff at each clinical site, REDCap (Research Electronic Data Capture) was used for electronic data collection at each site. The central database for the trial resided at the Statistical and Data Management Center (SDMC) at the University of Minnesota. It was comprised of a number of database tables in Oracle, from which additional data views and analysis files were created. On a daily basis data queries based on pre-specified edits for clinical sites to address were posted to the INSIGHT study web site. Reports summarizing data quality (e.g., missing data) were posted to the INSIGHT web site and on a regular basis the protocol team and a committee comprised of ICC and SDMC staff reviewed site quality performance data.

IV: Supplemental Appendix D: Supplemental Results

This section briefly summarizes tables and figures included in this supplement. The subheadings of the text in the main paper are used to organize this section.

Participant characteristics

Table S1. This table shows enrollment by country. Eleven countries enrolled participants with the United States (43%), Denmark (13%), Greece (11%) and Spain (11%) enrolling the most participants.

Table S2. The baseline characteristics of all 593 participants randomized are summarized. This includes the 14 (6 hIVIG, 8 placebo) participants that were excluded from the modified intention to treat (mITT) population.

Table S3. The enrollment of participants by product is shown in this table. The number of participants randomized to each of the four products or their matching placebo are similar.

Table S4. The frequency distribution of Texcell potency levels by product and overall are shown. A total of 43 lots of hIVIG were used. The median (IQR) Texcell potency levels (IU/mL) of the 43 lots was 1220 (893, 1442).

Table S5. This table includes an expanded list of baseline characteristics by treatment group and overall for the mITT population. Some items in Table 1 are also included in Table S5, e.g., history of chronic health conditions, so that the complete list of baseline characteristics summarized are in one place.

Table S6. In this table, we present the baseline anti-nucleocapsid antibody and neutralizing anti-spike antibody results by baseline patient characteristics without categorizing patients into randomized group. Plasma specimens were collected at baseline (after consent for study participation and before administration of the study infusion) for measurement of: (1) total anti-nucleocapsid SARS-CoV-2 antibodies (BioRad Platelia SARS-CoV-2 Total Ab assay; BioRad, Hercules, California), (2) neutralizing anti-spike SARS-CoV-2 antibodies (GenScript SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) assay; GenScript, Piscataway, New Jersey), and (3) nucleocapsid SARS-CoV-2 antigen concentration (Quanterix assay; Quanterix, Billerica, MA). The laboratory measurements were completed for a total of 526 patients.

Efficacy outcomes

Table S7. Two sensitivity analyses for the primary endpoint are shown in this table; an analysis without imputing data for the 7 participants without Day 7 outcome data and an analysis combining ordinal outcome categories 3 and 4. Both sensitivity analyses were consistent with the primary analysis yielding ORs of 1.04 (95% CI: 0.76-1.43) and 0.99 (95% CI: 0.70-1.38).

A 3rd sensitivity analysis estimated the 6 definitions of improvement that can be formulated form the 7 categories of primary ordinal outcome. Estimates of these ORs and 95% CIs adjusted for the baseline ordinal category and the hIVIG product used by site pharmacies are 1.18 (95% CI: 0.59-2.36), 1.16 (0.73-1.86), 1.30 (0.79-2.12), 1.08 (0.55-2.13), 0.65 (0.20-2.16), 0.76 (nos. too small).

Table S8. Additional secondary efficacy outcomes are summarized in this table. The hIVIG/placebo odds ratios for the ordinal outcome at Days 3, 5, 14 and 28 range from 0.96 to 1.09. The hIVIG/placebo RRR for reaching one of the 3 least favorable outcomes is 0.85, 95% CI: 0.57, 1.28; p=0.45.

Table S9. In this table the primary ordinal outcome at Day 7 is classified as “better”, “same”, or “worse” compared to baseline for each baseline category. Over all baseline categories, the percentage in each of these 3 categories was 63% (better), 22% (same), and 15% (worse) for the hIVIG group and 64%, 18%, and 18%, respectively, for the placebo group.

Table S10. The pulmonary only components of the primary endpoint are summarized in this table. Three participants were categorized differently compared to the primary ordinal outcome.

Table S11. Odds ratios for the pulmonary only components of the primary endpoint at Days 3, 5, 14, and 28 are shown in this table.

Table S12A This table shows the number and percentage of participants who were hospitalized or had died at days 7, 14 and 28 by treatment group. The number and percent who had died or were hospitalized and not in the most favourable ordinal outcome category (can independently undertake usual activities with minimal or no symptoms) are also summarized. At Day 7, as compared to days 14 and 28, there were a larger number of participants in the hospital who were in the most favourable category of the ordinal outcome ("can independently undertake usual activities with minimal or no symptoms"). These participants were likely retained in the hospital for public health reasons.

Tables S12B and S12C. These tables repeat the results in Table 12A for 2 subgroups: 1) participants who were nAb positive at baseline; and 2) participants who were nAb negative at baseline. In both treatment groups the percentages with each of the two outcomes are higher among nAb negative than nAb positive participants.

All ORs in Table 12B (nAb positives) are greater than 1.0 favoring placebo; in Table 12C (nAbnegatives) all ORs are <1.0 favoring hIVIG. Interaction tests were performed to determine whether ORs varied by nAb status. For the hospitalization or death outcome, p-values for the interaction tests were: Day 7 = 0.02, Day 14 = 0.27, and Day 28 = 0.53.

Similar interaction tests were carried out for the outcome hospitalization and not in the most favorable ordinal outcome category or death, and these interaction p-values were: Day 7 = 0.10, Day 14 = 0.20, and Day 28 = 0.60.

Table S13. Mean and Median days alive outside of a hospital are shown in this table. Additionally, days alive and in the most favourable ordinal outcome category and days alive outside of a hospital or days in most favourable ordinal outcome category (whichever is greater) are summarized.

<u>Safety outcomes</u>

Table S14. Infusion reactions by severity grade and treatment group are summarized in table S11. Infusion reactions that occurred during or within 2 hours following the hIVIG or placebo infusion were recorded using a checklist. Percentages with infusion reactions (hIVIG vs placebo) ≥ grade 1, ≥ grade 2, and ≥ grade 3 are 19% vs 10% (p=0.002), 13% vs 6% (p=0.008), and 6% vs 1% (p=0.012), respectively.

Table S15. This table summarizes the hIVIG and placebo infusions. The median (IQR) infusion time was 2.9 (2.3, 3.3) hours. Seven percent of hIVIG infusions and 3% of placebo infusions were paused due to adverse events. Concomitant medications could be used prior to the infusion to prevent infusion reactions. Medications were used prior to the infusion in 30% of hIVIG participants and 31% placebo participants. Medications were used in response to adverse events in 14% and 4% of hIVIG and placebo participants, respectively.

Table S16 and S17. A site in Nigeria infused participants at a faster rate than was specified in the protocol. Table S16 summarizes infusion statistics for the 41 participants randomized at the site in Nigeria and Table S17 summarizes the same statistics for all sites except Nigeria. Table S15, mentioned previously, provides the summary for all 593 randomized participants.

Infusion times are lower and rates are greater for both the hIVIG and placebo groups for the site in Nigeria (Table S16) compared to all other sites (Table S17). For both treatment groups combined, infusion times and rates are 0.8 hours and 6.0 mg/kg/minute for Nigeria and 2.9 hours and 1.9 mg/kg/minute for all other sites.

The infusion was paused for one participant (5%) assigned hIVIG and none for placebo in Nigeria. For all other sites, 21 participants (8%) assigned hIVIG and 8 (3%) assigned placebo had the infusion paused for adverse events (p=0.02 for difference).

Tables S18 and S19. Table S18 summarizes infusion reactions for the 41 participants randomized at the site in Nigeria and Table S19 summarizes the same data for all sites except Nigeria. In Nigeria, none of the placebo participants experienced an infusion reaction; for those assigned hIVIG, 8 (38%), 7 (33%), and 6 (29%) experienced ≥ grade 1, ≥ grade 2, and ≥ grade 3 reactions, respectively. Like the Nigerian site, for all other sites, more participants assigned hIVIG as compared to placebo experienced infusion reactions: 17% vs 10%, 11% vs 6%, and 4% vs 2% for ≥ grade 1, ≥ grade 2, and ≥ grade 3 reactions, respectively. The most common reaction experienced by the participants in Nigeria was chills (6, all grade 3). For all other sites the most common reactions were fever (20 participants in the hIVIG group and 9 in the placebo group) and chills (14 participants in the hIVIG group and 1 in the placebo group).

Compared to Table S14, when the Nigerian site is excluded as in Table S18, the hIVIG – placebo differences in the percentages with infusion reactions are reduced: 9% (19%-10%) vs 7% (17%-10%) for reactions ≥ grade 1; 7% (13%-6%) vs 5% (11%-6%) for those ≥ grade 2; and 5% (6%-1%) vs 2% (4%-2%) ≥ grade 3 reactions. Based on these summaries we conclude that the higher percentage of infusion reactions reported for the hIVIG group compared to the placebo group is maintained with the exclusion of Nigeria but the differences between the treatment groups in any reaction as well as those that are more severe are reduced.

Table S20. The number and percentage of participants who experienced each of the components of the composite safety outcome at Day 7 and Day 28 are shown. Participants may have experienced more than one of the components.

Figure S1. This figure shows the Kaplan Meier curves for the time to the day 28 safety outcome (death, SAE, organ failure or serious infection).

Table S21. This table summarizes death, SAE or Grade 3 or 4 events through Day 7, by MedDRA (version 23.1) system organ class (SOC).

Table S22. This table shows the number and percent who experienced a clinical organ failure or serious infection event through Day 7. Overall, 14% hIVIG and 17% placebo participants experienced an event with respiratory failure being the most common (12% and 16%, respectively).

Table S23. This table summarizes death or SAEs through Day 28, by MedDRA (version 23.1) system organ class (SOC).

Table S24. Similar to Table S22, this table shows the number and percent who experienced a clinical organ failure or serious infection event, but now through Day 28. Overall, 19% hIVIG and 23% placebo participants experienced an event through Day 28 with respiratory failure being the most common (15% and 19%, respectively).

Tables S25, S26, S27 and S28. The prevalence of adverse events of any grade at Days 1, 3, 7 and 28 are summarized in Tables S25, S26, S27 and S28, respectively, by MedDRA SOC. ORs (hIVIG/placebo) for an AE of any type or grade did not differ significantly from 1.0 on Days 1, 3, 7. On Day 28, the OR was 1.62 (95% CI: 1.07-2.45). The percentages of participants with AEs of any grade severity were 28.6% for the hIVIG group and 19.7% for the placebo group on Day 28. The most common AEs were in the SOC corresponding to respiratory, thoracic, mediastinal events.

Table S29. Changes between baseline and Day 7 are given in this table for protocol-required locally determined laboratory markers.

Table S03. The use of selected concomitant medications was collected at Day 7. These treatments are summarized in this table by treatment group. No consistent differences by treatment group were evident.

Table S31. This table provides more detailed summaries of the use of antibacterial, heparin, and corticosteroid medications at baseline and day 7 by treatment group.

Subgroup Analyses

Table S32. In this table, the Day 7 ordinal outcome OR is examined for heterogeneity across baseline-defined subgroups. ORs are estimated with a proportional odds model that included terms for the baseline category of the ordinal outcome, hIVIG/placebo product, treatment group, the subgrouping variable, and interaction terms between the subgrouping variable and treatment group. The only interaction evident was by age – with increasing age, the day 7 ordinal outcome was more favorable for hIVIG compared to placebo.

Figure S2. The Day 7 composite safety outcome (death, SAE or grade 3 or 4 adverse events, organ failure or serious infection) by baseline-defined subgroups are shown in this figure.

Table S33. The Day 7 composite safety outcome (death, SAE or grade 3 or 4 adverse events, organ failure or serious infection) by baseline-defined subgroups are shown in table S26. Significant interactions by age, nAb status, and nAb and antigen/viral RNA status were noted. The nAb status subgroup is described in the main text of the paper. A higher risk of the composite safety outcome at Day 7 for the hIVIG group compared to placebo among those nAb positive was evident for those with low and high antigen or viral RNA levels; for nAb negative a lower risk of the composite safety outcome at Day 7 was evident for those low and high antigen and viral RNA levels.

With increasing age the Day 7 composite safety outcome was more favorable for hIVIG than placebo.

Table S34. In this table, additional subgroup analyses for the Day 28 composite outcome (SAE, death, organ failure or serious infection) are shown. There was no evidence of heterogeneity among the subgroups considered.

Figure S3. Figure S3 shows the Kaplan Meier curves for the time to the day 28 safety outcome (death, SAE, organ failure or serious infection) restricted to those nAb positive at baseline.

Figure S4. Figure S4 shows the Kaplan Meier curves for the time to the day 28 safety outcome (death, SAE, organ failure or serious infection) restricted to those nAb negative at baseline.

Further Analyses of Safety Outcomes by Baseline Antibody Status

Table S35. This table shows the number and percentage of nAb positive participants who experienced each of the components of the composite safety outcome at Day 7 and Day 28. All of the components of the composite at Day 7 favored placebo.

Table S36. This table shows the number and percentage of nAb negative participants who experienced each of the components of the composite safety outcome at Day 7 and Day 28.

Table S37. Table S37 summarizes death, SAE or Grade 3 or 4 events through Day 7, by MedDRA (version 23.1) system organ class (SOC), restricted to those nAb positive at baseline. The most common events were in the Respiratory, Thoracic, Mediastinal SOC.

Table S38. Table S38 summarizes death, SAE or Grade 3 or 4 events through Day 7, by MedDRA (version 23.1) system organ class (SOC), restricted to those nAb negative at baseline. . The most common events were in the Respiratory, Thoracic, Mediastinal SOC.

Table S39. Table S39 summarizes clinical organ failure and serious infection events through Day 7, restricted to those nAb positive at baseline. Respiratory failure was the most common end organ failure event.

Table S40. Table S40 summarizes clinical organ failure and serious infection events through Day 7, restricted to those nAb negative at baseline. Respiratory failure was the most common end organ failure event.

Table S41. Table S41 summarizes deaths or SAEs through Day 28, by MedDRA (version 23.1) system organ class (SOC), restricted to those nAb positive at baseline.

Table S42. Table S42 summarizes deaths or SAEs through Day 28, by MedDRA (version 23.1) system organ class (SOC), restricted to those nAb negative at baseline.

Table S43. Table S43 summarizes clinical organ failure and serious infection events through Day 28, restricted to those nAb positive at baseline. Respiratory failure was the most common end organ failure event.

Table S44. Table S44 summarizes clinical organ failure and serious infection events through Day 28, restricted to those nAb negative at baseline. Respiratory failure was the most common end organ failure event.

Table S1: Enrollment by Country

Country	hIVIG (n=301)	Placebo (n=292)	Total (n=593)
Argentina	3	1	4
Denmark	39	38	77
Germany	5	5	10
Greece	34	36	70
Indonesia	17	16	33
Israel	3	3	6
Japan	7	8	15
Nigeria	21	20	41
Spain	33	32	65
UK	10	9	19
USA	129	124	253

Table S2: Baseline characteristics of all participants randomized

Characteristic		hIVIG (n=301)	Placebo (n=292)	Total (n=593)
Age	Median (IQR) – yr	58 (48,70)	60 (51,70)	59 (50, 70)
Female sex	No. (%)	149 (50%)	108 (37%)	257 (43%)
Race	No. (%)			
White		174 (58%)	160 (55%)	334 (56%)
Hispanic		41 (14%)	47 (16%)	88 (15%)
Black		42 (14%)	48 (16%)	90 (15%)
Asian		39 (13%)	31 (11%)	70 (12%)
Other		5 (2%)	6 (2%)	11 (2%)
Ordinal category	No. (%)			
Not receiving supplementary oxygen		80 (27%)	86 (30%)	166 (28%)
Supplementary oxygen < 4 liter/min		109 (37%)	94 (32%)	203 (34%)
Supplementary oxygen > 4 liter/min		87 (29%)	79 (27%)	166 (28%)
High-flow oxygen		25 (8%)	33 (11%)	58 (10%)
Days since symptom onset	Median (IQR) - days	8 (5,10)	8 (6,10)	8 (6,10)
C-reactive protein	Median – mg/L	61 (20,111)	63 (28,120)	62 (23,112)
Lymphocytes	Median (IQR) – 10^9/L	.95 (.70,1.39)	.89 (.62,1.30)	.93 (.65,1.35)
Body-mass index	No. (%) – kg/m^2			
	≥30	146 (49%)	140 (49%)	286 (49%)
	≥40	34 (11%)	30 (10%)	64 (11%)
History of:	No. (%)			
Hypertension requiring Medication		127 (42%)	125 (43%)	252 (42%)
Diabetes requiring medication		88 (29%)	82 (28%)	170 (29%)
Renal impairment		17 (6%)	26 (9%)	43 (7%)
Asthma		33 (11%)	27 (9%)	60 (10%)
COPD		23 (8%)	16 (5%)	39 (7%)
Heart failure		17 (6%)	11 (4%)	28 (5%)
Compromised immune function*		15 (5%)	14 (5%)	29 (5%)
At least one co-morbidity		191 (63%)	174 (60%)	365 (62%)
SARS-CoV-2 vaccination prior to enrolment		9 (3%)	4 (1%)	13 (2%)
Use of Remdesivir prior to enrolment	No. (%)	145 (48%)	143 (49%)	288 (49%)
Concomitant medications				
Corticosteroids		175 (58%)	155 (53%)	330 (56%)
Antibacterial		126 (42%)	118 (41%)	244 (41%)
Heparin		182 (61%)	177 (61%)	359 (61%)
Other antiplatelets/anticoagulants		38 (13%)	40 (14%)	78 (13%)
ACE inhibitor or ARB		56 (19%)	71 (24%)	127 (21%)
NSAID		24 (8%)	22 (8%)	46 (8%)

* HIV, an immunosuppressive condition other than HIV, taking antirejection medication, immune modulators, or biologic treatment for autoimmune disease or cancer

Table S3: Enrollment by product

Product	hIVIG (n=301)	Placebo (n=292)	Total (n=593)
CSL Behring	77	78	155
Emergent	81	72	153
Grifols	74	72	146
Takeda	69	70	139

Table S4: Frequency distribution of Texcell potency levels (IU/mL) by product

Distribution	CSL Behring	Emergent	Grifols	Takeda	Overall
Minimum	1379	1031	660	637	637
25th percentile	1537	1031	952	732	893
Median	1593	1300	1161	1098	1220
75th percentile	2018	1631	1431	1312	1442
Maximum	2365	1631	1549	1651	2365
Number of lots used	5	3	21	14	43
Number of sites	14	19	15	15	63

Table S5: Additional baseline characteristics of mITT population by treatment group

Baseline Characteristic		hIVIG (n=295)	Placebo (n=284)	Total (n=579)
NEW Score	Median (IQR)	4 (2, 5)	3 (2, 5)	3 (2, 5)
	No. (%)			
< 2		44 (15%)	41 (14%)	85 (15%)
2-3		102 (35%)	110 (39%)	212 (37%)
4-5		100 (34%)	74 (26%)	174 (30%)
≥ 6		49 (17%)	59 (21%)	108 (19%)
Modified Borg Dyspnea Scale Score	No. (%) - available	290 (98%)	280 (99%)	570 (98%)
0 – Nothing at all		62 (21%)	62 (22%)	124 (22%)
0.5 – Very, very slight		16 (6%)	26 (9%)	42 (7%)
1 – Very slight		31 (11%)	36 (13%)	67 (12%)
2 – Slight		53 (18%)	45 (16%)	98 (17%)
3 – Moderate		57 (20%)	46 (16%)	103 (18%)
4 – Somewhat severe		21 (7%)	23 (8%)	44 (8%)
5 – Severe		23 (8%)	23 (8%)	46 (8%)
6		8 (3%)	5 (2%)	13 (2%)
7 – Very severe		9 (3%)	7 (3%)	16 (3%)
8		7 (2%)	6 (2%)	13 (2%)
9 – Very, very severe		3 (1%)	0 (0%)	3 (1%)
10 – Maximal		0 (0%)	1 (0%)	1 (0%)
History of any of the below	No. (%)	186 (63%)	168 (59%)	354 (61%)
Hypertension requiring medication		125 (42%)	122 (43%)	247 (43%)
Diabetes requiring medication		84 (28%)	80 (28%)	164 (28%)
Asthma		32 (11%)	26 (9%)	58 (10%)
Renal impairment		17 (6%)	24 (8%)	41 (7%)
COPD		23 (8%)	16 (6%)	39 (7%)
Heart failure		17 (6%)	10 (4%)	27 (5%)
Malignancy		10 (3%)	10 (4%)	20 (3%)
HIV or other immune suppression		12 (4%)	6 (2%)	18 (3%)
MI or acute coronary syndrome		9 (3%)	5 (2%)	14 (2%)
Hepatic impairment		7 (2%)	4 (1%)	11 (2%)
Cerebrovascular event		3 (1%)	2 (1%)	5 (1%)
Ongoing use of	No. (%)			
Antiplatelets/anticoagulants		217 (74%)	212 (75%)	429 (74%)
Aspirin		29 (10%)	33 (12%)	62 (11%)
Other antiplatelets		24 (8%)	23 (8%)	47 (8%)
Heparin prophylactic dose		148 (50%)	147 (52%)	295 (51%)
Heparin intermediate dose		23 (8%)	21 (7%)	44 (8%)
Heparin therapeutic dose		8 (3%)	5 (2%)	13 (2%)
Warfarin		0 (0%)	2 (1%)	2 (0%)
DOAC		12 (4%)	14 (5%)	26 (4%)
Antibacterials		124 (42%)	118 (42%)	242 (42%)

IV	90 (31%)	93 (33%)	183 (32%)
Oral	55 (19%)	61 (21%)	116 (20%)
Antivirals	8 (3%)	10 (4%)	18 (3%)
Antifungals	2 (1%)	1 (0%)	3 (1%)
ACE inhibitors	20 (7%)	38 (13%)	58 (10%)
ARBs	37 (13%)	31 (11%)	68 (12%)
Antirejection medications	0 (0%)	2 (1%)	2 (0%)
Immune modulators	3 (1%)	5 (2%)	8 (1%)
NSAID	24 (8%)	20 (7%)	44 (8%)
Biologics for cancer/autoimmune disease	2 (1%)	1 (0%)	3 (1%)
Corticosteroids	172 (58%)	155 (55%)	327 (56%)

Table S6. Anti-SARS-CoV-2 antibodies at baseline by patient characteristics

		Anti-nucleocapsid antibody		Neutralizing anti-spike antibody	
	No. patients	**Sample/control ratio; median (IQR)**	**Antibody positive (%)**	**Binding inhibition; median (IQR)**	**Antibody positive (%)**
All patients	**539**	**3.5 (0.4, 4.0)**	**69.4**	**27.1 (9.7, 61.0)**	**48.4**
Duration of symptoms prior to enrollment (days)					
0-5 days	124	0.3 (0.1, 3.9)	43.5	12.8 (5.2, 35.5)	27.4
6-7 days	116	2.0 (0.2, 4.0)	55.2	21.2 (4.3, 50.4)	34.5
8-9 days	129	4.0 (1.2, 4.1)	78.3	36.2 (12.2, 67.8)	56.6
10-12 days	170	4.0 (3.3, 4.1)	91.2	47.4 (22.0, 74.1)	67.1
Age (years)					
<50	122	3.4 (0.5, 4.0)	73.8	39.3 (13.3, 71.5)	58.2
50-59	144	3.5 (0.7, 4.1)	74.3	26.6 (9.4, 56.0)	49.3
60-69	126	3.9 (0.3, 4.0)	67.5	35.2 (10.3, 65.7)	52.4
≥70	147	3.3 (0.2, 4.0)	62.6	19.9 (8.5, 47.4)	36.1
Supplement oxygen use					
No oxygen	135	2.7 (0.1, 4.0)	57.8	15.2 (5.6, 37.2)	31.1
Oxygen flow rate <4 L/min	193	3.3 (0.3, 4.0)	65.3	31.0 (10.1, 58.5)	50.8
Oxygen flow rate ≥4 L/min	154	4.0 (1.4, 4.1)	79.9	39.6 (16.9, 70.8)	55.8
High flow oxygen	57	4.0 (2.8, 4.0)	82.5	49.9 (15.9, 78.1)	61.4
Nucleocapsid antigen					
< 1400 pg/ml	273	4.0 (1.1, 4.1)	75.1	49.9 (17.2, 78.2)	62.3
≥ 1400 pg/ml	265	3.1 (0.3, 4.0)	63.8	17.0 (7.0, 38.6)	34.3

Table S7. Primary endpoint sensitivity analyses

	OR (95%CI)[1]	P-value
No multiple imputation (excludes 7 without Day 7 outcome data)	1.04 (0.76, 1.43)	0.80
Combining categories 3 and 4 (supplemental oxygen < 4 liters/min and supplemental oxygen ≥ 4 liters/min)	0.99 (0.70, 1.38)	0.94

[1]Summary odds ratio (hIVIG/placebo) of being in a better category using proportional odds model with adjustment for participant's baseline ordinal category, hIVIG/placebo product and interaction terms

Table S8: Summary of Secondary Efficacy Outcomes by Treatment Group

Outcome	hIVIG (n=295)	Placebo (n=284)	OR or HR (95%CI)	P-value
Ordinal outcome at Day 3	-	-	0.96 (0.68, 1.37)	.83
Ordinal outcome at Day 5	-	-	1.05 (0.77, 1.45)	.74
Ordinal outcome at Day 14	-	-	1.09 (0.78, 1.53)	.61
Ordinal outcome at Day 28	-	-	1.05 (0.71, 1.54)	.81
N reaching one of three least favorable categories (categories 5, 6, and 7)	45	48	0.85 (0.57, 1.28)	.45

ORs are cited for the ordinal outcomes and an HR is cited for the last outcome in the table.

Table S9: Change in ordinal outcome category by baseline oxygen requirement

Baseline category	hIVIG No. (%)	Placebo No. (%)
No oxygen use[1]		
Better category on Day 7	45 (58%)	47 (59%)
Same category on Day 7	25 (32%)	23 (29%)
Worse category on Day 7	8 (10%)	10 (13%)
Supplemental oxygen < 4 L/min[2]		
Better category on Day 7	79 (74%)	66 (73%)
Same category on Day 7	17 (16%)	7 (8%)
Worse category on Day 7	11 (10%)	17 (19%)
Supplemental oxygen ≥ 4 L/min[2]		
Better category on Day 7	48 (57%)	48 (63%)
Same category on Day 7	16 (19%)	12 (16%)
Worse category on Day 7	20 (24%)	16 (21%)
High flow oxygen		
Better category on Day 7	12 (50%)	18 (55%)
Same category on Day 7	7 (29%)	8 (24%)
Worse category on Day 7	5 (21%)	7 (21%)
All participants		
Better category on Day 7	184 (63%)	179 (64%)
Same category on Day 7	65 (22%)	50 (18%)
Worse category on Day 7	44 (15%)	50 (18%)

[1]Or same oxygen requirement as pre-COVID flow rate, if applicable

[2]Compared to pre-COVID flow rate, if applicable

Table S10: Pulmonary components of the ordinal outcome on Day 7

Category		hIVIG (n=293) No. (%)	Placebo (n=279) No. (%)
1	Can independently undertake usual activities with minimal or no symptoms	129 (44%)	116 (42%)
2	No supplemental oxygen; symptomatic and unable to independently undertake usual activities	67 (23%)	61 (22%)
3	Supplemental oxygen < 4 liters/min[1]	33 (11%)	30 (11%)
4	Supplemental oxygen ≥ 4 liters/min[1]	24 (8%)	28 (10%)
5	Non-invasive ventilation or high flow oxygen	26 (9%)	26 (9%)
6	Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy or renal replacement therapy	9 (3%)	13 (5%)
7	Death	5 (2%)	5 (2%)
Unadjusted odds ratio (95% CI)[2]		1.15 (0.85, 1.55)	
Odds ratio (95% CI)[3]		1.04 (0.76, 1.43)	
p-value		0.80	

[1]Compared to pre-COVID flow rate, if applicable
[2]Summary odds ratio (hIVIG/placebo) of being in a better category using proportional odds model
[3]Summary odds ratio (hIVIG/placebo) of being in a better category using proportional odds model with adjustment for participant's baseline ordinal category, hIVIG/placebo product and interaction terms

Table S11. Odds ratios for pulmonary components of the ordinal outcome at Days 3, 5, 14 and 28

Study day	OR (95%CI)[1]	P-value
Day 3	0.97 (0.69, 1.38)	.89
Day 5	1.06 (0.77, 1.45)	.72
Day 14	1.08 (0.77, 1.51)	.67
Day 28	1.04 (0.71, 1.53)	.84

[1]Summary odds ratio (hIVIG/placebo) of being in a better category using proportional odds model with adjustment for participant's baseline ordinal category, hIVIG/placebo product and interaction terms

Table S12A: Hospitalization status at study days 7, 14 and 28

	hIVIG	Placebo	OR (95% CI)[1]	p-value
Hospitalized or died				
Day 7	153 (52%)	157 (55%)	0.91 (0.65, 1.28)	0.58
Day 14	54 (18%)	63 (22%)	0.82 (0.53, 1.26)	0.37
Day 28	33 (11%)	41 (14%)	0.80 (0.48, 1.32)	0.38
Hospitalized and not in most favorable ordinal outcome category or died				
Day 7	106 (36%)	107 (38%)	0.97 (0.68, 1.40)	0.88
Day 14	51 (17%)	62 (22%)	0.77 (0.50, 1.20)	0.25
Day 28	31 (11%)	38 (13%)	0.81 (0.48, 1.38)	0.45

[1]hIVIG/placebo odds ratio adjusted for baseline ordinal category and hIVIG/placebo product

Table S12B: Hospitalization status at study days 7, 14 and 28 – nAb positive

	hIVIG	Placebo	OR (95% CI)[1]	p-value
Hospitalized or died				
Day 7	65 (48.9%)	54 (42.2%)	1.50 (0.87, 2.58)	0.14
Day 14	18 (13.5%)	16 (12.5%)	1.31 (0.58, 2.97)	0.52
Day 28	13 (9.8%)	13 (10.2%)	1.10 (0.46, 2.61)	0.83
Hospitalized and not in most favorable ordinal outcome category or died				
Day 7	47 (35.3%)	39 (30.5%)	1.36 (0.77, 2.40)	0.29
Day 14	18 (13.5%)	16 (12.5%)	1.31 (0.58, 2.97)	0.52
Day 28	12 (9.1%)	12 (9.4%)	1.11 (0.45, 2.75)	0.82

[1]hIVIG/placebo odds ratio adjusted for baseline ordinal category and hIVIG/placebo product

Table S12C: Hospitalization status at study days 7, 14 and 28 – nAb negative

	hIVIG	Placebo	OR (95% CI)[1]	p-value
Hospitalized or died				
Day 7	75 (51.1%)	86 (62.8%)	0.64 (0.38, 1.07)	0.09
Day 14	32 (22.7%)	42 (30.7%)	0.71 (0.40, 1.28)	0.26
Day 28	20 (14.2%)	27 (19.9%)	0.72 (0.37, 1.41)	0.34
Hospitalized and not in most favorable ordinal outcome category or died				
Day 7	51 (36.2%)	62 (45.3%)	0.74 (0.44, 1.26)	0.27
Day 14	30 (21.3%)	42 (30.7%)	0.64 (0.36, 1.18)	0.15
Day 28	19 (13.5%)	24 (18.4%)	0.75 (0.38, 1.50)	0.41

[1]hIVIG/placebo odds ratio adjusted for baseline ordinal category and hIVIG/placebo product

Table S13. Days alive outside of a hospital through Day 28

	hIVIG	Placebo
Days alive outside of a hospital[1]		
Median (IQR)	21 (18, 24)	21 (16, 24)
Mean (SD)	19 (8)	18 (8)
Treatment difference[2]		
Mean (SE)	1.03 (0.65)	
P-value	0.12	
Days alive and in most favorable ordinal outcome category		
Median (IQR)	17 (0, 23)	15 (0, 23)
Mean (SD)	13 (10)	13 (11)
Treatment difference[2]		
Mean (SE)	0.60 (0.84)	
P-value	0.48	
Days alive outside of a hospital or in most favorable ordinal outcome category[3]		
Median (IQR)	23 (19, 25)	23 (18, 24)
Mean (SD)	21 (7)	20 (7)
Treatment difference[2]		
Mean (SE)	0.82 (0.55)	
P-value	0.14	

[1]Participants who died are assigned a value of 0
[2]Treatment difference (hIVIG-Placebo) adjusted for baseline ordinal category and hIVIG/placebo product
[3]Whichever is greater

Table S14: Infusion reactions by treatment group and grade

Infusion reaction[1]	hIVIG (n=295)				Placebo (n=284)			
	Grade ≥ 1 No. (%)	Grade ≥2 No. (%)	Grade ≥ 3 No. (%)	Grade ≥ 4 No. (%)	Grade ≥ 1 No. (%)	Grade ≥ 2 No. (%)	Grade ≥ 3 No. (%)	Grade ≥ 4 No. (%)
Acute allergic reaction	2 (1%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bronchospasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	21 (7%)	10 (3%)	4 (1%)	0 (0%)	9 (3%)	6 (2%)	1 (0%)	0 (0%)
Headache	7 (2%)	3 (1%)	0 (0%)	0 (0%)	4 (1%)	1 (0%)	0 (0%)	0 (0%)
Hypotension	3 (1%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myalgia	3 (1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea	13 (4%)	8 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash (non-urticarial)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Shortness of breath	10 (3%)	6 (2%)	4 (1%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0 (0%)
Tachycardia	7 (2%)	2 (1%)	1 (0%)	0 (0%)	1 (0%)	1 (0%)	1 (0%)	0 (0%)
Urticaria/hives	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	2 (1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Chills	20 (7%)	17 (6%)	9 (3%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertension	3 (1%)	2 (1%)	1 (0%)	1 (0%)	3 (1%)	1 (0%)	1 (0%)	0 (0%)
Fatigue	1 (0%)	1 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Other reaction	14 (5%)	11 (4%)	4 (1%)	0 (0%)	10 (4%)	6 (2%)	1 (0%)	1 (0%)
Any of the above	55 (19%)	38 (13%)	17 (6%)	1 (0%)	27 (10%)	17 (6%)	4 (1%)	1 (0%)
p-value[2]	0.002	0.008	0.012					

[1]Collected via checklist during and within 2 hours following infusion of hIVIG or placebo. Limited to signs and symptoms that are new or increased in grade compared to pre-infusion.

[2]p-value from logistic regression model with adjustment for hIVIG/placebo product and baseline ordinal category

Table S15: Infusion summary

		hIVIG	Placebo	Total
Received complete infusion	No. (%)	288 (96%)	279 (96%)	567 (96%)
Received partial infusion	No. (%)	9 (3%)	5 (2%)	14 (2%)
Was not infused	No. (%)	4 (1%)	8 (3%)	12 (2%)
Infusion duration (hours)	Median (IQR)	2.8 (2.3, 3.4)	2.9 (2.3, 3.3)	2.9 (2.3, 3.3)
Infusion volume (mg/kg)	Median (IQR)	340 (288, 399)	343 (286, 400)	340 (288, 400)
Received maximum dose (400 mg/kg)	No. (%)	73 (25%)	90 (32%)	163 (28%)
Infusion rate (mg/kg/min)	Median (IQR)	2.0 (1.5, 2.5)	2.0 (1.6, 2.5)	2.0 (1.6, 2.5)
Infusion paused for AEs	No (%)	22 (7%)	8 (3%)	30 (5%)
Restarted after pause		15 (5%)	6 (2%)	21 (4%)
Did not restart after pause		7 (2%)	2 (1%)	9 (2%)
Concomitant Medications	No. (%)			
Used to prevent AEs		89 (30%)	87 (31%)	176 (30%)
Used in response to AEs		40 (14%)	12 (4%)	52 (9%)

Note – the first 3 rows include all participants randomized. The rest of the table is restricted to the mITT population.

Table S16: Infusion summary – Nigeria

		hIVIG	Placebo	Total
Received complete infusion	No. (%)	21 (100%)	20 (100%)	41 (100%)
Received partial infusion	No. (%)	0 (0%)	0 (0%)	0 (0%)
Was not infused	No. (%)	0 (0%)	0 (0%)	0 (0%)
Infusion duration (hours)	Median (IQR)	0.8 (0.7, 0.9)	0.7 (0.7, 1.0)	0.8 (0.7, 1.0)
Infusion volume (mg/kg)	Median (IQR)	296 (264, 354)	284 (256, 332)	292 (260, 340)
Received maximum dose (400 mg/kg)	No. (%)	4 (19%)	1 (5%)	5 (12%)
Infusion rate (mg/kg/min)	Median (IQR)	6.3 (5.7, 7.7)	5.7 (5.1, 7.8)	6.0 (5.3, 7.7)
Infusion paused for AEs	No (%)	1 (5%)	0 (0%)	1 (2%)
Restarted after pause		1 (5%)	0 (0%)	1 (2%)
Did not restart after pause		0 (0%)	0 (0%)	0 (0%)
Concomitant Medications	No. (%)			
Used to prevent AEs		0 (0%)	0 (0%)	0 (0%)
Used in response to AEs		5 (24%)	0 (0%)	5 (12%)

Note – the first 3 rows include all participants randomized. The rest of the table is restricted to the mITT population.

Table S17: Infusion summary – Excluding Nigeria

		hIVIG	Placebo	Total
Received complete infusion	No. (%)	267 (95%)	259 (95%)	526 (95%)
Received partial infusion	No. (%)	9 (3%)	5 (2%)	14 (3%)
Was not infused	No. (%)	4 (1%)	8 (3%)	12 (2%)
Infusion duration (hours)	Median (IQR)	2.9 (2.5, 3.4)	3.0 (2.5, 3.4)	2.9 (2.5, 3.4)
Infusion volume (mg/kg)	Median (IQR)	341 (292, 400)	347 (292, 400)	344 (292, 400)
Received maximum dose (400 mg/kg)	No. (%)	69 (25%)	89 (34%)	158 (29%)
Infusion rate (mg/kg/min)	Median (IQR)	1.9 (1.5, 2.4)	1.9 (1.6, 2.3)	1.9 (1.5, 2.4)
Infusion paused for AEs	No (%)	21 (8%)	8 (3%)	29 (5%)
Restarted after pause		14 (5%)	6 (2%)	20 (4%)
Did not restart after pause		7 (3%)	2 (1%)	9 (2%)
Concomitant Medications	No. (%)			
Used to prevent AEs		89 (32%)	87 (33%)	176 (33%)
Used in response to AEs		35 (13%)	12 (5%)	47 (9%)

Note – the first 3 rows include all participants randomized. The rest of the table is restricted to the mITT population.

Table S18: Infusion reactions by treatment group and grade – Nigeria

Infusion reaction[1]	hIVIG (n=21)				Placebo (n=20)			
	Grade ≥ 1 No. (%)	Grade ≥2 No. (%)	Grade ≥ 3 No. (%)	Grade ≥ 4 No. (%)	Grade ≥ 1 No. (%)	Grade ≥ 2 No. (%)	Grade ≥ 3 No. (%)	Grade ≥ 4 No. (%)
Acute allergic reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bronchospasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	1 (5%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypotension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myalgia	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash (non-urticarial)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Shortness of breath	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urticaria/hives	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chills	6 (29%)	6 (29%)	6 (29%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertension	0 (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any of the above	8 (38%)	7 (33%)	6 (29%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1]Collected via checklist during and within 2 hours following infusion of hIVIG or placebo. Limited to signs and symptoms that are new or increased in grade compared to pre-infusion.

Table S19: Infusion reactions by treatment group and grade – Excluding Nigeria

Infusion reaction[1]	hIVIG (n=274)				Placebo (n=264)			
	Grade ≥ 1 No. (%)	Grade ≥2 No. (%)	Grade ≥ 3 No. (%)	Grade ≥ 4 No. (%)	Grade ≥ 1 No. (%)	Grade ≥ 2 No. (%)	Grade ≥ 3 No. (%)	Grade ≥ 4 No. (%)
Acute allergic reaction	2 (1%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bronchospasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	20 (7%)	9 (3%)	3 (1%)	0 (0%)	9 (3%)	6 (2%)	1 (0%)	0 (0%)
Headache	7 (3%)	3 (1%)	0 (0%)	0 (0%)	4 (2%)	1 (0%)	0 (0%)	0 (0%)
Hypotension	3 (1%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myalgia	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea	12 (4%)	8 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash (non-urticarial)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Shortness of breath	9 (3%)	6 (2%)	4 (1%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0 (0%)
Tachycardia	7 (3%)	2 (1%)	1 (0%)	0 (0%)	1 (0%)	1 (0%)	1 (0%)	0 (0%)
Urticaria/hives	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	1 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Chills	14 (5%)	11 (4%)	3 (1%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertension	3 (1%)	2 (1%)	1 (0%)	1 (0%)	3 (1%)	1 (0%)	1 (0%)	0 (0%)
Fatigue	1 (0%)	1 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Other reaction	14 (5%)	11 (4%)	4 (1%)	0 (0%)	10 (4%)	6 (2%)	1 (0%)	1 (0%)
Any of the above	47 (17%)	31 (11%)	11 (4%)	1 (0%)	27 (10%)	17 (6%)	4 (2%)	1 (0%)
p-value[2]	0.019	0.060	0.091					

[1]Collected via checklist during and within 2 hours following infusion of hIVIG or placebo. Limited to signs and symptoms that are new or increased in grade compared to pre-infusion.

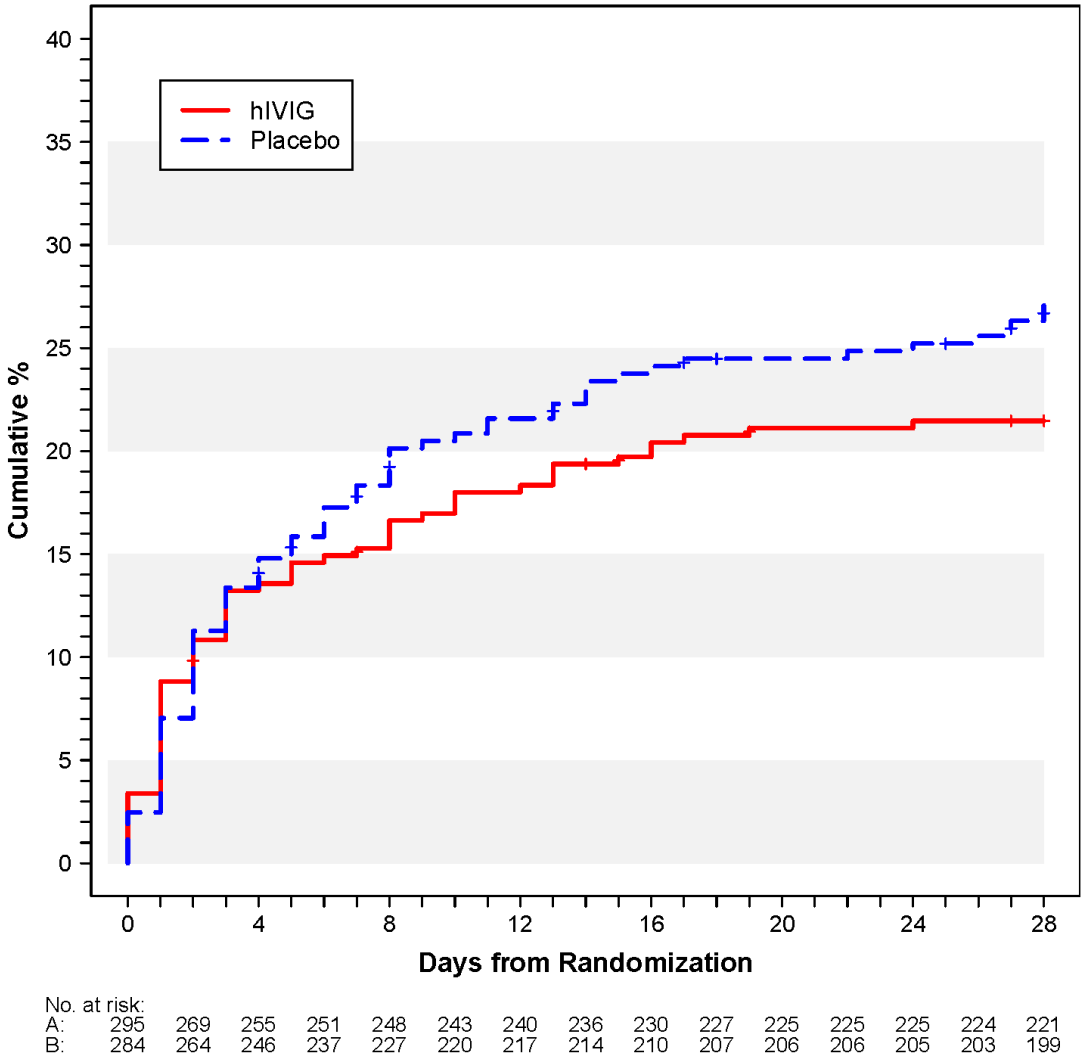
[2]p-value from logistic regression model with adjustment for hIVIG/placebo product and baseline ordinal category

Table S20: Components of composite safety outcomes through Day 7 and Day 28

Composite safety outcome and components	hIVIG (n=295)	Placebo (n=284)	OR (95% CI)[1]	p-value[1]
Day 7				
No. (%) deaths	5 (1.7%)	5 (1.8%)	1.01 (0.29, 3.60)	0.98
No. (%) SAEs	8 (2.7%)	6 (2.1%)	1.32 (0.45, 3.92)	0.61
No. (%) Grade 3 or 4 adverse events	46 (15.6%)	35 (12.3%)	1.36 (0.83, 2.21)	0.22
No. (%) with deaths, SAEs or Grade 3 or 4 events	49 (16.6%)	43 (15.1%)	1.15 (0.72, 1.82)	0.56
No (%) organ failure or serious infection	42 (14.2%)	48 (16.9%)	0.80 (0.50, 1.28)	0.34
No. (%) with composite safety outcome	71 (24.1%)	70 (24.6%)	0.98 (0.66, 1.46)	0.91
Day 28			**HR (95% CI)[2]**	**p-value[2]**
No. (%) deaths	18 (6.1%)	22 (7.7%)	0.80 (0.42, 1.51)	0.49
No. (%) SAEs	16 (5.4%)	20 (7.0%)	0.72 (0.37, 1.40)	0.33
No. (%) deaths or SAEs	28 (9.5%)	37 (13.0%)	0.73 (0.44, 1.20)	0.21
No. (%) organ failure or serious infection	56 (19.0%)	64 (22.5%)	0.84 (0.59, 1.21)	0.35
No. (%) with composite safety outcome	63 (21.4%)	76 (26.8%)	0.79 (0.57, 1.11)	0.18

[1]hIVIG/placebo odds ratio adjusted for company and baseline ordinal category
[2]hIVIG/placebo hazard ratio stratified by company and baseline ordinal category

Figure S1. Time to Day 28 Composite Safety Outcome



*Lines are Kaplan–Meier estimates.

Table S21: Death, SAE or Grade 3 or 4 events through Day 7 by MedDRA System Organ Class (SOC)

MedDRA SOC	hIVIG (n=295) No. (%)	Placebo (n=284) No. (%)
Blood and Lymphatic System	3 (1.0%)	0 (0.0%)
Cardiac	2 (0.7%)	5 (1.8%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)
Eye	1 (0.3%)	0 (0.0%)
Gastrointestinal	3 (1.0%)	2 (0.7%)
General and Administration Site	20 (6.8%)	10 (3.5%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	7 (2.4%)	4 (1.4%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	1 (0.3%)	1 (0.4%)
Metabolism and Nutrition	1 (0.3%)	1 (0.4%)
Musculoskeletal, Connective Tissue	1 (0.3%)	2 (0.7%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	2 (0.7%)	3 (1.1%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	1 (0.3%)	2 (0.7%)
Renal and Urinary	2 (0.7%)	1 (0.4%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	21 (7.1%)	22 (7.7%)
Skin and Subcutaneous Tissue	0 (0.0%)	0 (0.0%)
Social Circumstances	1 (0.3%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	4 (1.4%)	2 (0.7%)
Any of above	49 (16.6%)	43 (15.1)

Table S22: Clinical organ failure and serious infection events through Day 7

Diagnoses	hIVIG (n=295) No. (%)	Placebo (n=284) No. (%)
MI	2 (0.7%)	0 (0.0%)
NYHA class III or IV heart failure	0 (0.0%)	1 (0.4%)
Institution of vasopressor therapy	5 (1.7%)	9 (3.2%)
Myocarditis	0 (0.0%)	1 (0.4%)
Pericarditis	0 (0.0%)	0 (0.0%)
DIC	0 (0.0%)	0 (0.0%)
Thromboembolic events	5 (1.7%)	3 (1.1%)
Hepatic decompensation	0 (0.0%)	0 (0.0%)
Microbiologically proven severe infection (not including SARS-CoV-2)	3 (1.0%)	5 (1.8%)
Acute delirium	2 (0.7%)	3 (1.1%)
Cerebrovascular event (stroke)	0 (0.0%)	1 (0.4%)
Encephalitis	1 (0.3%)	0 (0.0%)
Meningitis	0 (0.0%)	0 (0.0%)
Myelitis	0 (0.0%)	0 (0.0%)
Renal replacement therapy[1]	3 (1.0%)	2 (0.7%)
Respiratory failure[2]	32 (11.9%)	40 (15.9%)
Any of the above	42 (14.2%)	48 (16.9%)

[1]Excludes those on RRT prior to entry
[2]Excludes those on high flow oxygen at entry

Table S23: Deaths or SAEs through Day 28 by MedDRA System Organ Class (SOC)

MedDRA SOC	hIVIG (n=295) No. (%)	Placebo (n=284) No. (%)
Blood and Lymphatic System	3 (1.0%)	2 (0.7%)
Cardiac	2 (0.7%)	3 (1.1%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)
Eye	0 (0.0%)	0 (0.0%)
Gastrointestinal	2 (0.7%)	0 (0.0%)
General and Administration Site	0 (0.0%)	3 (1.1%)
Hepatobiliary	0 (0.0%)	1 (0.4%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	12 (4.1%)	16 (5.6%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	0 (0.0%)
Metabolism and Nutrition	0 (0.0%)	0 (0.0%)
Musculoskeletal, Connective Tissue	0 (0.0%)	0 (0.0%)
Neoplasms - Benign and Malignant	1 (0.3%)	0 (0.0%)
Nervous System	0 (0.0%)	1 (0.4%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	1 (0.3%)	1 (0.4%)
Renal and Urinary	1 (0.3%)	0 (0.0%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	8 (2.7%)	12 (2.4%)
Skin and Subcutaneous Tissue	0 (0.0%)	0 (0.0%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	1 (0.3%)	0 (0.0%)
Any of above	28 (9.5%)	37 (13.0%)

Table S24: Clinical organ failure and serious infection events through Day 28

Diagnoses	hIVIG (n=295) No. (%)	Placebo (n=284) No. (%)
MI	2 (0.7%)	0 (0.0%)
NYHA class III or IV heart failure	0 (0.0%)	1 (0.4%)
Institution of vasopressor therapy	12 (4.1%)	22 (7.7%)
Myocarditis	0 (0.0%)	1 (0.4%)
Pericarditis	0 (0.0%)	0 (0.0%)
DIC	0 (0.0%)	1 (0.4%)
Thromboembolic events	7 (2.4%)	9 (3.2%)
Hepatic decompensation	0 (0.0%)	0 (0.0%)
Microbiologically proven severe infection (not including SARS-CoV-2)	6 (2.0%)	12 (4.2%)
Acute delirium	2 (0.7%)	3 (1.1%)
Cerebrovascular event (stroke)	0 (0.0%)	2 (0.7%)
Encephalitis	1 (0.3%)	0 (0.0%)
Meningitis	0 (0.0%)	0 (0.0%)
Myelitis	0 (0.0%)	0 (0.0%)
Renal replacement therapy[1]	6 (2.1%)	7 (2.5%)
Respiratory failure[2]	41 (15.2%)	47 (18.7%)
Any thrombotic event[3]	9 (3.0%)	11 (3.9%)
Any of the above	56 (19.0%)	64 (22.5%)

[1]Excludes those on RRT prior to entry
[2]Excludes those on high flow oxygen at entry
[3]Stroke, MI, thromboembolic events, or DIC

Table S25. Prevalence of AEs of any grade on Day 1 by MedDRA System Organ Class (SOC)

MedDRA SOC	hIVIG (n=295) No. (%)	Placebo (n=284) No. (%)
Blood and Lymphatic System	1 (0.3%)	1 (0.4%)
Cardiac	12 (4.1%)	10 (3.5%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	3 (1.0%)	1 (0.4%)
Eye	2 (0.7%)	1 (0.4%)
Gastrointestinal	24 (8.1%)	24 (8.5%)
General and Administration Site	43 (14.6%)	49 (17.3%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	16 (5.4%)	15 (5.3%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	5 (1.7%)	4 (1.4%)
Metabolism and Nutrition	10 (3.4%)	13 (4.6%)
Musculoskeletal, Connective Tissue	14 (4.7%)	11 (3.9%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	29 (9.8%)	24 (8.5%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	5 (1.7%)	9 (3.2%)
Renal and Urinary	3 (1.0%)	4 (1.4%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	93 (31.5%)	94 (33.1%)
Skin and Subcutaneous Tissue	3 (1.0%)	2 (0.7%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	6 (2.0%)	10 (3.5%)
Any of above[1]	127 (43.1%)	125 (44.0%)

[1] hIVIG/placebo odds ratio (95% CI) with adjustment for hIVIG/placebo product and baseline ordinal category = 0.97 (0.70, 1.35)

Table S26. Prevalence of AEs of any grade on Day 3 by MedDRA System Organ Class (SOC)

MedDRA SOC	hIVIG (n=291) No. (%)	Placebo (n=282) No. (%)
Blood and Lymphatic System	2 (0.7%)	0 (0.0%)
Cardiac	10 (3.4%)	9 (3.2%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	1 (0.3%)	0 (0.0%)
Endocrine	3 (1.0%)	1 (0.4%)
Eye	0 (0.0%)	1 (0.4%)
Gastrointestinal	20 (6.9%)	18 (6.4%)
General and Administration Site	32 (11.0%)	43 (15.2%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	13 (4.5%)	16 (5.7%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	2 (0.7%)
Metabolism and Nutrition	9 (3.1%)	12 (4.3%)
Musculoskeletal, Connective Tissue	8 (2.7%)	7 (2.5%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	29 (10.0%)	20 (7.1%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	1 (0.3%)	6 (2.1%)
Renal and Urinary	4 (1.4%)	3 (1.1%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	75 (25.8%)	83 (29.4%)
Skin and Subcutaneous Tissue	0 (0.0%)	2 (0.7%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	9 (3.1%)	10 (3.5%)
Any of above[1]	107 (36.8%)	118 (41.8%)

[1] hIVIG/placebo odds ratio (95% CI) with adjustment for hIVIG/placebo product and baseline ordinal category = 0.82 (0.58, 1.15)

Table S27. Prevalence of AEs of any grade on Day 7 by MedDRA System Organ Class (SOC)

MedDRA SOC	hIVIG (n=286) No. (%)	Placebo (n=279) No. (%)
Blood and Lymphatic System	3 (1.0%)	1 (0.4%)
Cardiac	9 (3.1%)	9 (3.2%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	1 (0.3%)	0 (0.0%)
Endocrine	3 (1.0%)	1 (0.4%)
Eye	2 (0.7%)	1 (0.4%)
Gastrointestinal	15 (5.2%)	11 (3.9%)
General and Administration Site	28 (9.8%)	21 (7.5%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	9 (3.1%)	13 (4.7%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	1 (0.3%)	1 (0.4%)
Metabolism and Nutrition	8 (2.8%)	8 (2.9%)
Musculoskeletal, Connective Tissue	10 (3.5%)	5 (1.8%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	15 (5.2%)	20 (7.2%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	5 (1.7%)	8 (2.9%)
Renal and Urinary	2 (0.7%)	5 (1.8%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	69 (24.1%)	61 (21.9%)
Skin and Subcutaneous Tissue	1 (0.3%)	2 (0.7%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	4 (1.4%)	5 (1.8%)
Any of above[1]	102 (35.7%)	94 (33.7%)

[1] hIVIG/placebo odds ratio (95% CI) with adjustment for hIVIG/placebo product and baseline ordinal category = 1.09 (0.77, 1.55)

Table S28. Prevalence of AEs of any grade on Day 28 by MedDRA System Organ Class (SOC)

MedDRA SOC	hIVIG (n=269) No. (%)	Placebo (n=259) No. (%)
Blood and Lymphatic System	0 (0.0%)	0 (0.0%)
Cardiac	8 (3.0%)	4 (1.5%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	2 (0.7%)	0 (0.0%)
Eye	2 (0.7%)	1 (0.4%)
Gastrointestinal	9 (3.3%)	6 (2.3%)
General and Administration Site	31 (11.5%)	17 (6.6%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	4 (1.5%)	2 (0.8%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	1 (0.4%)	1 (0.4%)
Metabolism and Nutrition	6 (2.2%)	4 (1.5%)
Musculoskeletal, Connective Tissue	8 (3.0%)	4 (1.5%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	18 (6.7%)	19 (7.3%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	5 (1.9%)	8 (3.1%)
Renal and Urinary	2 (0.7%)	2 (0.8%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	45 (16.7%)	34 (13.1%)
Skin and Subcutaneous Tissue	5 (1.9%)	3 (1.2%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	1 (0.4%)
Vascular	2 (0.7%)	1 (0.4%)
Any of above[1]	77 (28.6%)	51 (19.7%)

[1] hIVIG/placebo odds ratio (95% CI) with adjustment for hIVIG/placebo product and baseline ordinal category = 1.62 (1.07, 2.45)

Table S29: Changes in laboratory values at Day 7

	Day 7 Mean		Change from Baseline		Difference[1]	
	hIVIG (n=266)	Placebo (n=251)	hIVIG (n=266)	Placebo (n=251)	Diff. (SE)	p-value
Serum creatinine (mg/dL)	1.10	1.12	-0.06	-0.08	0.01 (0.06)	0.90
AST/SGOT (U/L)	37.0	35.0	-9.0	-11.3	1.88 (2.73)	0.49
ALT/SGPT (U/L)	76.6	60.0	32.8	15.6	16.6 (15.8)	0.29
WBC (x 10^9/L)	11.1	12.2	3.51	4.06	-0.13 (0.57)	0.82
Hemoglobin (g/dL)	12.8	13.2	-0.18	-0.04	-0.16 (0.12)	0.16
Platelets (x 10^9/L)	387.2	366.2	151.2	134.9	16.4 (12.2)	0.18
Lymphocytes (x10^9/L)	1.97	1.72	0.70	0.72	0.03 (0.10)	0.73
CRP (log_2 mg/dL)	3.24	3.52	-2.14	-1.96	-0.24 (0.17)	0.15

[1]Treatment group difference (hIVIG – Placebo) in Day 7 lab values adjusted for baseline value and hIVIG product/placebo

Table S30: Concomitant medications taken in past 24 hours at Day 7

Concomitant Medication	hIVIG (n=285)[1] No. (%)	Placebo (n=276)[1] No. (%)
Antiplatelets/anticoagulants	138 (48%)	145 (53%)
Aspirin	29 (10%)	20 (7%)
Other antiplatelets	19 (7%)	11 (4%)
Heparin prophylactic dose	75 (26%)	85 (31%)
Heparin intermediate dose	13 (5%)	13 (5%)
Heparin therapeutic dose	9 (3%)	10 (4%)
Warfarin	0 (0%)	3 (1%)
DOAC	17 (6%)	15 (5%)
Antibacterials	58 (20%)	70 (25%)
IV	32 (11%)	34 (12%)
Oral	28 (10%)	38 (14%)
Antivirals	0 (0%)	2 (1%)
Antifungals	4 (1%)	4 (1%)
ACE inhibitors	21 (7%)	24 (9%)
ARBs	23 (8%)	24 (9%)
Antirejection medications	1 (0%)	1 (0%)
Immune modulators	2 (1%)	3 (1%)
NSAID	17 (6%)	12 (4%)
Biologics for cancer or autoimmune disease	3 (1%)	0 (0%)
Corticosteroids	93 (33%)	108 (39%)

[1]Denomenator includes those with Day 7 assessment

Table S31: Antibacterial, heparin, and corticosteroid use at baseline and Day 7

	hIVIG (n=285)[1] No. (%)	**Placebo (n=276)[1] No. (%)**
Antibacterial use		
Baseline and Day 7	45 (16%)	51 (18%)
Baseline, not Day 7	76 (27%)	64 (23%)
Day 7, not Baseline	13 (5%)	19 (7%)
Neither Baseline nor Day 7	151 (53%)	142 (51%)
Heparin use		
Baseline and Day 7	80 (28%)	84 (30%)
Baseline, not Day 7	91 (32%)	85 (31%)
Day 7, not Baseline	17 (6%)	24 (9%)
Neither Baseline nor Day 7	97 (34%)	83 (30%)
Corticosteroid use		
Baseline and Day 7	75 (26%)	79 (29%)
Baseline, not Day 7	90 (32%)	73 (26%)
Day 7, not Baseline	18 (6%)	30 (11%)
Neither Baseline nor Day 7	102 (36%)	95 (34%)

[1]Denomenator includes those with Day 7 assessment

Table S32: Primary outcome subgroup analyses

Baseline Subgroup	hIVIG		Placebo		Odds Ratio[1]		Int. p-value
	N pts	Score[2]	N pts	Score[2]	OR (95% CI)	P-value	
Age							0.04
18-49	80	1.8	62	1.7	0.57 (0.26, 1.26)	0.17	
50-59	74	2.5	77	2.1	0.81 (0.43, 1.54)	0.52	
60-69	65	2.2	67	2.5	1.26 (0.63, 2.55)	0.51	
70+	74	2.9	73	3.4	1.29 (0.69, 2.41)	0.42	
Gender							0.50
Male	148	2.6	177	2.6	0.88 (0.57, 1.33)	0.54	
Female	145	2.1	102	2.1	1.13 (0.67, 1.89)	0.65	
Race/ethnicity							0.50
Black	41	1.9	45	2.1	0.97 (0.26, 3.64)	0.97	
Hispanic/Latino	40	2.7	46	2.8	1.23 (0.00, 26276)	0.97	
White/other	212	2.3	188	2.5	1.18 (0.80, 1.76)	0.41	
Geographical region							0.50
Europe/UK/Israel	121	2.2	117	2.4	1.29 (0.78, 2.13)	0.33	
USA	125	2.7	117	2.8	0.85 (0.51, 1.41)	0.52	
Argentina/Indonesia/Japan/ Nigeria	47	1.7	45	1.8	0.98 (0.00, 121E3)	1.00	
hIVIG/placebo product							0.95
CSL Behring	74	2.1	76	2.1	0.84 (0.42 - 1.70)	0.63	
Emergent	80	2.2	67	2.5	1.20 (0.62 - 2.31)	0.59	
Grifols	71	2.3	68	2.3	1.23 (0.64 - 2.38)	0.54	
Takeda	68	2.7	68	3.0	1.05 (0.54 - 2.04)	0.89	
Texcell potency (IU/mL)							0.82
< 1050	117	2.3	104	2.4	0.98 (0.58, 1.66)	0.95	
1050 to < 1400	91	2.5	90	2.8	1.23 (0.66, 2.31)	0.51	
1400+	84	2.2	85	2.2	0.92 (0.00, 2015)	0.98	
BMI							0.28
< 25	57	2.2	60	2.6	1.50 (0.66, 3.42)	0.34	
25-29.9	90	2.2	84	2.3	1.07 (0.58, 1.97)	0.82	
30-39.9	102	2.5	105	2.5	0.89 (0.51, 1.54)	0.67	
40+	33	2.2	28	2.5	1.37 (0.46, 4.05)	0.57	
Days since symptom onset							0.24
< 6 days	82	2.3	52	2.4	0.74 (0.35 - 1.53)	0.41	
6-7 days	65	2.2	61	2.9	1.43 (0.71 - 2.89)	0.32	
8-9 days	66	2.4	70	2.3	1.03 (0.50 - 2.12)	0.93	
10-12 days	80	2.3	96	2.3	1.24 (0.69 - 2.25)	0.47	
Oxygen requirement							0.90
Not on Sup O2	78	1.7	80	1.7	0.94 (0.48 - 1.81)	0.85	
Sup O2 < 4 L/min	107	2.0	90	2.1	0.94 (0.55 - 1.61)	0.83	
Sup O2 ≥ 4 L/min	84	2.9	76	3.0	1.13 (0.64 - 1.99)	0.67	
High flow O2	24	3.8	33	4.1	1.06 (0.38 - 2.99)	0.91	

Heparin dose							0.63
None	78	2.1	70	2.4	1.26 (0.60 - 2.66)	0.55	
Prophylactic	147	2.2	145	2.6	1.10 (0.69 - 1.75)	0.68	
Intermediate/therapeutic[5]	68	2.8	64	2.3	0.77 (0.38 - 1.58)	0.48	
hsCRP							0.81
< 62 mg/L	148	1.9	137	2.1	1.21 (0.71, 2.06)	0.49	
62+ mg/L	145	2.7	140	2.8	0.96 (0.61, 1.50)	0.85	
Neutralizing anti-spike Ab							0.79
nAb positive	131	2.2	124	2.3	1.02 (0.59 - 1.75)	0.95	
nAb negative	141	2.4	136	2.7	0.97 (0.60 - 1.57)	0.90	
Anti-N Abs							0.24
Positive	183	2.3	185	2.4	0.94 (0.63 - 1.40)	0.75	
Negative	89	2.3	75	2.6	1.16 (0.58 - 2.29)	0.68	
Quanterix antigen							0.38
< 225 pg/mL	66	1.5	68	1.9	1.26 (0.52 - 3.04)	0.60	
225-1399 pg/mL	68	1.9	66	2.1	1.40 (0.69 - 2.86)	0.35	
1400-4359 pg/mL	68	2.4	64	2.4	1.00 (0.47 - 2.14)	1.00	
4360+ pg/mL	70	3.5	61	3.7	0.87 (0.44 - 1.71)	0.68	
Viral RNA							0.17
< 10,000 copies/mL	102	2.1	89	2.1	0.77 (0.44, 1.37)	0.38	
10,000+ copies/mL	157	2.5	153	2.8	1.11 (0.69, 1.80)	0.67	
Quanterix antigen x nAb							0.76
Ag 1000+, nAb neg	99	2.8	91	3.1	0.92 (0.52 - 1.63)	0.78	
Ag 1000+, nAb pos	58	2.9	47	2.7	1.19 (0.47 - 3.00)	0.72	
Ag < 1000, nAb neg	42	1.5	44	1.8	1.88 (0.65 - 5.45)	0.25	
Ag < 1000, nAb pos	73	1.7	77	2.0	1.17 (0.58 - 2.39)	0.66	
Viral RNA x nAb							0.49
RNA 10,000+, nAb neg	107	2.5	98	3.0	1.19 (0.66, 2.13)	0.57	
RNA 10,000+, nAb pos	49	2.4	53	2.5	0.83 (0.27, 2.53)	0.74	
RNA < 10,000, nAb neg	28	2.3	26	2.2	0.42 (0.12, 1.49)	0.18	
RNA < 10,000, nAb pos	73	2.1	63	2.1	0.73 (0.35, 1.54)	0.40	

[1]Summary odds ratio (hIVIG/placebo) of being in a better category using proportional odds model with adjustment for baseline category, hIVIG/placebo product and interaction terms.

[2]Mean score (7=death, 1=return to normal activities with minimal or no symptoms)

[3]1 degree of freedom test with time since symptom onset included in model as a continuous variable

[4]3 degrees of freedom test with time since symptom onset included in model as 4 categorical variables

[5]Or other platelet use

Figure S2. Composite safety outcome (death, SAE, grade3 or 4 events, organ failure or serious infection) through Day 7 subgroup analyses

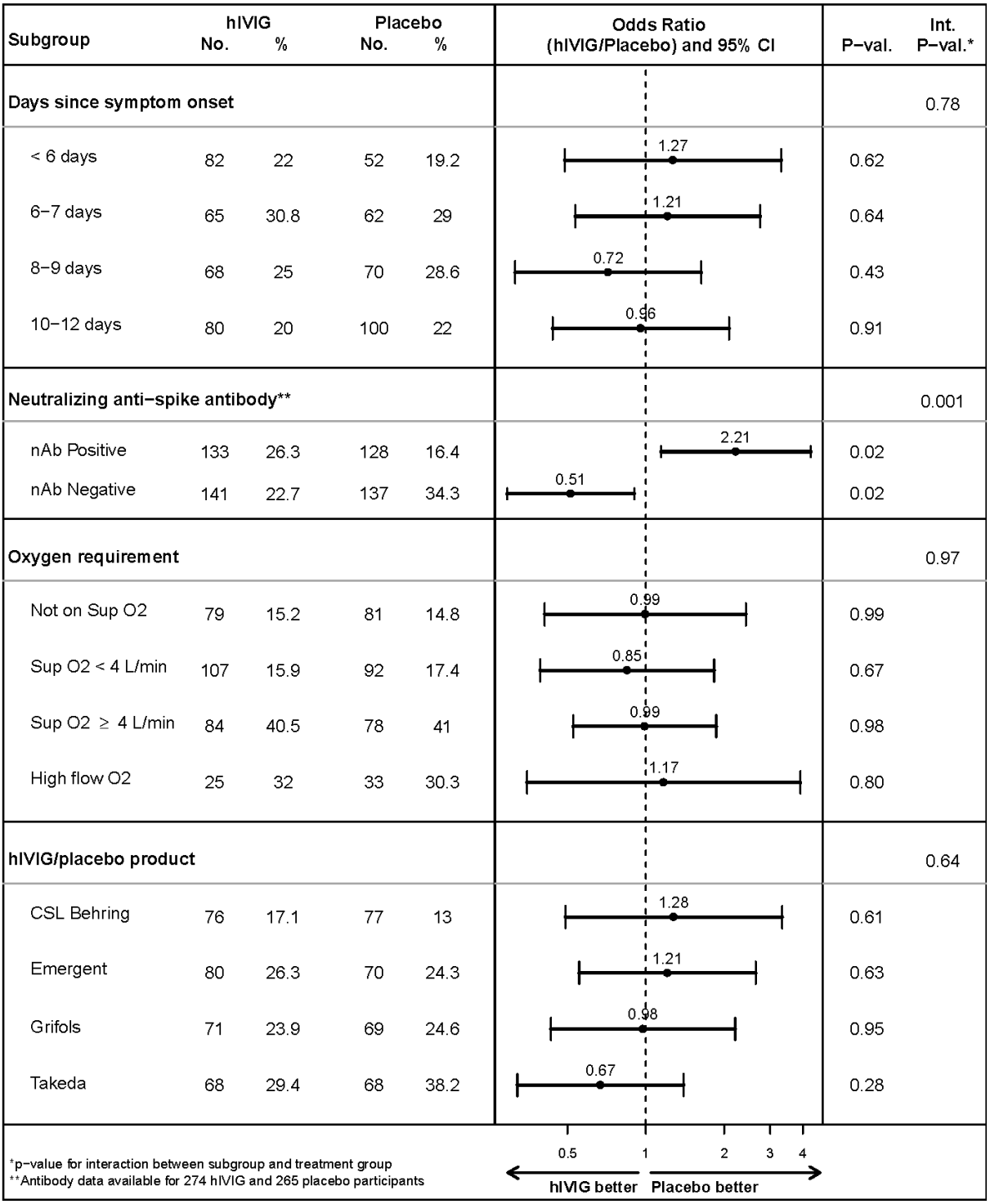


Table S33: Composite safety outcome (death, SAE, grade3 or 4 events, organ failure or serious infection) through Day 7 subgroup analyses

Baseline Subgroup	hIVIG		Placebo		Odds Ratio[1]		Int. p-value
	N pts	N (%)[2]	N pts	N (%)[2]	OR (95% CI)	P-value	
Age							0.05
18-49	81	10 (12%)	64	8 (13%)	1.05 (0.37, 2.99)	0.93	
50-59	74	26 (35%)	77	15 (19%)	1.96 (0.88, 4.36)	0.10	
60-69	65	14 (22%)	68	14 (21%)	0.96 (0.39, 2.37)	0.94	
70+	75	21 (28%)	75	33 (44%)	0.46 (0.22, 0.98)	0.05	
Gender							0.71
Male	149	40 (27%)	180	47 (26%)	1.09 (0.64, 1.84)	0.75	
Female	146	31 (21%)	104	23 (22%)	0.90 (0.48, 1.71)	0.76	
Race/ethnicity							0.24
Black	41	7 (17%)	46	9 (20%)	1.16 (0.34, 3.99)	0.81	
Hispanic/Latino	41	5 (12%)	47	13 (28%)	0.34 (0.10, 1.18)	0.09	
White/other	213	59 (28%)	191	48 (25%)	1.15 (0.71, 1.84)	0.57	
Geographical region							0.47
Europe/UK/Israel	121	29 (24%)	118	31 (26%)	0.87 (0.47, 1.64)	0.67	
USA	127	30 (24%)	121	32 (26%)	0.92 (0.49, 1.71)	0.79	
Argentina/Indonesia/Japan/ Nigeria	47	12 (26%)	45	7 (16%)	1.86 (0.61, 5.63)	0.27	
hIVIG/placebo product							0.64
CSL Behring	76	13 (17%)	77	10 (13%)	1.28 (0.49, 3.34)	0.61	
Emergent	80	21 (26%)	70	17 (24%)	1.21 (0.55, 2.64)	0.63	
Grifols	71	17 (24%)	69	17 (25%)	0.98 (0.43, 2.20)	0.95	
Takeda	68	20 (29%)	68	26 (38%)	0.67 (0.32, 1.40)	0.28	
Texcell potency (IU/mL)							0.64
< 1050	117	29 (25%)	106	22 (21%)	1.41 (0.72, 2.75)	0.32	
1050 to < 1400	91	25 (27%)	91	33 (36%)	0.70 (0.36, 1.39)	0.31	
1400+	86	17 (20%)	87	15 (17%)	1.08 (0.47, 2.50)	0.85	
BMI							0.82
< 25	57	13 (23%)	61	20 (33%)	0.51 (0.21, 1.22)	0.13	
25-29.9	90	26 (29%)	85	16 (19%)	2.11 (0.95, 4.68)	0.07	
30-39.9	103	25 (23%)	107	27 (25%)	0.95 (0.49, 1.83)	0.88	
40+	34	6 (18%)	29	7 (24%)	0.51 (0.13, 2.00)	0.33	
Days since symptom onset							0.78
< 6 days	82	18 (22%)	52	10 (19%)	1.27 (0.49, 3.31)	0.62	
6-7 days	65	20 (31%)	62	18 (29%)	1.21 (0.54, 2.75)	0.64	
8-9 days	68	17 (25%)	70	20 (29%)	0.72 (0.32, 1.63)	0.43	
10-12 days	80	16 (20%)	100	22 (22%)	0.96 (0.44, 2.08)	0.91	
Oxygen requirement							0.97
Not on Sup O2	79	12 (15%)	81	12 (15%)	0.99 (0.41, 2.42)	0.99	
Sup O2 < 4 L/min	107	17 (16%)	92	16 (17%)	0.85 (0.39, 1.83)	0.67	
Sup O2 ≥ 4 L/min	84	34 (40%)	78	32 (41%)	0.99 (0.53, 1.86)	0.98	

High flow O2	25	8 (32%)	33	10 (30%)	1.17 (0.35, 3.92)	0.80	
Heparin dose							0.33
None	78	22 (28%)	72	15 (21%)	1.42 (0.63, 3.21)	0.40	
Prophylactic	148	32 (22%)	147	40 (27%)	0.73 (0.42, 1.28)	0.27	
Intermediate/therapeutic[5]	69	17 (25%)	65	15 (23%)	0.83 (0.34, 2.05)	0.69	
hsCRP							0.48
< 62 mg/L	150	27 (18%)	138	27 (20%)	1.06 (0.56, 2.02)	0.85	
62+ mg/L	145	44 (30%)	144	43 (30%)	0.96 (0.57, 1.61)	0.88	
Neutralizing anti-spike Ab							0.001
nAb positive	133	35 (26%)	128	21 (16%)	2.21 (1.14, 4.29)	0.02	
nAb negative	141	32 (23%)	137	47 (34%)	0.51 (0.29, 0.90)	0.02	
Anti-N Abs							0.55
Positive	185	46 (25%)	189	47 (25%)	1.02 (0.62, 1.66)	0.94	
Negative	89	21 (24%)	76	21 (28%)	0.76 (0.35, 1.63)	0.48	
Quanterix antigen							0.04
< 225 pg/mL	67	10 (15%)	70	10 (14%)	1.36 (0.48, 3.85)	0.56	
225-1399 pg/mL	69	16 (23%)	67	12 (18%)	1.20 (0.48, 3.00)	0.69	
1400-4359 pg/mL	68	14 (21%)	64	13 (20%)	1.16 (0.46, 2.97)	0.75	
4360+ pg/mL	70	27 (39%)	63	33 (52%)	0.41 (0.19, 0.88)	0.02	
Viral RNA							0.29
< 10,000 copies/mL	103	24 (23%)	91	19 (21%)	1.24 (0.61, 2.52)	0.56	
10,000+ copies/mL	157	39 (25%)	156	45 (29%)	0.78 (0.46, 1.34)	0.37	
Quanterix antigen x nAb							0.01
Ag 1000+, nAb neg	99	28 (28%)	92	39 (42%)	0.46 (0.24, 0.88)	0.02	
Ag 1000+, nAb pos	58	20 (34%)	48	10 (21%)	2.46 (0.84, 7.20)	0.10	
Ag < 1000, nAb neg	42	4 (10%)	44	8 (18%)	0.64 (0.16, 2.57)	0.53	
Ag < 1000, nAb pos	75	15 (20%)	80	11 (14%)	1.97 (0.79, 4.90)	0.14	
Viral RNA x nAb							0.01
RNA 10,000+, nAb neg	107	26 (24%)	99	36 (36%)	0.50 (0.26, 0.96)	0.04	
RNA 10,000+, nAb pos	49	13 (27%)	55	9 (16%)	2.29 (0.71, 7.34)	0.16	
RNA < 10,000, nAb neg	28	5 (18%)	26	9 (35%)	0.38 (0.10, 1.53)	0.17	
RNA < 10,000, nAb pos	74	19 (26%)	65	10 (15%)	2.27 (0.91, 5.67)	0.08	

[1]Odds ratio (hIVIG/placebo) with adjustment for baseline category and hIVIG/placebo product

[2]N (%) of participants with deaths, SAEs, grade 3 or 4 events, organ failure or serious infection through Day 7

[3]1 degree of freedom test with time since symptom onset included in model as a continuous variable

[4]3 degrees of freedom test with time since symptom onset included in model as 4 categorical variables

[5]Or other platelet use

Table S34: Composite safety outcome (death, SAE, organ failure or serious infection) through Day 28 subgroup analyses

Baseline Subgroup	hIVIG		Placebo		Hazard Ratio[1]		Int. p-value
	N pts	N (%)[2]	N pts	N (%)[2]	HR (95% CI)	P-value	
Age							0.77
18-49	81	5 (6.2)	64	9 (14.1)	0.51 (0.15 - 1.78)	0.29	
50-59	74	19 (25.7)	77	14 (18.2)	1.03 (0.50 - 2.13)	0.93	
60-69	65	13 (20.0)	68	17 (25.0)	0.67 (0.31 - 1.44)	0.31	
70+	75	26 (34.7)	75	36 (48.0)	0.73 (0.43 - 1.23)	0.24	
Gender							0.21
Male	149	41 (27.5)	180	53 (29.4)	1.04 (0.68 - 1.59)	0.85	
Female	146	22 (15.1)	104	23 (22.1)	0.61 (0.33 - 1.11)	0.10	
Race/ethnicity							0.65
Black	41	6 (14.6)	46	10 (21.7)	1.49 (0.40 - 5.50)	0.55	
Hispanic/Latino	41	6 (14.6)	47	12 (25.5)	0.53 (0.20 - 1.44)	0.21	
White/other	213	51 (23.9)	191	54 (28.3)	0.79 (0.53 - 1.18)	0.25	
Geographical region							0.98
Europe/UK/Israel	121	28 (23.1)	118	38 (32.2)	0.70 (0.42 - 1.17)	0.17	
USA	127	30 (23.6)	121	32 (26.4)	0.95 (0.57 - 1.58)	0.83	
Argentina/Indonesia/Japan/ Nigeria	47	5 (10.6)	45	6 (13.3)	0.83 (0.24 - 2.80)	0.76	
hIVIG/placebo product							0.27
CSL Behring	76	12 (15.8)	77	12 (15.6)	0.90 (0.40 - 2.02)	0.79	
Emergent	80	19 (23.8)	70	22 (31.4)	0.82 (0.43 - 1.53)	0.53	
Grifols	71	18 (25.4)	69	16 (23.2)	1.12 (0.57 - 2.21)	0.74	
Takeda	68	14 (20.6)	68	26 (38.2)	0.53 (0.27 - 1.01)	0.05	
Texcell potency (IU/mL)							0.50
< 1050	117	28 (23.9)	106	27 (25.5)	1.06 (0.61 - 1.83)	0.85	
1050 to < 1400	91	19 (20.9)	91	31 (34.1)	0.60 (0.33 - 1.07)	0.08	
1400+	86	16 (18.6)	87	18 (20.7)	0.81 (0.41 - 1.61)	0.55	
BMI							0.23
< 25	57	12 (21.1)	61	17 (27.9)	0.66 (0.31 - 1.42)	0.29	
25-29.9	90	23 (25.6)	85	15 (17.6)	1.68 (0.84 - 3.38)	0.14	
30-39.9	111	21 (18.9)	107	37 (34.6)	0.60 (0.34 - 1.06)	0.08	
40+	34	5 (14.7)	29	7 (24.1)	1.00 (0.28 - 3.60)	1.00	
Days since symptom onset							0.70
< 6 days	82	17 (20.7)	52	15 (28.8)	0.71 (0.32 - 1.61)	0.42	
6-7 days	65	19 (29.2)	62	23 (37.1)	0.82 (0.42 - 1.59)	0.55	
8-9 days	68	13 (19.1)	70	17 (24.3)	0.61 (0.29 - 1.32)	0.21	
10-12 days	80	14 (17.5)	100	21 (21.0)	0.97 (0.49 - 1.93)	0.94	
Oxygen requirement							0.82
Not on Sup O2	79	9 (11.4)	81	11 (13.6)	0.79 (0.33 - 1.92)	0.61	
Sup O2 < 4 L/min	107	15 (14.0)	92	16 (17.4)	0.74 (0.37 - 1.51)	0.41	
Sup O2 ≥ 4 L/min	84	31 (36.9)	78	33 (42.3)	0.86 (0.52 - 1.40)	0.54	

High flow O2	25	8 (32.0)	33	16 (48.5)	0.68 (0.28 - 1.65)	0.40	
Heparin dose							0.81
None	78	17 (21.8)	72	16 (22.2)	0.76 (0.35 - 1.63)	0.47	
Prophylactic	148	27 (18.2)	147	46 (31.3)	0.60 (0.37 - 0.97)	0.04	
Intermediate/therapeutic[5]	69	19 (27.5)	65	14 (21.5)	1.20 (0.58 - 2.45)	0.62	
hsCRP							0.48
< 62 mg/L	150	20 (13.3)	138	31 (22.5)	0.63 (0.35 – 1.12)	0.12	
62+ mg/L	145	43 (29.7)	144	45 (31.3)	0.96 (0.63 – 1.47)	0.84	
Neutralizing anti-spike Ab							0.18
nAb positive	133	25 (18.8)	128	26 (20.3)	1.01 (0.57 - 1.79)	0.96	
nAb negative	141	35 (24.8)	137	49 (35.8)	0.62 (0.39 - 0.98)	0.04	
Anti-N Abs							0.75
Positive	185	37 (20.0)	189	47 (24.9)	0.79 (0.51 - 1.22)	0.28	
Negative	89	23 (25.8)	76	28 (36.8)	0.75 (0.41 - 1.39)	0.37	
Quanterix antigen							0.34
< 225 pg/mL	67	4 (6.0)	70	14 (20.0)	0.41 (0.13 - 1.33)	0.14	
225-1399 pg/mL	69	10 (14.5)	67	11 (16.4)	0.92 (0.37 - 2.30)	0.86	
1400-4359 pg/mL	68	15 (22.1)	64	15 (23.4)	0.76 (0.35 - 1.65)	0.49	
4360+ pg/mL	70	31 (44.3)	63	35 (55.6)	0.68 (0.39 - 1.17)	0.16	
Viral RNA							0.67
< 10,000 copies/mL	103	18 (17.5)	91	18 (19.8)	0.92 (0.47 – 1.81)	0.81	
10,000+ copies/mL	157	40 (25.5)	156	53 (34.0)	0.75 (0.49 – 1.16)	0.20	
Quanterix antigen x nAb							0.77
Ag 1000+, nAb neg	99	33 (33.3)	92	40 (43.5)	0.68 (0.41 - 1.13)	0.13	
Ag 1000+, nAb pos	58	17 (29.3)	48	13 (27.1)	1.29 (0.57 - 2.94)	0.54	
Ag < 1000, nAb neg	42	2 (4.8)	44	9 (20.5)	0.20 (0.04 - 1.05)	0.06	
Ag < 1000, nAb pos	75	8 (10.7)	80	13 (16.3)	0.70 (0.28 - 1.72)	0.44	
Viral RNA x nAb							0.35
RNA 10,000+, nAb neg	107	28 (26.2)	99	40 (40.4)	0.63 (0.37 – 1.07)	0.09	
RNA 10,000+, nAb pos	49	12 (24.5)	55	13 (23.6)	0.93 (0.38 – 2.29)	0.87	
RNA < 10,000, nAb neg	28	7 (25.0)	26	7 (26.9)	0.62 (0.17 – 2.21)	0.46	
RNA < 10,000, nAb pos	74	11 (14.9)	65	11 (16.9)	0.92 (0.39 – 2.17)	0.84	

[1]Hazard ratio (hIVIG/placebo) stratified by baseline category and hIVIG/placebo product

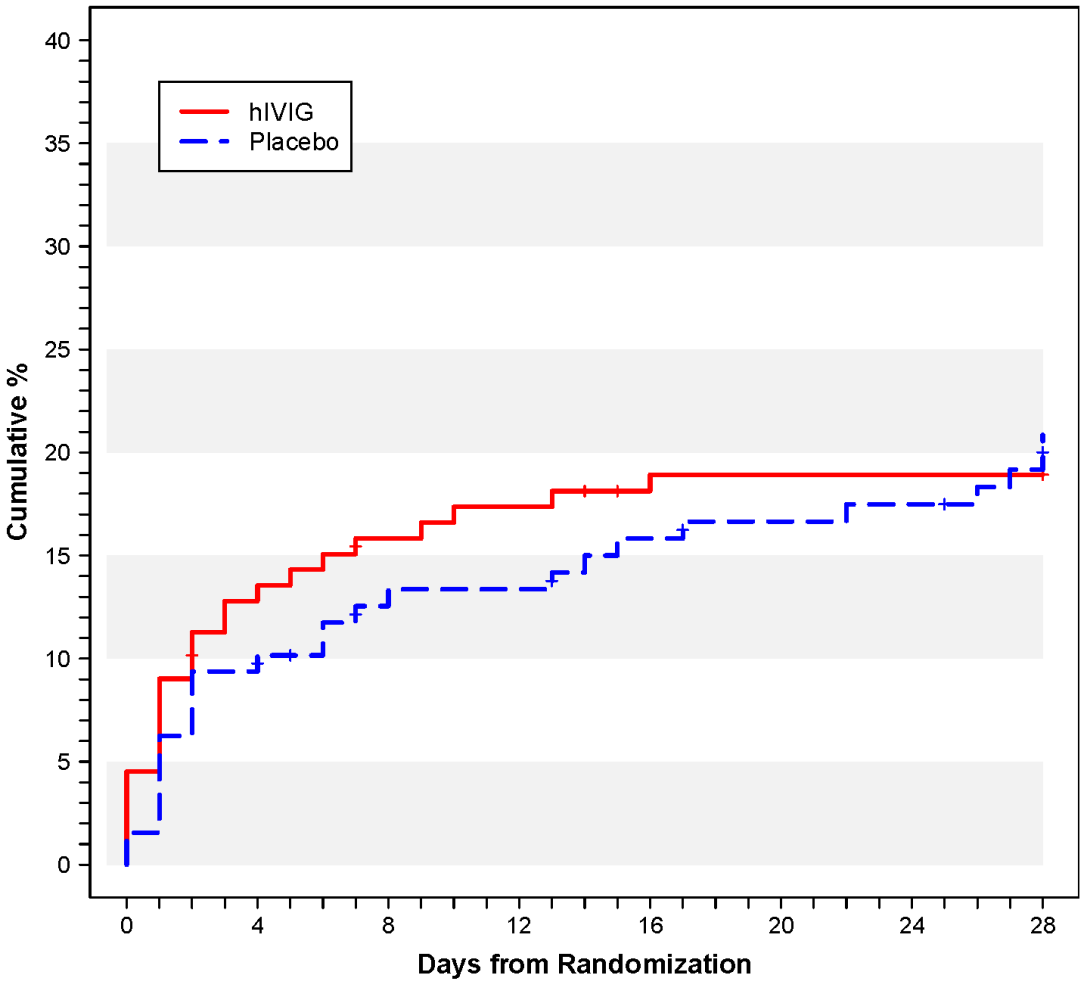
[2]N (%) of participants with deaths, SAEs, organ failure or serious infection through Day 28

[3]1 degree of freedom test with time since symptom onset included in model as a continuous variable

[4]3 degrees of freedom test with time since symptom onset included in model as 4 categorical variables

[5]Or other platelet use

Figure S3. Time to Day 28 Composite Safety Outcome – nAb positive participants

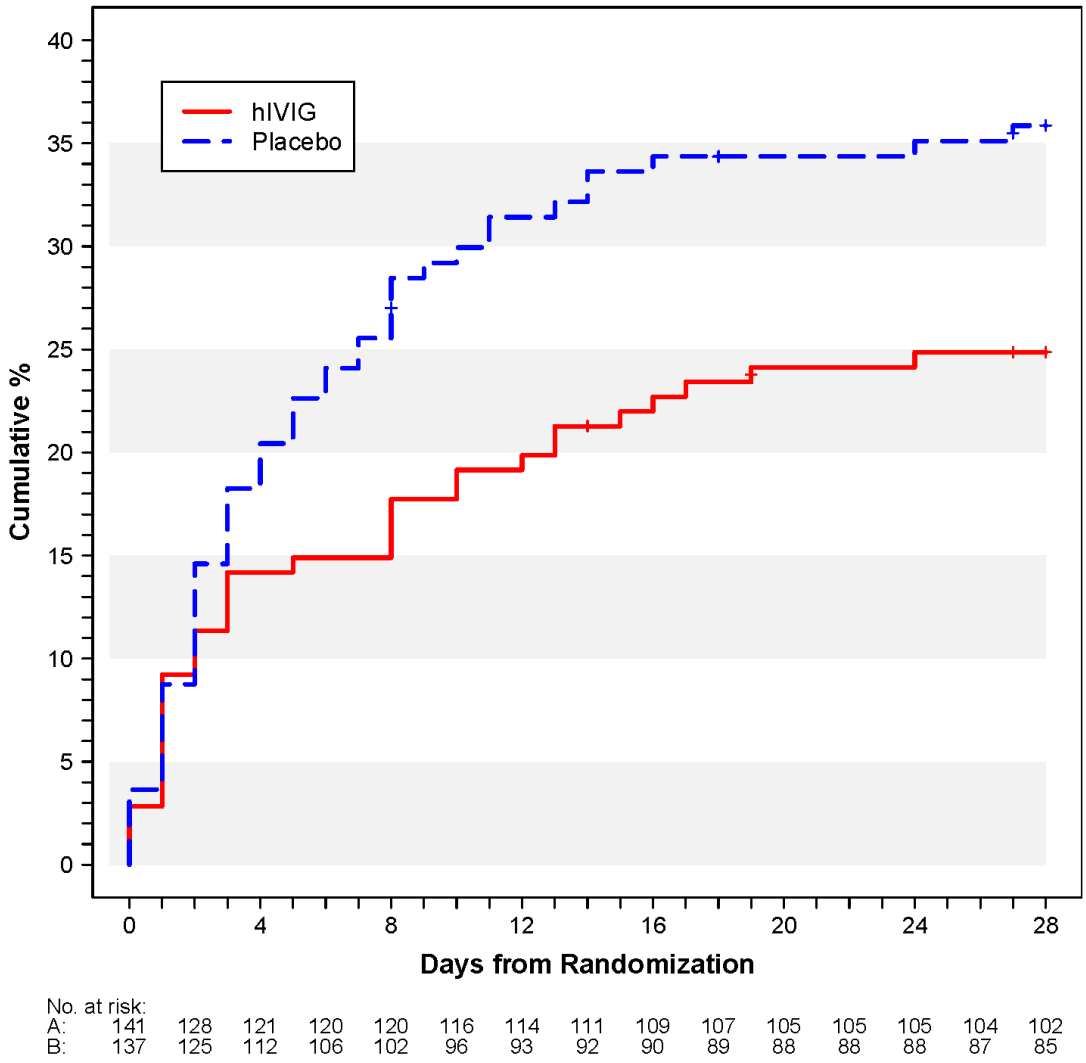


No. at risk:

A:	133	121	115	113	110	109	108	107	103	102	102	102	102	102	101
B:	128	120	116	113	107	106	106	104	102	100	100	100	99	98	96

*Lines are Kaplan–Meier estimates.

Figure S4. Time to Day 28 Composite Safety Outcome – nAb negative participants



*Lines are Kaplan–Meier estimates.

Table S35: Components of composite safety outcomes through Day 7 and Day 28 – nAb positive participants

Composite safety outcome and components	hIVIG (n=133)	Placebo (n=128)	OR (95% CI)[1]	p-value[1]
Day 7				
No. (%) deaths	1 (0.8%)	1 (0.8%)	1.13 (0.07, 18.75)	0.93
No. (%) SAEs	3 (2.3%)	2 (1.6%)	1.50 (0.23, 9.74)	0.67
No. (%) Grade 3 or 4 adverse events	23 (17.3%)	10 (7.8%)	3.16 (1.37, 7.31)	0.007
No. (%) with deaths, SAEs, or Grade 3 or 4 events	23 (17.3%)	11 (8.6%)	2.86 (1.26, 6.49)	0.01
No (%) organ failure or serious infection	21 (15.8%)	16 (12.5%)	1.48 (0.70, 3.15)	0.31
No. (%) with composite safety outcome	35 (26.3%)	21 (16.4%)	2.21 (1.14, 4.29)	0.02
Day 28			**HR (95% CI)[2]**	**p-value[2]**
No. (%) deaths	6 (4.5%)	5 (3.9%)	1.13 (0.33, 3.87)	0.85
No. (%) SAEs	3 (2.3%)	8 (6.3)	0.38 (0.10, 1.48)	0.16
No. (%) organ failure or serious infection	24 (18.0%)	23 (18.0%)	1.09 (0.61, 1.98)	0.76
No. (%) with composite safety outcome	25 (18.8%)	26 (20.3%)	1.01 (0.57, 1.79)	0.96

[1]Odds ratio (hIVIG/placebo) from logistic regression with adjustment for hIVIG/placebo product and baseline ordinal category.

[2]Hazard ratio (hIVIG/placebo) from Cox regression stratified by hIVIG/placebo product and baseline ordinal category

Table S36: Components of composite safety outcomes through Day 7 and Day 28 – nAb negative participants

Composite safety outcome and components	hIVIG (n=141)	Placebo (n=137)	OR (95% CI)[1]	p-value[1]
Day 7				
No. (%) deaths	4 (2.8%)	4 (2.9%)	1.01 (0.23, 4.34)	0.99
No. (%) SAEs	5 (3.5%)	4 (2.9%)	1.05 (0.26, 4.23)	0.94
No. (%) Grade 3 or 4 adverse events	21 (14.9%)	23 (16.8%)	0.87 (0.44, 1.69)	0.67
No. (%) with deaths, SAEs or Grade 3 or 4 events	24 (17.0%)	30 (21.9%)	0.72 (0.38, 1.34)	0.30
No (%) organ failure or serious infection	18 (12.8%)	31 (22.6%)	0.43 (0.22, 0.84)	0.01
No. (%) with composite safety outcome	32 (22.7%)	47 (34.3%)	0.51 (0.29, 0.90)	0.02
Day 28			**HR (95% CI)[2]**	**p-value[2]**
No. (%) deaths	12 (8.5%)	16 (11.7%)	0.85 (0.38, 1.89)	0.68
No. (%) SAEs	13 (9.2%)	12 (8.8%)	0.92 (0.40, 2.11)	0.84
No. (%) organ failure or serious infection	29 (20.6%)	40 (29.2%)	0.62 (0.38, 1.03)	0.07
No. (%) with composite safety outcome	35 (24.8%)	49 (35.8%)	0.62 (0.39, 0.98)	0.04

[1]Odds ratio (hIVIG/placebo) from logistic regression with adjustment for hIVIG/placebo product and baseline ordinal category.

[2]Hazard ratio (hIVIG/placebo) from Cox regression stratified by hIVIG/placebo product and baseline ordinal category

Table S37: Death, SAE or Grade 3 or 4 events through Day 7 by MedDRA System Organ Class (SOC) – nAb positive participants

MedDRA SOC	hIVIG (n=133) No. (%)	Placebo (n=128) No. (%)
Blood and Lymphatic System	1 (0.8%)	0 (0.0%)
Cardiac	1 (0.8%)	1 (0.8%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)
Eye	0 (0.0%)	0 (0.0%)
Gastrointestinal	1 (0.8%)	0 (0.0%)
General and Administration Site	8 (6.0%)	3 (2.3%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	1 (0.8%)	2 (1.6%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	1 (0.8%)	0 (0.0%)
Metabolism and Nutrition	0 (0.0%)	0 (0.0%)
Musculoskeletal, Connective Tissue	0 (0.0%)	1 (0.8%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	2 (1.5%)	3 (2.3%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	1 (0.8%)	1 (0.8%)
Renal and Urinary	0 (0.0%)	0 (0.0%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	12 (9.0%)	6 (4.7%)
Skin and Subcutaneous Tissue	0 (0.0%)	0 (0.0%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	1 (0.8%)	0 (0.0%)
Any of above	23 (17.3%)	11 (8.6)

Table S38: Death, SAE or Grade 3 or 4 events through Day 7 by MedDRA System Organ Class (SOC) – nAb negative participants

MedDRA SOC	hIVIG (n=141) No. (%)	Placebo (n=137) No. (%)
Blood and Lymphatic System	2 (1.4%)	0 (0.0%)
Cardiac	1 (0.7%)	4 (2.9%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)
Eye	1 (0.7%)	0 (0.0%)
Gastrointestinal	2 (1.4%)	1 (0.7%)
General and Administration Site	10 (7.1%)	7 (5.1%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	6 (4.3%)	2 (1.5%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	1 (0.7%)
Metabolism and Nutrition	1 (0.7%)	1 (0.7%)
Musculoskeletal, Connective Tissue	1 (0.7%)	1 (0.7%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	0 (0.0%)	0 (0.0%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	0 (0.0%)	0 (0.0%)
Renal and Urinary	2 (1.4%)	1 (0.7%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	9 (6.4%)	16 (11.7%)
Skin and Subcutaneous Tissue	0 (0.0%)	0 (0.0%)
Social Circumstances	1 (0.7%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	3 (2.1%)	1 (0.7%)
Any of above	24 (17.0%)	30 (21.9)

Table S39: Clinical organ failure and serious infection events through Day 7 – nAb positive participants

Diagnoses	hIVIG (n=133) No. (%)	Placebo (n=128) No. (%)
MI	2 (1.5%)	0 (0.0%)
NYHA class III or IV heart failure	0 (0.0%)	0 (0.0%)
Institution of vasopressor therapy	2 (1.5%)	3 (2.3%)
Myocarditis	0 (0.0%)	0 (0.0%)
Pericarditis	0 (0.0%)	0 (0.0%)
DIC	0 (0.0%)	0 (0.0%)
Thromboembolic events	4 (3.0%)	1 (0.8%)
Hepatic decompensation	0 (0.0%)	0 (0.0%)
Microbiologically proven severe infection (not including SARS-CoV-2)	1 (0.8%)	1 (0.8%)
Acute delirium	1 (0.8%)	0 (0.0%)
Cerebrovascular event (stroke)	0 (0.0%)	0 (0.0%)
Encephalitis	0 (0.0%)	0 (0.0%)
Meningitis	0 (0.0%)	0 (0.0%)
Myelitis	0 (0.0%)	0 (0.0%)
Renal replacement therapy[1]	0 (0.0%)	0 (0.0%)
Respiratory failure[2]	16 (13.8%)	12 (10.9%)
Any of the above	21 (15.8%)	16 (12.5%)

[1]Excludes those on RRT prior to entry
[2]Excludes those on high flow oxygen at entry

Table S40: Clinical organ failure and serious infection events through Day 7 – nAb negative participants

Diagnoses	hIVIG (n=141) No. (%)	Placebo (n=137) No. (%)
MI	0 (0.0%)	0 (0.0%)
NYHA class III or IV heart failure	0 (0.0%)	1 (0.7%)
Institution of vasopressor therapy	3 (2.1%)	5 (3.6%)
Myocarditis	0 (0.0%)	1 (0.7%)
Pericarditis	0 (0.0%)	0 (0.0%)
DIC	0 (0.0%)	0 (0.0%)
Thromboembolic events	1 (0.7%)	2 (1.5%)
Hepatic decompensation	0 (0.0%)	0 (0.0%)
Microbiologically proven severe infection (not including SARS-CoV-2)	1 (0.7%)	3 (2.2%)
Acute delirium	1 (0.7%)	2 (1.5%)
Cerebrovascular event (stroke)	0 (0.0%)	1 (0.7%)
Encephalitis	1 (0.7%)	0 (0.0%)
Meningitis	0 (0.0%)	0 (0.0%)
Myelitis	0 (0.0%)	0 (0.0%)
Renal replacement therapy[1]	3 (2.2%)	1 (0.8%)
Respiratory failure[2]	14 (10.4%)	28 (23.0%)
Any of the above	18 (12.8%)	31 (22.6%)

[1]Excludes those on RRT prior to entry
[2]Excludes those on high flow oxygen at entry

Table S41. Death or SAE through Day 28 by MedDRA System Organ Class (SOC) – nAb positive participants

MedDRA SOC	hIVIG (n=133) No. (%)	Placebo (n=128) No. (%)
Blood and Lymphatic System	1 (0.8%)	2 (1.6%)
Cardiac	1 (0.8%)	0 (0.0%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)
Eye	0 (0.0%)	0 (0.0%)
Gastrointestinal	0 (0.0%)	0 (0.0%)
General and Administration Site	0 (0.0%)	1 (0.8%)
Hepatobiliary	0 (0.0%)	1 (0.8%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	3 (2.3%)	4 (3.1%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	0 (0.0%)
Metabolism and Nutrition	0 (0.0%)	0 (0.0%)
Musculoskeletal, Connective Tissue	0 (0.0%)	0 (0.0%)
Neoplasms - Benign and Malignant	0 (0.0%)	0 (0.0%)
Nervous System	0 (0.0%)	1 (0.8%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	1 (0.8%)	1 (0.8%)
Renal and Urinary	0 (0.0%)	0 (0.0%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	3 (2.3%)	1 (0.8%)
Skin and Subcutaneous Tissue	0 (0.0%)	0 (0.0%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	0 (0.0%)	0 (0.0%)
Any of above	8 (6.0%)	11 (8.6%)

Table S42. Death or SAE through Day 28 by MedDRA System Organ Class (SOC) – nAb negative participants

MedDRA SOC	hIVIG (n=141) No. (%)	Placebo (n=137) No. (%)
Blood and Lymphatic System	2 (1.4%)	0 (0.0%)
Cardiac	1 (0.7%)	3 (2.2%)
Congenital, Familial, Genetic	0 (0.0%)	0 (0.0%)
Ear and Labyrinth	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)
Eye	0 (0.0%)	0 (0.0%)
Gastrointestinal	2 (1.4%)	0 (0.0%)
General and Administration Site	0 (0.0%)	2 (1.5%)
Hepatobiliary	0 (0.0%)	0 (0.0%)
Immune System	0 (0.0%)	0 (0.0%)
Infections and Infestations	9 (6.4%)	11 (8.0%)
Injury, Poisoning, Procedural	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	0 (0.0%)
Metabolism and Nutrition	0 (0.0%)	0 (0.0%)
Musculoskeletal, Connective Tissue	0 (0.0%)	0 (0.0%)
Neoplasms - Benign and Malignant	1 (0.7%)	0 (0.0%)
Nervous System	0 (0.0%)	0 (0.0%)
Pregnancy, puerperium, perinatal	0 (0.0%)	0 (0.0%)
Psychiatric	0 (0.0%)	0 (0.0%)
Renal and Urinary	1 (0.7%)	0 (0.0%)
Reproductive System and Breast	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, Mediastinal	5 (3.5%)	11 (8.0%)
Skin and Subcutaneous Tissue	0 (0.0%)	0 (0.0%)
Social Circumstances	0 (0.0%)	0 (0.0%)
Surgical and Medical Procedures	0 (0.0%)	0 (0.0%)
Vascular	1 (0.7%)	0 (0.0%)
Any of above	20 (14.2%)	25 (18.2%)

Table S43: Clinical organ failure and serious infection events through Day 28 – nAb positive participants

Diagnoses	hIVIG (n=133) No. (%)	Placebo (n=128) No. (%)
MI	2 (1.5%)	0 (0.0%)
NYHA class III or IV heart failure	0 (0.0%)	0 (0.0%)
Institution of vasopressor therapy	5 (3.8%)	9 (7.0%)
Myocarditis	0 (0.0%)	0 (0.0%)
Pericarditis	0 (0.0%)	0 (0.0%)
DIC	0 (0.0%)	0 (0.0%)
Thromboembolic events	4 (3.0%)	3 (2.3%)
Hepatic decompensation	0 (0.0%)	0 (0.0%)
Microbiologically proven severe infection (not including SARS-CoV-2)	1 (0.8%)	5 (3.9%)
Acute delirium	1 (0.8%)	0 (0.0%)
Cerebrovascular event (stroke)	0 (0.0%)	0 (0.0%)
Encephalitis	0 (0.0%)	0 (0.0%)
Meningitis	0 (0.0%)	0 (0.0%)
Myelitis	0 (0.0%)	0 (0.0%)
Renal replacement therapy[1]	1 (0.8%)	3 (2.4%)
Respiratory failure[2]	17 (14.7%)	14 (12.7%)
Any of the above	24 (18.0%)	23 (18.0%)

[1]Excludes those on RRT prior to entry
[2]Excludes those on high flow oxygen at entry

Table S44: Clinical organ failure and serious infection events through Day 28 – nAb negative participants

Diagnoses	hIVIG (n=141) No. (%)	Placebo (n=137) No. (%)
MI	0 (0.0%)	0 (0.0%)
NYHA class III or IV heart failure	0 (0.0%)	1 (0.7%)
Institution of vasopressor therapy	7 (5.0%)	12 (8.8%)
Myocarditis	0 (0.0%)	1 (0.7%)
Pericarditis	0 (0.0%)	0 (0.0%)
DIC	0 (0.0%)	1 (0.7%)
Thromboembolic events	3 (2.1%)	6 (4.4%)
Hepatic decompensation	0 (0.0%)	0 (0.0%)
Microbiologically proven severe infection (not including SARS-CoV-2)	4 (2.8%)	6 (4.4%)
Acute delirium	1 (0.7%)	2 (1.5%)
Cerebrovascular event (stroke)	0 (0.0%)	2 (1.5%)
Encephalitis	1 (0.7%)	0 (0.0%)
Meningitis	0 (0.0%)	0 (0.0%)
Myelitis	0 (0.0%)	0 (0.0%)
Renal replacement therapy[1]	5 (3.6%)	3 (2.3%)
Respiratory failure[2]	22 (16.4%)	33 (27.0%)
Any of the above	29 (20.6%)	40 (29.2%)

[1]Excludes those on RRT prior to entry
[2]Excludes those on high flow oxygen at entry

V. References

1. Bennett RS, Postnikova EN, Liang J, et al. Scalable, micro-neutralization assay for assessment of SARS-CoV-2 (COVID-19) virus-neutralizing antibodies in human clinical samples. Viruses 2021, 13, 893. https//doi.org/10.3390/v13050893.
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3. Whitehead J. Sample size calculations for ordered categorical data. Stat Med 1993; 12: 2257-2271.

Statistical Data Analysis Plan

An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

INSIGHT Protocol Number: 013

1 Introduction

2 Objective of the Statistical Analysis Plan

The objective of this statistical analysis plan (SAP) is to provide a description of the analytic strategy and the statistical methods that will be used to analyze the data for the Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) Phase III randomized, double-blind, placebo-controlled trial. The primary objective of the trial is to determine whether hyperimmune intravenous immunoglobulin (hIVIG) to SARS-CoV-2, derived from the plasma of individuals who recover and develop neutralizing antibodies, is a potentially safe and effective therapeutic approach to COVID-19 compared to placebo (each treatment is given with standard of care [SOC]). The primary endpoint of this trial is an ordinal outcome based on the patient's clinical status on Day 7.

In Version 1.0, this SAP provided:

- A short description of the study design (Section 10)
- Goals of the interim reviews by the independent DSMB and the planned format of the review meetings (Section 11)
- A description of the planned data analyses presented in the reports to the DSMB (Sections 12-23). Guidelines for stopping the study because of early proof of efficacy, futility, or harm are described in Sections 17, 18, and 19, respectively.
- A description of data summaries to be provided to study leadership to aid in monitoring trial conduct and data quality; these data summaries, which will be regularly updated and posted to the INSIGHT website, will be restricted to enrollment (Section 12), baseline data (Section 13), and summaries of follow-up data completeness (Section 23).

Version 2.0 of the SAP was prepared prior to unblinding of the data by statisticians and other members of the core ITAC team who have been blinded to interim treatment comparisons for the duration of the trial.

Below we briefly summarize the status of the trial and some key blinded data that informed the preparation of this updated SAP (Version 2.0).

3 Trial Status and Information That Informed the Updated SAP

4 Trial Status

Version 1.0 of the protocol was used for the duration of the trial. On November 24, 2020 a letter of amendment was issued that extended the exclusion criteria in the trial to "Prior receipt of any SARS-CoV-2 monoclonal antibody treatments at any time." The DSMB carried out two full reviews of the protocol, on November 24, 2020 and on January 5, 2021. Following each review, the DSMB recommended the study continue as planned. Between these full reviews and until enrollment was completed, the DSMB also reviewed safety data on a weekly basis that was provided to them by the unblinded statisticians.

Following the DSMB meeting on January 5, 2021, the DSMB approved the provision of the pooled (both treatment groups combined) category proportions to blinded statisticians in order to re-estimate sample size. Using the observed pooled proportions, power was estimated to be 0.83 for the planned sample size of 500. Based on this, no change in sample size was recommended.

5 Enrollment Summary

The first participant was enrolled on October 8, 2020; the last participant was enrolled on February 10, 2021. On February 3, 2021 we notified the central IRB for ITAC, Advarra, that the final accrual would be more than planned and that it likely would be between 550 and 600 participants. A total of 593 participants were enrolled by 63 sites in 11 countries (93 more participants than were planned). These 63 sites were provided study drug infusion bags following randomization by 47 study site pharmacies. The number enrolled by site ranged from 1 to 41 participants. Twenty three sites enrolled 1-4 participants; 17 sites enrolled 5-9 participants; 11 enrolled 10-14; and 12 sites enrolled 15 or more participants.

Two participants did not meet strict eligibility criteria. One participant was enrolled 13 days after symptom onset, and the second participant had a condition that did not allow venipuncture; this participant did not receive an infusion.

6 Summary of Baseline Characteristics

Selected baseline characteristics that were considered (as of March 23, 2021) in revising the SAP are given below.

1. As noted above, participants are from 11 countries. Numbers enrolled by country are: Denmark (77), Germany (10), Spain (65), Greece (70), UK (19), Indonesia (33), Argentina (4), Israel (6), Japan (15), Nigeria (41), and U.S. (253).
2. Median (25^{th}, 75^{th} percentile) of age is 59 (50, 70) years.
3. Median (25^{th}, 75^{th} percentile) of symptom onset is 8 (6, 10) days.
4. Oxygen status (above pre-COVID-19 requirement): 28% were not receiving oxygen; 34% were receiving < 4 L/min; 28% were receiving ≥ 4 L/min; and 10% were receiving high-flow oxygen.
5. 541 (93%) received remdesivir prior to randomization or on the same day as randomization as part of SOC.
6. 329 (56%) were receiving corticosteroids at entry; 48 (84%) among those on high-flow oxygen and 229 (62%) among those on supplemental oxygen.
7. 355 (60%) were receiving heparin (prophylactic, intermediate, or therapeutic dose) at entry.
8. Median (10^{th}, 25^{th}, 75^{th}, 90^{th} percentile) BMI is 29.8 (23.0, 25.8, 34.7, 40.2) kg/m^2.
9. Selected diagnoses (% reported) collected as part of a medical history and an elevated BMI are summarized below:
    - Asthma (10%)
    - Cerebrovascular event (1%)
    - COPD (6%)
    - Diabetes (28%)
    - Heart failure (4.6%)
    - Hepatic impairment (2%)
    - HIV (2%)
    - Hypertension requiring medication (42%)
    - Immunosuppressive disorder other than HIV (1%)
    - Malignancy (4%)
    - MI (3%)
    - Renal impairment (7%)
    - BMI ≥ 30 kg/m^2 (49%)

7 hIVIG/Placebo Assignment and Completeness of Infusions

As indicated in the protocol, each study site pharmacy was assigned an hIVIG product/matching placebo to use. The product assignment is summarized below:

Product Manufacturer	No. of Study Site Pharmacies	No. of Lots of hIVIG Used	No. of Participants
CSL Behring	11	5	155
Emergent	11	3	153
Grifols	11	22	146
Takeda	14	14	139
Total	47	44	593

Lot potency was measured by Texcell for each of the 44 lots used. The potency measures were reported in AY/mL units; these levels were multiplied by 1.73674589 to obtain units in IU/mL. The median (25^{th}, 75^{th} percentile) potency level of the 44 lots of hIVIG used was 1220 (893, 1442) IU/mL.

Twelve participants did not receive an infusion. Ten of these participants withdrew consent prior to being infused; for one participant, venous access could not be achieved; and one participant refused the infusion but continued in follow-up.

8 Summary of Pooled (Both Treatment Groups Combined) Follow-up Results

The last 28 day follow-up was to be completed by March 14, 2021.

Selected follow-up data for both treatment groups combined were considered.

The median (25^{th}, 75^{th} percentile) of time to discharge from randomization is 6 (4, 9) days.

During regular investigator meeting, it became clear that some sites were retaining participants in the hospital for public health reasons and/or for the collection of the Day 7 primary outcome data. There were 7 sites (all that enrolled 5 or more participants) in 6 countries that enrolled a total of 93 participants where no one was discharged before day 7.

The Day 3 NEW score is missing for 82 participants (13.8% of randomized participants). The score can only be determined for hospitalized participants and most of the missing data is for participants discharged before Day 3.

A total of 581 participants received a full or partial infusion; as noted above, 12 (2%) participants were not infused.

Among participants meeting the eligibility criteria and who received an infusion, there are 7 participants missing the 7-category primary ordinal endpoint that is assessed on Day 7 (see table below). Six of these 7 participants were discharged prior to day 7 with no further contact. One participant was transferred to another hospital before day 7. Details of the participants missing the Day 7 endpoint due to reasons other than missing forms are below.

Pt	Study Day of Discharge	Discharged to	Oxygen use on day of discharge	Study Day last known alive	Additional information

1	Day 2	Home	None	Day 2	
2	Day 4	Home	2.0 l/min	Day 4	
3	Day 3	Home	None	Day 28	Paramedics visited pt at home to collect Day 7 and Day 28 specimens. No other study data was collected.
4	Day 1	Home	1.5 l/min	Day 5	
5	Day 3	Home	4.0 l/min	Day 7	
6	Day 2	Transferred to another hospital	None	Day 27	Transferred to another hospital due to pt preference. Known alive day 27, but no other contact.
7	Day 5	Home	None	Day 25	Pt did not want to be contacted anymore, but allowed access of medical records

Among all randomized participants, 18 (3.0%) are missing the Day 7 primary endpoint, and 36 (6.1%) have unknown survival status on Day 28. Of these, 11 withdrew consent, all before the infusion.

9 Summary of Changes to SAP

Based on the above information and additional data expected we made the following changes to the SAP:

1. The secondary outcomes of hospitalization status at days 7, 14, and 28, time to discharge, and days alive outside of the hospital at Day 28 will be supplemented with the following additional outcomes: i) time to discharge or being able to independently undertake usual activities with minimal or no symptoms; ii) time to being able to independently undertake usual activities with minimal or no symptoms (discharge status will be ignored); iii) the binary outcome of hospitalization will also be defined as alive and either discharged from the hospital or being able to independently undertake usual activities with minimal or no symptoms; iv) days alive and able to independently undertake usual activities with minimal or no symptoms at Day 28; and v) days alive and out of the hospital or able to independently undertake usual activities with minimal or no symptoms at Day 28 (whichever lead to greatest time).

   Additionally, as a sensitivity analysis for the analysis of time-to-discharge and days outside the hospital we will exclude participants from the 7 sites where no participants were discharged prior to Day 7.

   In all of the outcomes related to “discharge”, “discharge” will refer to home, to a rehabilitation center or to a post-acute care facility.

2. The change in NEW score from baseline to Day 3 will not be considered as a secondary outcome because it is only collected for hospitalized participants, and

the Day 3 New score is missing for 80 participants (nearly all the participants with missing data had been discharged before Day 3).

3. A key subgroup analysis defined in the protocol is according to duration of symptoms. The primary ordinal outcome will be summarized for the following approximately equal subgroups (<6, 6-7, 8-9, and 10-12 days). The presence of a treatment by subgroup interaction will be estimated in 2 ways, with a 1 degree of freedom (df) test with duration of symptoms included in the ordinal regression model as a continuous variable and with a 3 df test with indicators for categories of duration of symptoms in the regression model.

4. Another important subgroup is by age. The median (25^{th}, 75^{th} percentile) of age is 59 (50, 70) years. Therefore, we will present age in approximate quartiles (<50, 50-59, 60-69, and ≥ 70) years.

5. For the subgroup by geographic region the following subgroups will be defined: U.S.; Europe, UK, or Israel; and Argentina, Indonesia, Japan or Nigeria.

6. Subgroup analyses by chronic conditions will be carried out for individual conditions which have prevalence at least 5% at baseline (asthma, COPD, diabetes, hypertension requiring medication, renal impairment, and BMI ≥ 40 kg/m^2).

7. The following other subgroups that combine chronic conditions and concomitant treatments will be carried out:
    a. Participants with and without compromised immune function; participants with HIV, an immunosuppressive condition other than HIV, or taking antirejection medication, immune modulators, or biologic treatment for autoimmune disease or cancer will be considered to have compromised immune function.
    b. BMI < 40 and ≥ 40 kg/m^2 according to history of diabetes (4 groups)
    c. Hypertension with and without history of other metabolic and vascular co-morbidity (4 groups): i) no hypertension or other metabolic/vascular co-morbidity; ii) hypertension without metabolic/vascular co-morbidity; iii) metabolic/vascular condition without hypertension; and iv) hypertension and a metabolic/vascular co-morbidity. Metabolic/vascular co-morbidities include a history of diabetes, a cerebrovascular event, heart failure, or an MI or acute coronary syndrome.
    d. Number of vascular co-morbidities (0, 1, 2, 3+)
    e. Quartile of Charlson Comorbidity Index (for conditions assessed)
    f. Risk calculator for vaccine prioritization (JHU)
    g. Quartile of disease progression risk score for Day 7 outcome that considers baseline antigen and antibody levels, age, gender, duration of symptoms, oxygen saturation, ordinal category, NEW score, and history of chronic health conditions.

8. Subgroup analyses by concomitant medications will be carried out for corticosteroids, overall and in combination with oxygen requirements (baseline ordinal scale).

9. Planned subgroup analyses by baseline antigen and antibody levels and antibody comparisons during follow-up have been added to the SAP as a new section.

10. The analysis population for the efficacy outcomes has been changed from the intention-to-treat (ITT) population to a modified intention-to-treat (mITT).

10 Description of the Study Design

This section is adapted from the ITAC protocol version 1.0. *Italicized sections have been added as part of this update.*

Design

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of hIVIG in adult participants who are hospitalized with COVID-19 with symptoms for no more than 12 days, and who do not have life-threatening organ dysfunction or organ failure. Remdesivir will be provided to participants in both the hIVIG and placebo groups as SOC unless contraindicated for an individual participant.

Primary Objective and Primary Outcome

The primary objective is to compare the clinical status of participants in the hIVIG + SOC and placebo + SOC groups on Day 7 using an ordinal outcome with seven mutually exclusive categories. On Day 7, the worst of the seven categories the participant was in that day will constitute the primary outcome. The seven categories are:

7. Death
6. End-organ failure
5. Life-threatening end-organ dysfunction
4. Serious end-organ dysfunction
3. Moderate end-organ dysfunction
2. Limiting symptoms due to COVID-19
1. No limiting symptoms due to COVID-19

Appendix F of the protocol provides clinical definitions of each category.

The primary ordinal outcome captures the range of severity experienced by hospitalized patients with COVID-19, recognizing that end-organ manifestations in addition to pneumonia and acute respiratory distress syndrome are increasingly emerging as significant contributors to morbidity. The ordinal outcome includes both pulmonary manifestations as assessed in prior COVID-19 trials and additional components representing key non-pulmonary outcomes; the latter are highlighted as *"extra-pulmonary"* in the guidance table (Appendix F). The primary endpoint will include both pulmonary and extra-pulmonary components, while the pulmonary manifestation scale only will be reported as a secondary endpoint.

Day 7 was chosen for the timing of the primary endpoint for several reasons based on the following assumptions. The impact of hIVIG on disease progression may not be immediate; a few days may be needed to see the effects on clinical outcomes as measured by the ordinal outcome. Also,

transient treatment effects that are no longer present at Day 7 may be clinically less relevant. Assessment of the ordinal outcome at a later time point may result in a diminished treatment difference because spontaneous recovery from COVID-19 may have begun in many participants. Also, antibody differences between the treatment groups, an important biologic mechanism for observing a clinical benefit, are assumed to be greatest during the first week after infusion.

Lastly, use of Day 7 to characterize the clinical severity of participants in seven categories as studied here, results in a distribution of participants in the placebo group for the ordinal outcome that is sufficiently granular and not overly skewed to the most severe or least severe categories and, therefore, provides good power for comparing the two treatment groups with a feasible sample size given the difficulty in producing large quantities of hIVIG.

The primary and secondary objectives of ITAC are addressed by pooling the four hIVIG products and making comparisons with the corresponding placebo groups. To justify this pooling, each hIVIG lot prepared has a neutralizing potency that provides an appreciable dose margin over convalescent plasma. A standard dose of 400 mg/kg is used for each hIVIG product (see section 8.1.2 of the protocol).

Key Secondary Outcomes

A number of secondary endpoints to assess safety and efficacy have been specified. Four endpoints are defined as key secondary outcomes: 1) a composite of death, end-organ failure, or life threatening end-organ dysfunction (categories 5-7 of the primary ordinal outcome at Day 7); 2) time to the two most favorable categories of the primary ordinal outcome; 3) percentage in two most favorable categories of the ordinal outcome at Day 7; and hospitalization status at Day 14.

Mortality, adverse events (AEs), including infusion reactions, and biological correlates of therapeutic activity are also assessed. Because there is no established endpoint for evaluating the clinical efficacy of treatments for COVID-19, other clinically relevant outcomes, including outcomes used in other COVID-19 treatment trials, will be recorded. Thus, the randomized groups (hIVIG + SOC versus placebo + SOC) can be compared for multiple outcomes, and results can be compared or combined with other trials. A list of secondary outcomes is given in Section 20.

Study Treatments

Anti-Coronavirus hIVIG is a human hyperimmune product of the purified gamma globulin (IgG) fraction of human plasma containing polyvalent neutralizing antibodies to SARS-CoV-2. hIVIG is prepared from pooled plasma collected from healthy, adult donors who have recovered from SARS-CoV-2 infection. Four hIVIG products (Emergent BioSolutions, Grifols Therapeutics, Inc., Takeda Pharmaceuticals, and CSL Bering) will be used in this trial.

Duration

All participants will be followed for 28 days. A subsample of participants is followed for 90 days. If the trial goes to completion, the primary analysis will be completed after all randomized participants are followed for 28 days.

Randomization

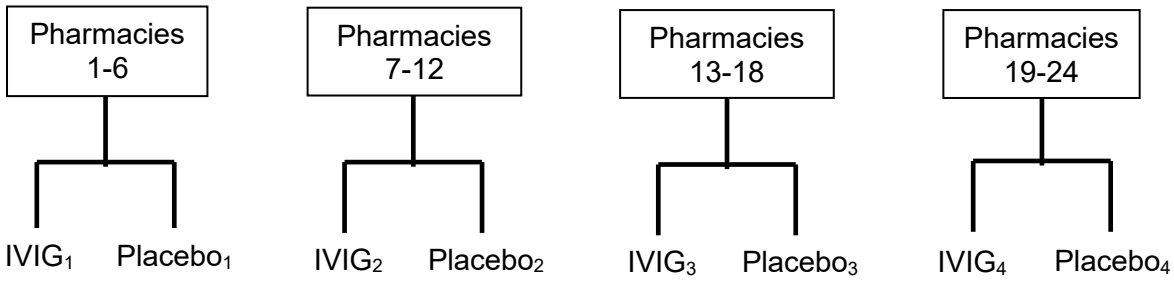
Randomization will be stratified by site pharmacy (clinical sites may share a pharmacy). Participants will be randomized (1:1) to a single infusion of hIVIG + SOC or placebo + SOC on the day of randomization (Day 0).

Hyperimmune IVIG will be manufactured by four companies; to simplify logistics related to the supply of hIVIG to clinical sites and to take advantage of the randomization, which is stratified by site pharmacy, the same hIVIG product will be provided to a given site pharmacy for the duration of

the trial to the extent possible. This is illustrated in Figure 1 with an example that assumes that there are 24 site pharmacies and the supply of each of hIVIG products will be the same.

Within each stratum permuted block randomization will be used to generate treatment assignments.

FIGURE 1. EXAMPLE OF ALLOCATION OF HIVIG TO 24 SITE PHARMACIES



Sample Size

The planned sample size is 500 participants (250 per group).

The following assumptions were made in estimating the required sample size.

h. The primary analysis will be modified intention-to-treat (mITT).

i. A proportional odds model with indicators for the six cut-offs corresponding to using any of categories 1 to 6 as cut-offs for determining clinical improvement, treatment group (hIVIG versus placebo), baseline severity of illness as defined by the ordinal outcome, two-way interactions between baseline severity of illness and the six cut-offs, hIVIG product/matching placebo used, and two-way interactions between hIVIG product/matching placebo used and the six cut-offs will be used to estimate the odds ratio (OR).

j. Type 1 error = 0.05 (2-sided) and power = 0.80.

k. The clinical status of participants in the placebo group at Day 7 is assumed as shown in the third column in Table 2. Since both randomized treatment groups will receive remdesivir as SOC (unless contraindicated), these percentages were estimated using Day 7 data from the ACTT-1 trial for a subgroup of patients similar to ours (the subgroup of participants who entered ACTT-1 in categories 4 and 5 of their eight-category ordinal outcome for disease severity and were randomized to the remdesivir group).

l. We assumed an OR (hIVIG/placebo) of 1.61 for a more favorable outcome. This corresponds to the percentage of participants in the hIVIG group at Day 7 shown in each level of the ordinal scale given in the second column in Table 1 below. For example, the percentage of participants in the two most favorable categories would be increased to 65.4% in the hIVIG group from 54.0% in the placebo group (an 11.4 percentage point increase from the placebo group). Conversely, the percentage of participants in the four most severe categories would decrease to 19.4% from 28.1% in the placebo group. The same proportional improvement was assumed across the ordinal scale.

m. Sample size depends on a number of assumptions, including the hypothesized odds ratio, the number of categories in the ordinal outcome, and the distribution of responses for the placebo group.[i] Hypothesized odds ratios closer to 1.0 correspond to a smaller treatment effect and require a larger sample size to maintain 80% power. The final sample size was chosen after consideration of a range of odds ratios and of category percentages for the placebo group.

n. *Based on the category percentages in Table 1, the estimated sample size is 494. This was increased to 500 to allow for a small number of participants who may be randomized but not receive the study infusion or meet strict eligibility criteria. These participants will be excluded from the mITT analysis.*

A planned blinded sample size re-estimation that utilized the observed pooled (both treatment groups combined) category percentages confirmed that the sample size of 500 participants would provide the planned power for detecting an odds ratio of 1.61.

TABLE 1. HYPOTHESIZED PERCENTAGE OF PARTICIPANTS IN EACH CATEGORY ON DAY 7 IN THE HIVIG AND PLACEBO GROUPS BASED ON AFOREMENTIONED ASSUMPTIONS

Category	hIVIG + SOC Group	Placebo + SOC Group
7. Death	0.6	1.0
6. End-organ failure	4.0	6.3
5. Life-threatening end-organ dysfunction	4.2	6.3
4. Serious end-organ dysfunction	10.6	14.5
3. Moderate end-organ dysfunction.	15.1	17.9
2. Limiting symptoms due to COVID-19	57.6	49.0
1. No limiting symptoms due to COVID-19	7.8	5.0
Total	100.0	100.0

For the key subgroup defined according to duration of symptoms at entry, in addition to analysis by quartile, the OR for the primary endpoint will be estimated for the participants in the lower 3 quartiles. Assuming the category percentages in Table 1, with an estimated 444 participants (75% of 593) (222 per treatment group), an OR of a more favorable outcome on hIVIG compared to placebo of 1.61 can be detected with 77% power.

The study is not powered to detect treatment differences in mortality because the mortality is expected to be low given the eligibility criteria and duration of follow-up.

The following outcomes are defined as key secondary outcomes:

Composite of death, end-organ failure, or life-threatening end-organ dysfunction (categories 5-7 of the ordinal outcome) at Day 7: This composite outcome comprises the most severe three categories of the ordinal outcome. Decreasing the probability that a participant enters one of these disease states and remains there through Day 7 has high clinical significance. *Comparing the hIVIG+SOC versus the placebo+SOC groups for the proportion of participants in the three worst categories on Day 7, a total sample size of 579 participants (the estimated number of participants in the mITT analysis) is sufficient to detect a decrease to 6.6% in the hIVIG group compared with 13.6% in the placebo group (difference 7.0%) with 80% power. A decrease from 13.6% to 8.8% as in Table 1 (OR = 1.61) can be detected with power of 45%.*

Time to the two most favorable categories of the primary ordinal outcome (first occurrence): We expect that by Day 28, almost all participants will be discharged from the hospital. Similarly, we expect most participants will be in in one of the two most favorable

categories of the primary ordinal outcome by Day 28. In the ACTT-1 trial, in the subset of participants who entered the trial with disease severity similar to our eligibility criteria (ACTT-1 ordinal outcome categories 4 and 5), 94.7% had been discharged from the hospital by Day 28. This percentage was similar for the ACTT-1 definition of "recovery" that includes a small percentage of participants who were hospitalized but no longer requiring medical care. Comparing the hIVIG versus placebo groups for time to the 2 most favorable categories, our study is powered to detect a relative rate ratio (RRR) of 1.3 with 80% power and a significance level of 0.05. *The power calculations assume that the RRR is approximately constant to Day 28, the overall cumulative percentage in the two most favorable categories (pooled across treatment groups) by Day 28 is 81% and that between 2.5 and 3% withdraw consent or are lost to follow-up by Day 28.*

Two most favorable categories at Day 7: *Comparing the hIVIG versus the placebo+SOC groups for the percentage in the two most favorable categories (a binary outcome) on Day 7, the total sample size of 579 participants is sufficient to detect an increase in the this percentage from 54% in the placebo group to 65.4% in the placebo group (as in Table 1) with 80% power.*

Hospitalization status at day 14: *The study has greater than 80% power to detect an increase to 87% in the hIVIG group compared with 77% in the placebo group for the percentage dischargedl at Day 14. Estimates from the ACTT-1 trial used for the placebo group were 51% discharged on Day 7, and 77% on Day 14, for participants that were similar to ours and who were randomized to the remdesivir arm (confidential data; personal communication). Power calculations assume that the treatment groups are compared by mITT.*

Data and Safety Monitoring

An independent Data and Safety Monitoring Board (DSMB) will review interim data and use pre-specified guidelines for early termination of the trial or protocol modification.

11 Interim DSMB Reviews: Goals and Format

Goals of the interim reviews:

- Protect the safety of study participants.
- Advise on stopping or modifying the trial for efficacy, for patient safety in case of emerging data on harm, or for futility.
- Review the conduct of the trial

The DSMB will conduct frequent safety reviews. The DSMB will review safety data for the first 20 to 30 participants randomized after they have been followed for 7 days. Thereafter, the DSMB will be asked to review safety data at 30 day intervals. The blinded sample size re-estimation will occur after 150 participants have been followed for 7 days. Futility reviews will be presented to the DSMB for the primary endpoint after 50% of information time (based on the percentage of participants who have completed 7 days of follow-up) is available.

The DSMB may request interim reports on safety and efficacy at any time.

Review meetings will typically consist of an Executive session (optional; closed), open session, closed session, and a second open session to give feedback to study leadership (optional).

Masking of treatment group labels in interim reports: In the open reports, any data reports will be pooled across the two treatment groups. In the closed reports, treatment group labels will be masked; for example as "Group A" versus "Group B". The treatment group labels will be consistent across all analyses and over subsequent reports. With each closed report, the DSMB will receive a separate, encrypted file that unmasks the treatment

group labels. This procedure ensures that the DSMB has the full information to weigh benefit versus harm.

Open report to the DSMB

The open reports will contain:

- A synopsis of the trial design and current status of the trial
- Responses of the study team to DSMB recommendations
- A summary prepared by the study leadership including any relevant emerging data from other studies
- Data summaries for enrollment (including enrollment by hIVIG product/matching placebo group) and eligibility violations (Section 12), baseline characteristics (Section 14) and protocol deviations
- Summary reports for data completeness and study conduct (including number infused), pooled across treatment groups (see Sections 15 and 23)
- Unanticipated problems

All data summaries in the open report will be pooled across treatment groups. The open report will be prepared by the blinded statisticians in cooperation with the unblinded statisticians. In addition to the DSMB, open reports will be provided to the study team, and posted on the study website following the DSMB meeting for access by study investigators.

While the study is ongoing, summaries by treatment group, and comparisons of the hIVIG versus placebo are restricted to the confidential closed report to the DSMB. Additionally, all summaries of follow-up data other than the data completeness and study conduct reports (pooled across the two treatment groups) will be restricted to the confidential closed report. For the planned sample size re-estimation, the pooled proportion of participants in each level of the seven-level ordinal outcome at Day 7 will be provided to the blinded study statisticians and study leadership.

Closed report to the DSMB

All data summaries in the closed report will be by (masked) treatment group. Comparisons between treatment groups will be by intention-to-treat among those randomized (efficacy outcomes) and among those receiving any infusion (safety outcomes). Specific details are given in the indicated sections. The closed reports for a full review will contain:

- Specific data summaries requested by the DSMB or study leadership
- Data summaries in the open report, by treatment group (enrollment, baseline characteristics, eligibility violations)
- Data summaries to assess safety of the investigational treatment including infusion reactions, AEs, SAEs, deaths, composite primary safety outcome are described in Section 18. Data summaries for the primary “efficacy outcomes”, and selected secondary outcomes will also be included in each report because these data

contain information about the risk/benefit profile of hIVIG. Analyses are described in Sections 17, 20, and 21.

- Summaries on data completeness and study conduct, described in Section 23.
- Interim monitoring boundaries for the primary safety outcomes (Section 18).
- Interim monitoring boundaries for efficacy when sufficient data have accrued (Section 17).
- Futility analyses when sufficient data have accrued (Section 19).
- Listings of incident (new or increase in severity from baseline) grade 3 and 4 adverse events, serious adverse events (SAE), unanticipated problems (UP), suspected unexpected serious adverse reactions (SUSAR), and deaths (Section 18).

12 Enrollment

For the open report, the following enrollment and eligibility summaries will be provided:

- Enrollment over calendar time: plot by day or week, cumulative and increments
- Enrollment by country: number (%)

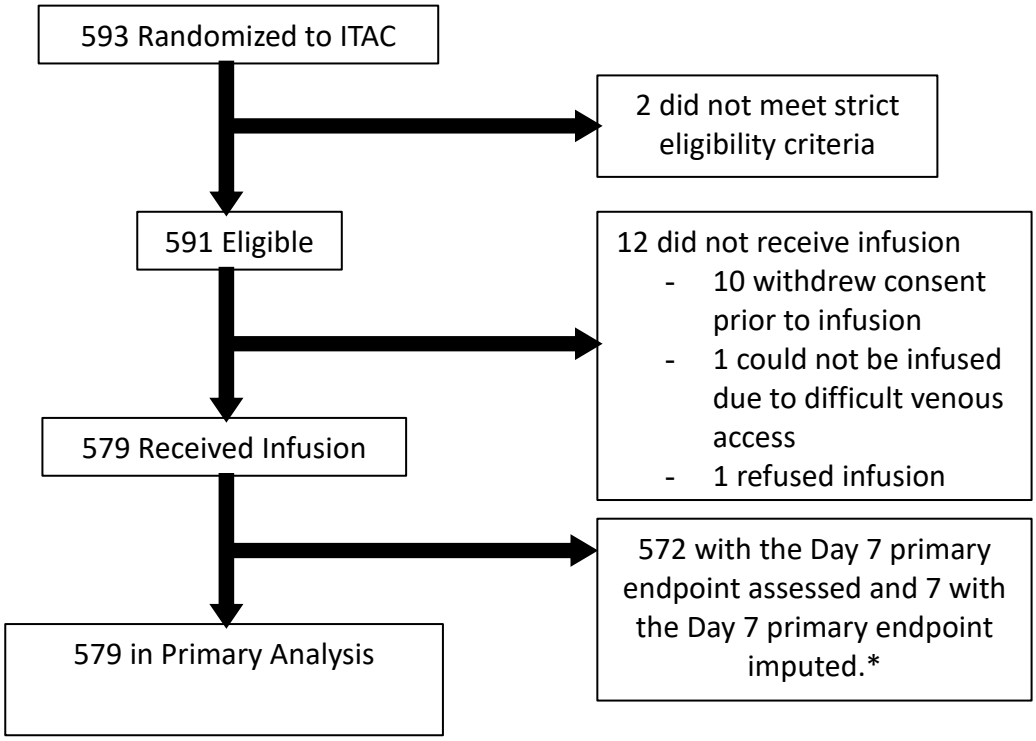
These summaries will be provided overall and by study product/matching placebo randomization stratum.

For the closed report, enrollment will be summarized by treatment group.

Eligibility violations will be reported as protocol deviations (see Section 23).

13 Analysis Populations

All analyses for both efficacy and safety outcomes, will be carried out for a modified intention-to-treat (mITT) population. This mITT population will include all participants who met the eligibility criteria (2 participants did not) AND who received an infusion (12 participants were not infused, 10 who withdrew consent before the infusion, one for whom venous access could not easily be achieved, and one who refused the infusion but continued in follow-up). The mITT population includes 579 participants, 97.6% of the 593 participants randomized.



*6 were discharged with no further information, 1 was transferred to another hospital

14 Baseline Characteristics

Baseline characteristics will be based on information collected on baseline and screening forms.

Baseline characteristics will be summarized by randomized treatment group and overall. Unless noted otherwise, categorical variables will be summarized with frequency (percentage) in each category, and continuous variables will be summarized with median (25^{th}, 75^{th} percentile) and/or mean (standard deviation). The following characteristics will be reported. Whether the variable will be summarized as a continuous or categorical covariate (and the categorization used) is given in brackets as needed.

- Demographics
    - Age [<50, 50-59, 60-69, ≥70 years; and summary as continuous variable]

- Sex at birth [male, female]
- *Race/Ethnic group: [Asian, Black, Latino/Hispanic, white, other]*
- Country of enrollment
- *Geographic region*

- COVID-19 related characteristics
  - *Duration of symptoms prior to enrollment (<6, 6-7, 8-9, 10-12 days)*
  - Use of remdesivir prior to enrollment
  - Ordinal outcome category
  - National Early Warning Score (NEWS) [summary as continuous variable]
  - Oxygen saturation
  - Respiratory function scale (modified Borg dyspnea scale; continuous outcome)
  - Receipt of SARS-CoV-2 vaccination (active or control)
  - Upper respiratory SARS-CoV-2 viral RNA
- Other clinical characteristics
  - *Concomitant treatments including corticosteroids and antiplatelet/anticoagulant medications*
  - *Corticosteroid use according to oxygen requirements*
  - History of chronic conditions (heart failure, diabetes, asthma, chronic obstructive pulmonary disease, hypertension requiring medication, renal impairment, hepatic impairment, malignancy, MI, stroke)
  - Requirement of continuous chronic supplemental oxygen
  - *Body mass index (BMI) [<25, 25.0-29.9, 30-39, 40+ kg/m^2]*
  - Pregnancy
  - *Participants with and without compromised immune function; participants with HIV, an immunosuppressive condition other than HIV, or taking antirejection medication, immune modulators, or biologic treatment for autoimmune disease or cancer will be considered to have compromised immune function.*
  - *BMI < 40 and ≥ 40 kg/m^2 according to history of diabetes (4 groups)*
  - *Hypertension with and without history of other metabolic and vascular co-morbidity (4 groups): i) no hypertension or other metabolic/vascular co-morbidity; ii) hypertension without a metabolic/vascular co-morbidity; iii) metabolic/vascular co-morbidity without hypertension; and iv) hypertension and a metabolic/vascular co-morbidity. Metabolic/vascular co-morbidities include a history of diabetes, a cerebrovascular event, heart failure, or an MI or acute coronary syndrome.*
  - *Number of vascular co-morbidities (0, 1, 2, 3+)*

- *Quartile of Charlson Comorbidity Index (for conditions assessed)*
- *Risk calculator for vaccine prioritization (JHU)*
- *Quartile of risk score for Day 7 outcome that considers baseline antigen and antibody levels, age, gender, duration of symptoms, oxygen saturation, ordinal categorty, NEW score, and history of chronic health conditions.*

- Laboratory values [as continuous outcomes and grade 3 or 4 abnormalities according to the *DAIDS AE Grading Table*]

15 Administration of Study Treatment

These data are an important part of the safety reviews by the DSMB, with particular emphasis on infusion-related reactions and symptoms occurring during or within up to 2 hours after the infusion. These reactions and symptoms will be graded according to the DAIDS AE Grading Table.

The administration of study treatment is also an essential element of study conduct. Several summaries, pooled across treatment groups, will be included in the open report or provided to study leadership. Any summaries of adverse events or infusion-related reactions are restricted to the closed report.

Following the completion of the trial, the summaries below will be used to describe the infusions given to each treatment group (hIVIG and control). Some of the summaries will be carried out for all participants who meet the strict eligibility criteria; safety summaries will be summarized for participants in the mITT population.

These summaries will be stratified by study product/matching placebo group.

- Number and percentage of participants receiving complete infusion, partial infusion, or not infused among all randomized participants.
- Number and percentage of participants for whom infusion was interrupted.
- Number and percentage of participants with infusion-related reactions and symptoms (reported during the infusion or within 2 hours after the infusion), by grade.
- Number and percentage of participants with an incident grade 3 or 4 AE, SAE, UP or SUSAR on the day of infusion. Types of AEs will be summarized by system organ class and by grade.
- Number and percentage of participants who received:
    - Prior to infusion, medication to prevent infusion reactions, and type of medication among all randomized participants
    - During or within 2 hours after infusion, medication to treat infusion reaction, and type of medication
- The day the infusion began (same day as randomization, next day, > 1 day after randomization), and time between randomization and beginning of infusion (median hours, 25^{th}, 75^{th} percentiles).
- Among participants receiving full infusion, duration of infusion (median minutes, 25^{th}, 75^{th} percentiles).

- Time from pooling of infusion bag (beginning of preparation of study product/matching placebo by the pharmacist) to the end of the infusion.
- *Actual dose received, infusion rate, infusion volume, and percentage who received the 400 mL dose (dose was capped at 400 mL corresponding to those who weighed 100 kg or greater).*
- Remdesivir:
    - Number and percentage of participants who received (any) remdesivir, and number of days remdesivir was administered: median, 25th, 75th percentiles, distribution (< 5 days, 5 days, > 5 days).
    - Number and percentage of participants who received remdesivir prior to the day of randomization, and number of doses (median, 25th, 75th percentiles).
    - On the day of randomization: Number and percent of participants who received remdesivir prior to the hIVIG/placebo; after the hIVIG/placebo; no remdesivir.

For these outcomes related to administration of study product, treatment groups will be compared using stratified Cochran Mantel Haenszel test stratified by study product/matching placebo group for binary outcomes and Wilcoxon rank-sum test for continuous outcomes.

Section 18 outlines halting rules for pausing the trial due to infusion related adverse events.

16 Statistical Analyses

All analyses will utilize 2-sided tests with a 0.05 significance level. Analyses will compare hIVIG treatment to placebo pooled across study products using the mITT population unless stated otherwise.

17 Primary Efficacy Analysis

The primary efficacy endpoint is the seven-level ordinal outcome described in Section 10.

For the primary endpoint, the percent of participants in the seven categories of the ordinal outcome will be compared. A proportional odds model will be used to estimate a summary OR (the ratio of the cumulative odds of being in a better category of the ordinal outcome for hIVIG versus placebo). The model uses the cumulative probabilities of being in any of categories 1 up to a threshold (or cutoff) to define six cumulative odds corresponding to cutoffs at categories 1,2,..,6. The model will include a single indicator for treatment, indicators for the participant's clinical state at entry (categories of ordinal outcome), and its two-way interactions with the six cutoffs for each of the six cumulative odds of improvement. The model will also include indicators for which of the four study product/matching placebo group was used and their two-way interactions with the six cutoffs. The primary test statistic will be a Wald test of the coefficient for the treatment indicator.

For the primary endpoint analysis only, multiple imputation based on baseline and follow-up data will be used to estimate participant status at Day 7 for participants with missing data on the ordinal outcome. Imputation will not be performed for secondary endpoints or for subgroup analyses of the primary endpoint.

Of the 7 participants with a missing Day 7 primary ordinal outcome, 6 were known to have been discharged. For these participants it will be assumed that they are in one of the three most favorable categories (3 of the 6 discharged participants were on oxygen the day of discharge). For this imputation, for those discharged by Day 7, in addition to treatment group, the following baseline covariates will be considered: age, clinical status based on the ordinal outcome at enrollment, duration of symptoms, presence of any comorbidity, and NEW score. In addition to the

baseline covariates, the day of discharge after randomization, and oxygen status on the day of discharge will be used in the imputation.

For the participant who was transferred to another hospital on Day 2 and who was known to be alive on Day 27, the ordinal category on Day 2 will be imputed for the Day 7 primary outcome.

We will impute ten data sets; parameter estimates (e.g., the summary odds ratio) from the 10 multiply imputed datasets will be combined using Rubin's combining rules.

Interim monitoring boundaries for superiority

The DSMB is to consider a recommendation for stopping the trial early for efficacy only if there is clear and convincing evidence of superiority of the hIVIG versus the control group with respect to the primary outcome.

For monitoring superiority, the Lan-DeMets spending function analogue of the O'Brien-Fleming boundaries will be used, with a 1-sided 0.025 level of significance over multiple looks. The boundary for harm is asymmetric, requiring less evidence to stop for harm than for superiority, described in Section 18. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the observed total number of participants with Day 7 ordinal outcome data divided by the planned number of participants.

It is important that each hIVIG product is well-represented in the number of participants enrolled at the time of a recommendation by the DSMB to stop early due to convincing evidence of efficacy. Thus, we recommend that early termination for efficacy not be considered until at least 250 participants have been enrolled and at the time such a decision is made the DSMB also consider the number assigned each product. As a guideline we recommend that at least 20% of the information (number with a Day 7 outcome), be from each hIVIG product.

At each interim analysis the following will be provided:

- The value of the primary test statistic (Wald test statistic defined as the standardized estimate of the summary log OR) from the cumulative logistic regression model, plotted over information time, at the current DSMB review, and the corresponding values of the test statistic presented at the previous reviews. The graph will also show the O'Brien-Fleming boundary with Lan-DeMets alpha-spending function. Boundaries will be shown for a one-sided test with alpha=0.025 for superiority of hIVIG, and an asymmetric, Haybittle-Peto boundary for harm (2.5 standard deviations for the first 100 participants; 2 standard deviations thereafter).
- The primary safety outcome is a composite of grade 3 and 4 AEs, SAEs, or death through Day 7, as described in Section 18 below (primary safety outcome). Along with the overall primary outcome, this measure will be used to assess whether benefits of the treatment outweigh the risk.
- Estimated proportion of participants in each level of the Day 7 ordinal scale by treatment group.
- The summary ORs from fitting a similar cumulative logistic regression model for the ordinal outcome at Days 3, 5, 14, and 28.

- History of the estimated ORs from the cumulative logistic regression model with 95% CIs and p-values at previous DSMB reviews, as presented.

Assessment of model assumptions

A test for the proportional odds assumption will be made from a model that allows different effect estimates for the hIVIG versus placebo according to the cut-off of the ordinal scale (a partial proportional odds model). That is, a cumulative logistic regression model with the same terms as above but including two-way interactions between the treatment indicator and the six cut-offs. A composite likelihood ratio test will be used to determine if any of the additional terms are significantly different from zero (i.e., a test of the proportional odds assumption). Even if the proportional odds assumption is violated, the overall summary OR will be the basis for inference for the primary analysis.

Sample size re-estimation

The sample size re-estimation was conducted by blinded statisticians and did not use any information on the treatment effect. The purpose was to re-estimate the sample size needed to obtain 80% power with an assumed odds ratio of 1.61 based on the distribution of the ordinal outcome at Day 7 observed in the trial pooled across study arms (as opposed to the hypothesized distribution informed by data from the ACTT-1 trial).

Sensitivity Analyses

- In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for each of the six dichotomized definitions of improvement that can be formulated from the components of the ordinal outcome. That is, we will fit six separate logistic regression models for each of the six dichotomized definitions of improvement. These models will include an indicator for treatment arm, study product/matching placebo group, and baseline ordinal outcome group.
- Categories 3 and 4 of the primary ordinal outcome differ in part by the amount of supplemental oxygen required, and a single cut point (4 liters/minute) defines the difference. Since, together, these two categories of the ordinal outcome are expected to include approximately 30% of participants, an analysis that combines these two categories (resulting in a six-category ordinal outcome) will be carried out to supplement the primary analysis using the same methods described above.
- *The adjusted cumulative logistic regression model for the final analysis will be refitted but exclude the 7 participants for whom the Day 7 outcome is missing (i.e., no multiple imputation will be performed).*
- *The adjusted cumulative logistic regression model for the final analysis will be refitted and include all participants randomized with a Day 7 primary outcome.*
- *The adjusted cumulative logistic regression model for the final analysis will be refitted and include a "worst case imputation". This was recommended by the FDA. Among the 593 participants randomized, 18 (3.0%) are missing the Day 7 outcome. Of these 18 participants, partial follow-up data are available for 7 participants. For 11 participants, all who were not infused, there are no follow-up data. Given the double-blind nature of the trial, a worse case analysis (e.g., imputation of category 1*

for those in the placebo group and category 7, death, in the hIVIG group) for these participants will not be done. These 11 participants will be excluded from this sensitivity analysis. Among the other 7 participants, 6 were discharged before Day 7. For these 6 participants, we assumed those in the placebo group were in category 1 and those in the hIVIG group were in category 4. For the other participant who was transferred to another hospital on Day 2 and was known to be alive on Day 27, category 1 will be imputed on Day 7 if assigned to the placebo group, and category 2 will be imputed on Day 7 if assigned to the hIVIG group. This is the same category of ordinal outcome the participant was in on Day 2 (i.e., no change is assumed).

- The adjusted cumulative logistic regression model will be refitted but will include geographic region as an additional covariate.

18 Safety Analyses

The following safety and tolerability outcomes will be analyzed:

- The **primary safety endpoint** is a composite of grade 3 and 4 adverse events, SAEs, or death through Day 7. The percent of participants experiencing the composite safety outcome will be compared. A logistic regression model will be used to estimate an OR for hIVIG versus placebo. The logistic regression model will include indicators for treatment group, study product/matching placebo group, and baseline ordinal outcome category. Over the first 28 days, the cumulative proportion of participants with a SAE or death will be estimated using Kaplan-Meier curves, by treatment group. The hazard ratio (HR) for hIVIG versus placebo will be estimated with a 95% CI using a Cox proportional hazards model with an indicator for treatment group, stratified by study product/matching placebo group and baseline ordinal outcome category.

  Stopping boundaries for harm: A Haybittle-Peto boundary of 2.5 standard deviations (SD) for the first 100 participants enrolled and 2.0 SD afterwards will be used as a guideline for harm. The SD refers to the standard deviation of the test statistic (standardized estimate of the summary log OR). With this boundary, less evidence is needed for stopping a trial early due to harm compared with stopping for efficacy.

  Similar to the efficacy analysis, the observed value of the test statistic for the primary safety outcome will be plotted over information time, for the current data, along with the boundaries and the values presented at previous DSMB reviews.

- Safety analyses will also include infusion reactions collected during or within 2 hours after the infusion of hIVIG/placebo. Percentages of participants who experience infusion reactions or prematurely terminated infusions will be summarized by treatment groups and compared as described in the preceding section.

- Other safety analyses will be conducted including the following outcomes:
  - Composite of grade 3 and 4 adverse events, SAEs, or death through Day 7 excluding exempt events

- Composite of grade 3 and 4 adverse events, SAEs, or death through Day 7 by MedDRA system organ class (SOC)
- Composite of SAE or death through Day 28 by MedDRA SOC
- Each component of the primary safety outcome analysed separately (deaths, SAEs nonexmpt, SAEs exempt, and grade 3 and 4 adverse events)
- A composite of SAEs and death through Day 28 (including and excluding exempt events and each component separately analyzed)
- Prevalence of clinical AEs of any grade on Days 0, 1, 3, 7, and 28; AEs will be summarized by grade and day, and by MedDRA® system organ class and grade. (AEs present on those days).
- Summaries of UPs and SUSARS, and listings of SAEs, UPs, SUSARs and deaths.
- Change in laboratory test values from baseline to Day 7, and incidence of grade 3 and 4 laboratory abnormalities at Day 7.

AEs will be coded with MedDRA, version 23.1. In addition to the tables, listing of participants with grade 3 or 4 events, SAEs or deaths will be provided with the MedDRA preferred term (PT) and study day of AE.

Further safety assessments may be considered including by study product/matching placebo group (see Section 21).

Because the infusion volume in this protocol is significant (250 mL for remdesivir and up to 400 mL for hIVIG/placebo), as a guideline, the DSMB will be asked to consider halting enrollment if more than 5% of participants experience a grade 3 or 4 infusion AE or if more than 10% do not complete the infusion due to an AE(s). This will be informed by the lower bound of the 95% confidence interval which will not be adjusted for multiplicity. When this occurs, differences will be compared by randomized group. If the study is temporarily halted or stopped for safety reasons, institutional review boards/ethics committees will be informed.

19 Monitoring for Futility

To assess futility, conditional power calculations based on an unadjusted model (as was done for the original power calculations) for the Day 7 ordinal outcome will be presented under a range of scenarios. In the primary futility analysis, it will be assumed that the treatment effect for the future, as yet unobserved follow-up, will be as hypothesized in the study design (adjusted OR = 1.61). As secondary analysis, the treatment effect for future follow-up will be assumed to be similar to the observed effect. Additional scenarios may be provided. Typical futility guidelines recommend stopping a trial when conditional power (assuming the originally hypothesized treatment effect for the future, as yet unobserved follow-up) is below 10%-20%.

As a guideline, futility will first be assessed after 50% of the planned number of participants have Day 7 ordinal outcome data, and a value of 20% will be suggested as a threshold for the conditional power. Conditional power will be computed using the test statistic for the treatment indicator in a cumulative logistic regression model.

Decisions to terminate the study for futility will include a broad assessment of the risk/benefit trade-off in addition to these guidelines.

20 Secondary Outcomes

The protocol defines a number of secondary endpoints in addition to the two key endpoints described in the previous section. These analyses will be carried out for the final report. No adjustment for multiplicity for all the treatment comparisons for the secondary outcomes will be made; they are supportive to the primary endpoint analysis.

Selected secondary endpoints may also be analyzed for the interim monitoring report to help evaluate the safety and efficacy of hIVIG.

Multiple imputation will only be used for data missing on the primary endpoint; all secondary endpoints will use complete case.

Below, the secondary outcomes from the protocol are cited, with a short description of the analysis methods. The secondary outcomes are grouped by analysis methods and are not listed in order of importance.

1. The primary ordinal outcome on Days 3, 5, 14 and 28.

2. Pulmonary only components of the primary outcome measure at Days 3, 5, 7, 14 and 28

3. Thrombotic components of the primary outcome measure (stroke, myocardial infarction, venous and arterial thrombosis or embolism, plus disseminated intravascular coagulation) at Days 3, 5, 7, 14, and 28.

4. Clinical organ dysfunction

5. The ordinal outcome similar to the one used in the ACCT trial of remdesivir will be used to compare treatment groups at Day 7. The ACCT ordinal outcome included 8 categories. We can only approximate the categories because data were not collected concerning hospitalization for infection-control reasons. It is similar to the ITAC primary ordinal outcome but considers hospitalization status. The following 8 categories will be defined for this ordinal outcome:

    - Not hospitalized, no limiting symptoms due to COVID-19
    - Not hospitalized, limiting symptoms due to COVID-19, home oxygen requirement, or both
    - Hospitalized, no limiting symptoms due to COVID-19, not requiring supplemental oxygen
    - Hospitalized, limiting symptoms due to COVID-19, not requiring supplemental oxygen
    - Hospitalized, requiring any supplemental oxygen
    - Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices.
    - Hospitalized, requiring invasive mechanical ventilation or ECMO
    - Death

6. Percentage in 2 most favorable categories at Day 7.

7. Hospitalization status at Days 14 and 28.

8. Hospitalization status (a binary outcome, alive and discharged from the hospital to home or rehabilitation OR able to independently undertake usual activities with minimal or no symptoms versus dead or hospitalized AND unable to independently undertake usual activities) at Days 7, 14 and 28.

   For outcomes 1-8, the proportion of participants in each category will be summarized by treatment group. For the ordinal outcomes, a summary OR will be estimated using a cumulative logistic regression model which includes a single indicator for treatment, indicators for the participant's clinical state at entry (categories of ordinal outcome), its two-way interactions with the six cutoffs for each of the six cumulative odds of improvement, indicators for which of the four study product/matching placebo group was used and their two-way interactions with the six cutoffs. For the binary outcomes, a summary OR will be estimated using a logistic regression model which includes a single indicator for treatment, indicators for the participant's clinical state at entry (categories of ordinal outcome), and indicators for which of the four study product/matching placebo group was used. For interim analyses we will consider clinical organ dysfunction as a binary composite endpoint at Day 7 and Day 28. At the end of the trial we will take into account the severity of each organ dysfunction by developing a weighting scheme by examining the pooled association of each item with subsequent death.

9. All-cause mortality through Day 28.

10. Time to the three least favorable categories of the primary outcome measure.

    For outcomes 9 and 10, the cumulative incidence of death (outcome 9) or the three least favorable categories (outcome 10) by treatment group will be estimated using Kaplan-Meier methods. The treatment groups will be compared using a log-rank test. A summary HR comparing the treatment groups will be estimated using a Cox proportional hazards model. These models will be stratified by study product/matching placebo group and baseline ordinal outcome group.

11. Time to the two most favorable categories of the primary outcome measure.

12. Time to discharge (this is similar to the recovery outcome used in the ACTT-1 trial)

13. Time to discharge or being able to independently undertake usual activities with minimal or no symptoms

14. Time to being able to independently undertake usual activities with minimal or no symptoms (discharge status will be ignored)

    For outcomes 11-14, time-to-event methods that take into account the competing risk of death will be used. Specifically, Gray's test with rho=0, the Fine-Gray model, and the Aalen-Johansen estimator for the cumulative incidence curve are the competing risk equivalents to the log-rank test, Cox proportional hazards model, and the Kaplan-Meier estimator for the cumulative proportion of participants with the event, respectively. Gray's test and the Fine-Gray model will be stratified by study product/matching placebo group and baseline ordinal category.

    Additionally, as a sensitivity analysis for the analysis of time-to-discharge and days outside the hospital we will exclude participants from the 5 sites where no participants were discharged prior to Day 7.

15. Days alive outside of a hospital through Day 28

16. Days alive and able to independently undertake usual activities with minimal or no symptoms through Day 28

17. Days alive and out of the hospital or able to independently undertake usual activities with minimal or no symptoms through Day 28 (whichever lead to greatest time)

    These outcomes (15-17) have been used in other trials of therapeutics for COVID-19. We will sum the number of days that each individual spends outside a short-term acute care hospital up to 28 days. A person who dies within 28 days will be assigned a value 0, consistent with the approach taken in trials of intensive care-based interventions. We will present the mean and median days by group. We will test the hypothesis of no mean difference between arms using methods for continuous outcomes (ANCOVA models), with baseline baseline ordinal outcome group and study product/matching placebo group as covariates. Because the residual distribution is unlikely to be normally distributed, we will use robust or sandwich standard errors. This analysis will be undertaken only when complete follow-up data are available. The outcome does have limitations due to its handling of death and withdrawal. We expect that there will be minimal missing data but may use multiple imputation for the final analysis.

18. Change in immunoglobulin levels (IgG, IgG subclasses, IgM, IgA) and neutralizing antibody titres from baseline to Days 1, 2, 3, 7, 28 and 90.

    Longitudinal random effects models will be used to summarize log-transformed antibody level differences between the hIVIG and placebo groups at Days 1, 3, 7 and 28 of follow-up. Baseline antibody levels will be included as a covariate in

these models. For the subset of participants for whom blood is collected at Day 90, antibody levels will be compared.

Exploratory analyses will be carried out if hIVIG is efficacious to determine if antibody differences post-infusion on Days 1 and 3 predict the primary outcome. First, post-infusion antibody level (perhaps also considering the pre-infusion level or change from baseline) will be considered as a predictor of the Day 7 ordinal outcome using a proportional odds model. If there is evidence that the post-infusion level or change predicts the Day 7 outcome, a model which includes the post-infusion level and treatment will be fit to determine the impact on the treatment estimate without the antibody level in the model. Second, we will examine the association between antibody treatment differences post-infusion by treatment group and the Day 7 summary OR from the cumulative logistic model. This could be done for each product separately (four data points) and/or according to the potency of each lot, grouped into more than four groups.

21 Subgroup Analyses

Subgroup analyses for the primary seven-category ordinal outcome (primary efficacy outcome), as well as for the primary safety outcome (Grade 3 and 4 adverse events, SAE or death through Day 7) will be performed to determine whether and how the treatment effect (hIVIG versus placebo) differs qualitatively across various subgroups defined at baseline, and whether there are safety concerns in specific subgroups.

The protocol denotes the subgroup analysis by the duration of symptoms at study entry as the "key subgroup analysis." In addition to the analysis by 4 categories of duration of symptoms (<6, 6-7, 8-9, 10-12 days), an analysis based on the upper quartile of symptom duration (e.g., less than or equal to the 75th percentile versus greater than the 75th percentile) (2 categories). The upper quartile is 10-12 days (75% of participants will have symptom duration < 10 days). In ACCT-1, a more severely ill target population than studied here, there was no limit to the duration of symptoms and the median was 9 days (25th and 75th percentile, 6 – 12 days). The quartile definitions for duration of symptoms will be determined following the completion of enrollment. For interim analyses, the quartiles will be determined based on interim data. For those with shorter duration of time since symptom onset, the treatment effect is hypothesized to be greater than among participants who have had symptoms for a longer period of time. A global test for heterogeneity of the treatment effect across the symptom duration subgroups will be carried out in 2 ways: 1) by adding the interaction between symptom duration as a continuous variable (1 df test) and the treatment group to the model; and 2) by adding the interaction between categories of symptom duration and the treatment group to the model (3 df test).

Other important subgroups include subgroups by disease severity, by age, and by pre-existing conditions. *A priori* we have no reason to believe the clinical efficacy or safety of hIVIG compared to placebo will be substantially different in relative terms in any of the following subgroups considered. Subgroup analyses for the primary efficacy endpoint and safety endpoint will use the adjusted (cumulative) logistic models described earlier. ORs with 95% CIs comparing the treatment group versus control will be estimated for each subgroup. Global tests for heterogeneity of the treatment effect across subgroups will be carried out by adding the interaction between the subgroup indicator and the treatment group indicator to the model. In case the subgroup was formed by categorizing a continuous variable, the interaction term will be formed between the subgroup indicator and the continuous variable.

Subgroup analyses will not be adjusted for multiple comparisons; they are supportive to the primary endpoint analysis. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

Subgroup analyses will be performed for a number of baseline factors. Unless otherwise stated, continuous outcomes will be summarized in quartiles. The following subgroups will be considered:

- *Age (18-49, 50-59, 60-69, 70+ years)*
- Sex at birth (male, female)
- Race/ethnicity (Asian, Black, Latino/Hispanic, White, other)
- *BMI [<25, 25.0-29.9, 30-39, 40+ kg/m^2]*
- *Presence of chronic medical conditions which had greater than 5% prevalence at baseline (diabetes, hypertension, COPD, asthma, renal impairment)*
- *Geographic location (U.S.; Europe, UK, or Israel; and Argentina, Indonesia, Japan or Nigeria)*
- Upper respiratory SARS-CoV-2 viral load
- Oxygen saturation level
- Dyspnea severity (Modified Borg dyspnea scale)
- Organ/respiratory dysfunction category based on ordinal primary outcome
- NEWS
- *Participants with and without compromised immune function; participants with HIV, an immunosuppressive condition other than HIV, or taking antirejection medication, immune modulators, or biologic treatment for autoimmune disease or cancer will be considered to have compromised immune function.*
- *BMI < 40 and ≥ 40 kg/m^2 according to history of diabetes (4 groups)*
- *Hypertension with and without history of other metabolic and vascular co-morbidity (4 groups): i) no hypertension or other metabolic/vascular co-morbidity; ii) hypertension without metabolic/vascular co-morbidity; iii) metabolic/vascular condition without hypertension; and iv) hypertension and a metabolic/vascular co-morbidity. Metabolic/vascular co-morbidities include a history of diabetes, a cerebrovascular event, heart failure, or an MI or acute coronary syndrome.*
- *Number of vascular co-morbidities (0, 1, 2, 3+)*
- *Quartile of Charlson Comorbidity Index (for conditions assessed)*
- *Risk calculator for vaccine prioritization (JHU)*
- *Corticosteroids, overall and in combination with oxygen requirements (ordinal category at baseline)*

- *Use of antiplatelet/anticoagulant therapy (prophylactic heparin, intermediate or therapeutic heparin or other anticoagulant therapy, none)*

- *Quartiles of disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the Day 7 ordinal outcome: age, gender, antigen and antibody level, duration of symptoms, oxygen saturation level, ordinal outcome category at entry, NEWS, and chronic health conditions). .*

We will analyse the association between lot potency and the primary outcome for participants assigned active hIVIG using a cumulative logistic regression model adjusted for hIVIG product and baseline ordinal category. The aim of this analysis will be to determine if the primary outcome varies by range in potency among the various lots of hIVIG used.

Additionally, we will explore if the association between lot potency and the primary outcome differs by baseline antibody titre. The potency of each lot will be measured by Texcell. In addition to the subgroup analyses above, a subgroup analysis by lot potency (by tertiles) will be carried out. Participants in the placebo group will be classified according to the lot potency they would have received had they been randomly assigned to the hIVIG group.

If there is a beneficial effect of hIVIG compared to placebo, in order to support regulatory claims for each hIVIG product used, sensitivity analyses comparing each hIVIG product to its matching placebo will be carried out for key efficacy and safety endpoints. First, we will assess the evidence for any difference in effect among the products. A test for heterogeneity of the treatment effect across study products will be carried out by adding the interaction between study product/matching placebo group and the treatment group indicator to the model. In addition to the models for efficacy and safety endpoints described above, we will also test for heterogeneity of the treatment effect across study product/matching placebo group after adjusting for lot potency. In one of the subgroup analyses by hIVIG product, the subgroups will be further divided by the potency level of the hIVIG lots used for that product (e.g., above and below the median level of lot potency for the product).

Second, we will obtain estimates of the effect for each product using two general approaches. a) We will estimate the effect for each hIVIG product using only data from participants receiving that particular product/matching placebo (e.g., separate analyses for each study product). b) We will use multisource exchangeability models[ii] (MEMs) to dynamically borrow information from other study products to improve estimation of the efficacy and safety of a single study product. MEMs work by enumerating all possible exchangeability patterns between the data sources (here data from different study products) and obtain a single posterior distribution for the parameter of interest using Bayesian model averaging. The key benefit of this approach is that it can borrow differentially from different study products. Estimates of the effect for each product will be done both adjusting for and not adjusting for lot potency.

These analyses will consider that each hIVIG product will be used by a different group of clinical sites (i.e., each comparison will represent a small multi-center trial), and that power will likely be very low for all of the outcomes. Because the hIVIG product that each site receives is not randomized, any comparisons of the efficacy among hIVIG products should be interpreted cautiously. These analyses are referred to as sensitivity analyses because overall therapeutic efficacy and safety will be based on the pooled analysis of the four hIVIG products with placebo.

22 Analyses of Stored Specimens

NIH plans to measure antibody and antigen levels on plasma samples from ITAC. Antibody levels will be determined using kits made by Bio-Rad, which measures total (IgA, IgG, and IgM) anti-nucleoprotein (NP), and by GenScript (anti-spike neutralizing antibody surrogate), which measures

a subset of antibodies capable of inhibiting binding by spike proteins. Antigen levels will be determined in plasma using an assay made by Quanterix.

Results of the Bio-Rad antibody measurement are reported in terms of "specimen ratios". Specimen ratios are defined as the specimen optical density (OD) divided by the optical density of the cut-off control R4 ($OD_M R4$). According to the manufacturer, specimen ratios less than 0.8 are considered negative, those with a specimen ratio between 0.8 and 1.0 are considered equivocal, and those greater than 1.0 are considered positive for the presence of anti-SARS-CoV-2 antibodies.

Results of the GenScript antibody assay are reported as binding inhibition percentages. For this assay, levels less than 30% are considered negative and those ≥ 30% are considered positive.

Results of the quantitative Quanterix assay are reported in pg/mL. The lower level of detection is 3 pg/mL.

Subgroup analyses will be carried out using the antigen and antibody data at baseline and the Day 7 pulmonary and pulmonary+ ordinal outcomes at Day 7.

Our hypothesis is as follows: Patients with negative or lower positive antibody levels will benefit more from hIVIG compared to placebo than patients with higher antibody levels. Furthermore, those with lower antibody levels AND with higher antigen levels, will benefit more from hIVIG compared to placebo than other subgroups categorized by both antibody and antigen levels.

23 Data Completeness and Study Conduct

The primary outcome (seven-level ordinal outcome) will be assessed daily through Day 28. In-person visits are scheduled on Days 1, 2, 3, 7, and 28, when blood is collected (plasma and serum); other visits on Days 5 and 14 may be conducted by phone. Participants at selected sites will return for a visit 90 days after randomization to obtain a blood draw; this subset will comprise all participants at selected sites where return for a later visit is practical for participants.

Data completeness and study conduct reports will be provided by treatment group (for the closed report) and pooled across treatment groups (for the open report). Data summaries for the infusion of hIVIG/placebo on Day 0 are described in Section 15; several of those reports are also relevant for monitoring study conduct and will be included in the open report or provided to study leadership, pooled across treatment groups.

24 The following data summaries will be provided:

- Number, percent and type of protocol deviations. Specific protocol deviations are reported in the protocol.
- Expected and observed number (% of expected) of participants who completed visits on Days 1, 2, 3, 5, 7, 14, 28, and 90.
- Ascertainment of the primary outcome: Expected and observed number (% of expected) of participants with outcome status for the ordinal outcome (Days 0-7, 14, and 28).
- Expected and observed number (% of expected) of participants with known vital status at Days 0-7, 14, and 28.

- Number and percent of participants who withdrew consent, or with missing primary outcome data for other reasons will be summarized.
- Listing of participants who withdrew consent, including dates of randomization, study product/matching placebo group, receipt of study treatment, date of withdrawal, and reason of withdrawal.
- Length of follow-up: Median, 25^{th}, 75^{th} percentiles, range and distribution
- Collection of specimens: Expected and observed number (% of expected) of participants with specimens collected as specified by the protocol, by visit.

A visit counts as “expected” if the visit window has closed or the data have been received.

The summaries for the final report will be provided for the mITT population unless otherwise stated.

25 Addendum to Statistical Analysis Plan for European Medicines Agency

During the review by EMA of INSIGHT 013 (ITAC), An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19, it was requested that the data analysis plan be revised to make the 7-category pulmonary ordinal outcome at day 7 (a secondary endpoint) the primary endpoint for submissions to the EMA instead of the 7-category ordinal outcome specified in the protocol (see section 4 and Appendix F of the protocol) which also includes a range of organ dysfunction in addition to respiratory dysfunction. The protocol-defined primary endpoint would be a secondary endpoint for EMA submissions.

An addendum to Version 1.0 of the Statistical Analysis Plan was prepared on January 11, 2021 to address this request from the EMA. It is reproduced here for ease of reference.

The statistical data analysis plan based on the protocol, dated 25 September 2020, will not be changed as it reflects the protocol. For the EMA submission, this document will be submitted with the protocol and the statistical data analysis plan. Should the data analysis plan be modified before the end of the study, this document will be submitted with the updated statistical data analysis plan.

For the EMA submission, the ordinal outcome shown in the table at the end of this section will be used as the primary endpoint. Sample size assumptions, as stated in section 5.5 of the protocol, are not expected to differ for this outcome compared to those stated in the protocol for the primary endpoint. This assumption is supported by results from another trial, INSIGHT 014 (TICO), for which similar endpoints were used. A paper describing the findings from TICO at day 5 for both ordinal outcomes reported that only 2 of 311 participants were in different categories of the two ordinal outcomes (ACTIV-3/TICO LY-CoV555 Study Group, N Engl J Med 2020, doi: 10.1056/NEJMoa20331.30).

The planned data analysis for the pulmonary ordinal outcome described in section 7 of the Statistical Data Analysis Plan for ITAC will be identical to those stated for the protocol-defined primary ordinal outcome. Likewise, the assessment of model assumptions and sensitivity analyses specified in the Statistical Data Analysis Plan will be carried out for pulmonary ordinal outcome as well as the protocol-defined primary endpoint.

Interim monitoring guidelines specified in the protocol for the primary endpoint will not change. Stopping boundaries for substantial evidence of benefit, for harm, and for futility will be based on the protocol-defined primary endpoint.

Sample size re-estimation was recently carried out using pooled (both treatment groups combined) category percentages for the protocol-defined primary endpoint. This re-estimation confirmed that 500 participants will be sufficient to detect an OR of 1.61 with 80% power.

This document was prepared by blinded statisticians and reviewed by the blinded protocol team. This document will be used with the protocol and the statistical data analysis plan to prepare the final study report for the EMA.

TABLE. CLINICAL CATEGORICAL DEFINITIONS FOR PULMONARY ORDINAL OUTCOME

Each participant is categorized in the highest applicable category.

Ordinal Category	Categorical Description	Categorical Definition*
7	Death	Death
6	End-organ failure	Currently requiring invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy
5	Life-threatening end-organ dysfunction	Currently requiring non-invasive assisted ventilation or high-flow oxygen or
4	Serious end-organ dysfunction	Currently requiring supplemental oxygen (≥ 4 liters/min, or ≥ 4 liters/min above premorbid requirements**) but not high-flow oxygen
3	Moderate end-organ dysfunction	Requiring supplemental oxygen < 4 liters/min, or < 4 liters/min above premorbid requirements**
2	Limiting symptoms due to COVID-19	Symptomatic and currently unable to independently undertake usual activities
1	No limiting symptoms due to COVID-19	Can independently undertake usual activities with minimal or no symptoms

**Continued hospitalization or presence in a particular category of inpatient facility (e.g. intensive care or high dependency) is not used to divide these categories, as indication for continued hospitalization among recovering COVID patients is intrinsically subjective, in part determined by social and financial factors, and varies markedly across the globe.*

*** Premorbid requirement refers to requirements prior to the development of COVID-19, for example in patients with chronic obstructive pulmonary disease, other chronic pulmonary diseases, or oxygen requirements related to altitude.*

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Addendum to Statistical Analysis Plan
Therapeutics for Inpatients with COVID-19 (ITAC)
INSIGHT 013

17 July 2021

This addendum specifies statistical analyses of SARS-CoV-2 antibody and antigen levels measured in plasma collected at baseline (day 0), and SARS-CoV-2 qualitative and quantitative measurements of SARS-CoV-2 RNA in viral transport media (also referred to as RNA) from a mid-turbinate swab sample collected at baseline. It follows closely the analysis plan for TICO, INSIGHT 014.

Longitudinal analyses of antibody and antigen levels will be carried out at a later time and follow the plan used for TICO (INSIGHT 014) and described in the paper describing the results for bamlanivimab versus placebo, the first trial carried out in the TICO master protocol.

Study Population:
The study population will include all participants in the ITAC trial of hIVIG who have received any of the investigational agent/placebo and were eligible for the study (modified intention-to-treat [mITT], n = 579). This is the study population for whom the main study results are reported. Participants without a baseline specimen collected will be excluded for this study population.

1. **As**sa**ys and** Data Collection

SARS-CoV-2 Antibody and **A**nt**igen Data**
SARS-CoV-2 antibody and antigen levels will be measured in plasma specimens collected at baseline (Day 0) and Days 1, 2, 3, 7, 28 and 90. Antibody and antigen levels will be determined centrally, by the NIH, NIAID laboratory. Initially, only baseline samples will be analyzed in order to carry out pre-planned subgroup analyses for major outcomes.

Antibody levels in plasma will be measured using two assays:

- SARS-CoV-2 antibody assay by **Bio-Rad**, measuring total (IgA, IgG, and IgM) anti-nucleoprotein (NP) (Platelia SARS-CoV-2 Total Ab, Bio-Rad, Hercules, CA, USA).

  Results of this antibody measurement are defined in terms of "specimen ratios". Specimen ratios are defined as the specimen optical density (OD) divided by the optical density of the cut-off control R4 (OD_MR4). According to the manufacturer, specimen ratios less than 0.8 are considered negative, those with a specimen ratio between 0.8 and 1.0 are considered equivocal, and those $\geq$ 1.0 are considered positive for the presence of anti-SARS-CoV-2 antibodies.

  Equivocal Bio-Rad antibody levels will be combined with negative levels for all analyses unless otherwise stated.

- SARS-CoV-2 anti-spike neutralizing antibody (nAb) surrogate by **GenScript**, measuring a subset of antibodies capable of inhibiting binding by spike proteins (SARS-CoV-2 Surrogate Virus Neutralization Test [sVNT], GenScript, Piscataway, NJ, USA).

Neutralizing antibody levels by GenScript are expressed as percent binding inhibition. Specimens with levels less than 30% are considered nAb negative (30% is the manufacturer's cutoff for positivity).

For the purpose of comparing natural immunity and whether hIVIG has potential benefit in those with such, the GenScript assay will be used. This attempts to quantify neutralizing titers, whereas the Bio-Rad assay captures any type of antibody against NP (a section of virus not causing neutralization).

Conversely, for the purpose of understanding whether antibody production by the host in some way affects antigen levels, the Bio-Rad assay is preferred because it identifies antibodies against the same virus antigen as is quantified by the Quanterix antigen assay.

Levels of SARS-CoV-2 nucleoprotein antigen in plasma will be measured using an assay made by **Quanterix** (Simoa® SARS-CoV-2 N Protein Advantage, Quanterix, Bellerica, MA, USA). For this assay, antigen levels of < 3 ng/L (the lower level of quantification) are considered "antigen negative".

When analyzed as continuous variable, Quanterix antigen levels <3 will be set to 2.9 ng/L. When analyzed as continuous variable, antigen levels will be $\log_{10}$-transformed.

SARS-CoV**-2 RNA Data**

Qualitative and quantitative assessments of SARS-CoV-2 RNA in viral transport media (proxy for viral load) by RT-PCR from mid-turbinate nasal swabs were determined at baseline. The qualitative and quantitative assessments were made centrally by ABML.

- *Qualitative RT-PCR analysis:* Extraction, master mix preparation, and RT-PCR were performed as described in the CDC 2019-Novel Coronavirus Real-Time RT-PCR Diagnostic Panel. RT-PCR was performed on an Applied Biosystems QuantStudio 7 Flex. Ct scores <40 for both nCoV N1 and nCoV N2 probe sets are scored as positive for the presence of SARS-CoV-2 RNA.
- *Quantitative RT-PCR analysis:* Quantitative RT-PCR analysis of the samples used the same RNA extracts prepared for the qualitative assay. Assay conditions were the same as outlined in the CDC protocol except the RNaseP probe was not used. The lower limit of quantification (LLoQ) for this measurement is 399 copies/mL. Viral RNA measurements were centrally determined by ABML.

For most analyses, RNA levels in viral transport media will be categorized as in TICO: negative or indeterminate, < 400, 400-9999, 10,000- 199,999, and > 200,000 copies/µL. In subgroup analyses RNA will dichotomized at the approximate median: in TICO, this was negative, indeterminate, or <10,000 versus 10,000+ copies/mL. When analyzed as continuous variable, RNA levels will be $\log_{10}$-transformed.

Biomarkers of Inflammation and Coagulation

Interleukin-6 (IL-6), D-dimer and hsCRP will be assessed centrally at NIH from stored plasma samples at baseline (Day 0), Days 1, 2, 3, and 7.

When analyzed as continuous variable, these biomarkers will be $\log_2$-transformed.

Analyses of these biomarkers will follow the plan used in TICO (INSIGHT 014).

Associations between Clinical Outcomes for hIVIG and Baseline Antibody and Antigen Levels

Associations between clinical outcomes for hIVIG and baseline SARS-CoV-2 antibody and antigen levels will be assessed using subgroup analyses, as described in Section 7.5 of the SAP. Subgroups will also be considered by SARS-CoV-2 RNA levels.

The overall results and the subgroup findings by days since symptoms onset of the trial of hIVIG in *hospitalized patients* did not reveal a treatment difference in the Day 7 ordinal scale, the primary endpoint. However, a growing body of evidence supports the possibility that anti-SARS-CoV-2 monoclonal antibodies may alter viral pathogenesis when given early following infection, before an immune response to the infection has been initiated This evidence may be relevant for other supportive immunotherapies including hIVIG products.

Our general hypothesis is that the population enrolled in the hIVIG trial was heterogeneous and that there may be subgroups defined by antigen, antibody and RNA levels for which the treatment may be beneficial. Specific hypotheses are below. Findings from these exploratory analyses will be considered hypothesis generating and will be used to define analyses for other supportive immunotherapeis.

Hypothesis 1: Patients with negative or lower positive neutralizing antibody levels (GenScript) will benefit more from the investigational agent compared to placebo than patients with higher antibody levels. Furthermore, those with lower neutralizing antibody levels AND with higher antigen levels, will benefit more from the investigational agent compared to placebo than other subgroups categorized by both antibody and antigen levels.

Hypothesis 2: Patients with lower neutralizing antibody levels (Genscript) AND with higher levels of RNA in nasal turbinates will benefit more from the investigational agent compared to placebo than other subgroups categorized by both antibody and RNA levels.

While our primary hypotheses consider the neutralizing antibody levels, we will test similar hypotheses for the total antibody levels.

Clinical Outcomes Considered for Subgroup Analyses

Subgroup analyses will be performed for the primary and intermediate efficacy outcomes, and a composite safety outcome. Below we are listing the clinical outcomes, and the statistical methodology. This is repeated from Sections 7.1, 7.2, and 7.4 of the SAP.

- *Ordinal Outcome on Day 7 (primary efficacy outcome):* Within each baseline subgroup, the mean category level will be estimated (by treatment group). Odds ratios (OR) comparing the treatment groups within each subgroup for the odds of being in a better category will be estimated with 95% CIs using a proportional odds model containing the treatment group indicator. Indicators for the participant's clinical state at entry (categories of ordinal outcome), its two-way interactions with the six cutoffs for each of the six cumulative odds of improvement, and indicators for which of the four study product/matching placebo group was used and their two-way interactions with the six cutoffs will be included. The p-value for a differential treatment effect across subgroups will be estimated as described below.
- *Composite of grade 3 and 4 adverse events, SAEs, or death through Day 7 (primary safety outcome) and composite of grade 3 and 4 adverse events, SAEs, organ failure or serious infection (protocol-*

specified events that are exempt from SAE reporting), or death through Day 7: Within each baseline subgroup, the number and % of participants with the event will be calculated (by treatment group). ORs comparing the treatment groups within each subgroup will be estimated with 95% CIs using a logistic regression model containing the treatment group indicator. The model will also include indicators for study product/matching placebo group, and baseline ordinal outcome category. The p-value for a differential treatment effect across subgroups will be estimated as described below.

- *Time to Death through Day 28 and time to the following composite outcome: death, SAE, organ failure, or serious infection through day 28. Components of this composite will also be summarized.*

  Within each baseline subgroup, the proportion experiencing the event through Day 28 will be estimated (by treatment group) using Kaplan-Meier estimates. Hazard ratios (HR) comparing the treatment groups within each subgroup will be estimated with 95% CIs using Cox proportional hazards models containing the treatment group indicator and stratified by product/matching placebo group and baseline ordinal outcome group. The p-value for a differential treatment effect across subgroups will be estimated as described below.
- *Time to discharge or reaching most favorable category of ordinal outcome through day 28:* Within each baseline subgroup, median time to recovery will be estimated (by treatment group) using Aalen-Johansen estimates for the cumulative incidence function (CIF). Recovery rate ratios (RR) comparing the treatment groups within each subgroup will be estimated with 95% CIs using Fine-Gray models containing the treatment group indicator and stratified by product/matching placebo group and baseline ordinal outcome group. The p-value for a differential treatment effect across subgroups will be estimated as described below.

Tests for differential treatment effects across subgroups: As described in the current SAP, tests for differential treatment effects will be carried out, by testing for interactions between the subgroup indicator and treatment indicator variables in the corresponding models across subgroups. In addition to the interactions based on the categorical subgroup indicators, the interaction effect will be estimated in models that include the subgrouping variable (baseline antibody level, antigen level, or RNA) as continuous variables, $\log_{10}$-transformed if necessary, for interaction tests; the latter will be the primary interaction test.

Stratification and covariates: all models will be stratified as described in the statistical analysis plan.

Definition of Baseline Subgroups by Antigen and Antibody Levels and by SARS-CoV-2 RNA levels.
Based on these distributions, we formulated the following subgroups defined by each antibody assay alone, by antigen level alone, and by antibody and antigen level jointly:

1. Antibody positive vs antibody negative (**Bio-Rad**). Those in the antibody negative group have a specimen ratio less than 0.8; those antibody positive have specimen ratios ≥ 1.0. Four groups will be defined, above and below the median for positives, and above and below the median for negatives. In this analysis of 4 groups, those with equivocal results will be combined with those who are negative.
2. Antibody positive vs antibody negative (**GenScript**). Those in the antibody negative group have a binding inhibition percent < 30%; those antibody positive are all $\underline{\geq}$ 30%. Approximate quartiles will also be considered. We anticipate the first 2 quartiles are for antibody negative patients and the 3rd and 4th quartiles are for antibody positive patients.
3. **Antigen** level < 1000 ng/L vs antigen level ≥ 1000 ng/L which we anticipate is close to the median. The group < 1000 ng/L includes all those classified as antigen negative. Approximate quartiles will also be considered.

4. **Bivariate combinations of antigen and antibody levels:** To understand the joint relationship of antibody and antigen levels on major outcomes the following 4 groups will be formed: i) antibody negative and antigen ≥ 1000 ng/mL(approximate median); ii) antibody positive and antigen ≥ 1000 pg/mL; iii) antibody negative and antigen < 1000 ng/mL; and iv) antibody positive and antigen < 1000 ng/mL. This subgroup analysis will be carried out for both the Bio-Rad and GenScript assays.

   We will also separately perform this analysis defining antibody positivity as being positive for EITHER assay, and negative otherwise

   As indicated in the hypothesis, we expect the investigational agent to have the most favorable response compared to placebo for subgroup i) (antibody negative and high antigen level). The least favorable response for the investigational agent compared to placebo is expected among those in group iv) (antibody positive and low antigen level).

5. Subgroups by **SARS-CoV-2 RNA** level (proxy for viral load from NP swab): negative or indeterminate, or <10,000, and >10K copies/µL.

6. Bivariate combinations of SARS-CoV-2 RNA and antigen levels.

An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

INSIGHT Protocol Number: 013

Version: 1.0, 20 August 2020

Funded by the National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH) and carried out by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
Study Sponsor: University of Minnesota

In collaboration with four International Coordinating Centers (ICCs) of the INSIGHT Network:

- -Copenhagen HIV Programme (CHIP) - Copenhagen, Denmark
- -Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) -London, United Kingdom
- -The Kirby Institute, University of New South Wales - Sydney, Australia
- -The Institute for Clinical Research at the Veterans Affairs Medical Center - Washington, D.C., USA

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1 PROTOCOL SUMMARY

1.1 Synopsis

1.1.1 Rationale for Proposed Clinical Study

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. This novel coronavirus has been designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this virus has been designated coronavirus disease 2019 (COVID-19). There were 59 confirmed cases on January 5, 2020, 2118 cases on January 26, 2020, rising to more than 20 million confirmed cases and 750,000 deaths as of August 16, 2020 according to various international health reporting agencies.
Hyperimmune intravenous immunoglobulin (hIVIG) to SARS-CoV-2, derived from the plasma of individuals who recover and develop neutralizing antibodies, is a potentially useful therapeutic approach to COVID-19. Augmentation of the humoral immune (antibody) response using passive immunotherapy with hIVIG to SARS-CoV-2 at the onset of clinical progression before end-organ failure has developed may reduce the subsequent risk of further disease progression and death.

1.1.2 Study Design

This protocol will serve as a platform for assessing treatments for adult patients hospitalized for medical management of COVID-19 without related serious end-organ failure. Trials will involve sites around the world strategically chosen to ensure rapid enrollment. Initially, this trial will compare hIVIG with matched placebo, when added to standard of care (SOC), for preventing further disease progression and mortality related to COVID-19. SOC will include remdesivir unless it is contraindicated for an individual patient.
In future versions of the protocol, one or more drugs from a different class and with different mechanisms of action may be studied. Such treatments could be studied along with hIVIG if it is found effective and safe in this initial version of the protocol.

The primary endpoint of this trial in hospitalized patients is an ordinal outcome based on the patient's clinical status on Day 7. It includes 7 mutually exclusive categories capturing the range of organ dysfunction that may be associated with progression of COVID-19, such as respiratory dysfunction and coagulation-related complications (see Appendix F for full definition):

7. Death

6. End-organ failure

5. Life-threatening end-organ dysfunction

4. Serious end-organ dysfunction

3. Moderate end-organ dysfunction

2. Limiting symptoms due to COVID-19

1. No limiting symptoms due to COVID-19

Secondary endpoints include time to the 3 least favorable categories, time to the 2 most favorable categories, and the pulmonary only and thrombotic only components of the primary ordinal outcome. Mortality, adverse events (AEs), including infusion reactions, and biological correlates of therapeutic activity are also assessed. Because there is no established endpoint for evaluating the clinical efficacy of treatments for COVID-19, other clinically relevant outcomes, including outcomes used in other COVID-19 treatment trials, will be recorded. Thus, the randomized groups (initially hIVIG + SOC versus placebo + SOC) can be compared for multiple outcomes, and results can be compared or combined with other trials.

Participants will be randomized (1:1) to a single infusion of hIVIG + SOC or placebo + SOC on the day of randomization (Day 0). Participants taking remdesivir prior to randomization may be enrolled if eligibility criteria are met. Randomized participants who were not taking remdesivir before randomization will start taking remdesivir immediately following the infusion of hIVIG or placebo unless remdesivir is contraindicated. Participants will be followed for 28 days and, if the trial goes to completion, the primary analysis will be completed after all participants are followed for 28 days.

The planned sample size is 500 participants (250 per group). After 150 participants are enrolled, sample size will be re-estimated, by investigators who are blinded to interim treatment results using pooled outcome data.

The study population will include consenting hospitalized patients with COVID-19 who have had COVID-19 symptoms ≤ 12 days, and who do not have life-threatening organ dysfunction or organ failure.

Many other clinical trials evaluating treatments for COVID-19 are either ongoing or being planned. If findings from another trial have implications for the design and conduct of this trial, the protocol may be modified depending on the strength of the trial results and the target population studied.

An independent Data and Safety Monitoring Board (DSMB) will review interim data and use pre-specified guidelines for early termination of the trial or protocol modification. The DSMB will also be consulted concerning protocol modifications for reasons described above (e.g., sample size re-estimation or other aspects of the design resulting from emerging data). All protocol modifications will be discussed with the independent DSMB. Protocol amendments will be submitted to ethics committees (ECs) and a central institutional review board (IRB) in the United States of America (US).

After consent and eligibility has been determined, a single infusion of hIVIG or placebo will be administered on the day of randomization (Day 0). Remdesivir infusions will follow the hIVIG/placebo infusion. Any infusion reactions and interruptions of the planned hIVIG/placebo infusion will be recorded. The ordinal outcome will be assessed throughout follow-up, including on Day 7 for the primary endpoint. On Day 0 (pre-hIVIG/placebo infusion), and on Days 1, 2, 3, 7, and 28, a blood sample will be obtained to centrally measure neutralizing antibody levels along with total immunoglobulin G (IgG) concentrations and its subclasses, immunoglobulin A (IgA), and immunoglobulin M (IgM); for participants at selected sites an additional blood sample for these measurements will be obtained at Day 90. Serious Adverse Events (SAEs), including deaths from any cause, will be collected through Day 28. hIVIG infusion related events of any grade will be collected. Grade 3 and 4 AEs will be collected through Day 7. AEs of any grade experienced on Days 1, 3, 7, and 28 will be recorded.

2 INTRODUCTION

2.1 Study Rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2). While some cases are mild or asymptomatic, progressive disease can result in hospitalization, requirement for mechanical ventilation, and is a cause of substantial morbidity and mortality.[3] While the most common mode of disease progression is progressive respiratory failure following the development of pneumonia, other severe complications including thrombosis and ischemia are increasingly recognized.[4,5]

There is currently no vaccine to prevent infection with SARS-CoV-2 and no licensed therapeutic agent to treat COVID-19; emergency use authorizations and expanded access schemes have been instituted for certain interventions (including convalescent plasma and remdesivir, described below) prior to licensure. Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe COVID-19 (see Section 2.2.7).

Our understanding of the humoral immune response is evolving, with some evidence that responses are variable between individuals and delayed in some cases. It may therefore be that viral replication may lead to extensive tissue damage and inflammatory responses in the lungs and other organs before the development of neutralizing antibodies. Augmentation of the humoral immune response to SARS-CoV-2 using passive immunotherapy with hIVIG to SARS-CoV-2 in hospitalized patients at the onset of clinical progression but before end-organ failure has developed may thus reduce the subsequent risk of further disease progression and death.

2.2 Background

2.2.1 SARS-CoV-2 Infection and Coronavirus Disease 19 (COVID-19)

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the illness caused by infection with SARS-CoV-2 has been named coronavirus disease 2019 (COVID-19).[6] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly [7,8] and have comorbidities[9] may progress to severe disease requiring hospitalization, mechanical ventilation in intensive care units, and death. As of 28 June 2020, just 14 weeks following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO),[6] there have been more than 20 million cases diagnosed and more than 750,000 deaths across 185 countries.[3] Over 100,000 cases continue to be reported daily.[6]

2.2.2 Natural History of COVID-19

SARS-CoV-2 has a median incubation period of 4 days (interquartile range 2-7 days)[10] and the mean serial interval defined as the time between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53–4.39) days.[11] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS) in advanced disease. Initial symptoms typically involve the upper respiratory tract with cough, sore

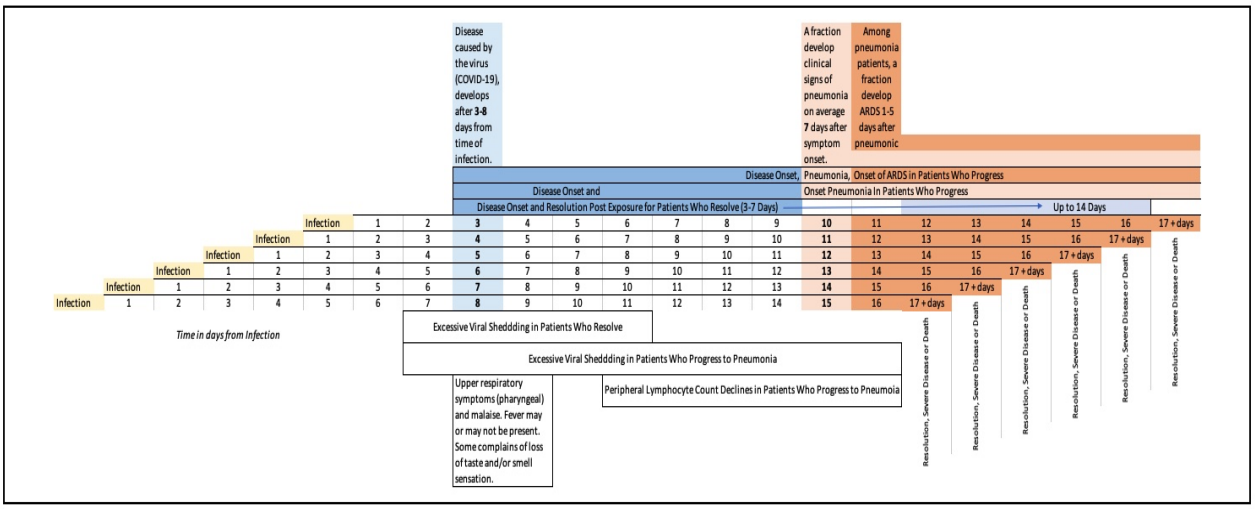
throat and malaise. Fever is present in approximately 44-98% of cases. Notably, persons with COVID-19 often complain of loss of smell or taste.

Advanced complications of COVID-19 illness include cytopenias (lymphopenia, thrombocytopenia and anemia), and acute cardiac events (raised troponin, changes on electrocardiogram), acute renal injury and renal failure, liver impairment, and neurological events including acute cerebrovascular events, impaired consciousness and muscle injury and thrombotic events.
The natural history of COVID-19 as we understand it thus far is illustrated in Figure 1. In most patients (approximately 80%) symptoms resolve without the need for intervention within five to seven days of symptom onset up to a maximum of 14 days. However, approximately 20% of patients show signs of clinical disease progression, most notably pneumonia, around day 3 to 8 following symptom onset. Other manifestations of disease progression include thrombotic episodes including stroke and myocardial infarction (MI). This resembles the documented 6-8 fold excess risk of thrombosis when patients are infected with influenza.[12]
A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after pneumonic symptom onset.[7,13,14,15] Acute kidney injury necessitating dialysis and failure of other organs may also occur at this severe stage of disease.

Of the nearly 1099 persons described in the Wuhan cohort, 16.0% had severe disease at presentation. 67 persons (6.1%) reached a composite primary endpoint of intensive care admission, mechanical ventilation and death; two-thirds had presented with severe disease.[10,16] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and approaches to prevent this late stage of the disease among those with early evidence of progression are critically needed.

In this trial, we aim to enroll patients hospitalized for medical management of COVID-19 at the onset of clinical progression but before end-organ failure has developed: the time period of their infection which is shaded light orange in Figure 1. The majority of these patients will have emerging evidence of pneumonia, but recognizing the expanding range of organs involved in clinical progression of COVID-19, neither the inclusion criteria nor primary endpoint are limited only to assessment of pneumonia and related clinical progression.

FIGURE 1. NATURAL HISTORY OF COVID-19



2.2.3 Risk Factors for Clinical Progression

Studies investigating risk factors for progression of COVID-19 and related hospital admission are currently few in the literature. Reports to date have predominately been conducted in individuals already hospitalized. These include a mix of descriptive information on the patients as well as estimates of associations between patient characteristics and disease severity. Older age has been found to be strongly related to greater severity[16,17] and poorer outcome as has the presence of conditions such as hypertension, diabetes and coronary heart disease.[14,16,18] Other risk factors identified include cigarette smoking[16,17,19] and raised body mass index (BMI).[20,21,22,23] Gender has not shown a consistent relationship with disease severity.[16,24] Specific symptoms at presentation that have notably been associated with greater likelihood of progression to more severe disease include shortness of breath and elevated body temperature.[16,25]

The COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) report on 1482 persons who were hospitalized in 14 states in the United States of America (US) in March 2020 show nearly 75% were aged over 50 years, and nearly 90% had at least one or more underlying comorbid illness.[26] Based on 2.6 million users of the COVID Symptom Tracker App, predominantly in the United Kingdom, being older, obese, diabetic, or suffering from pre-existing lung, heart or renal disease placed participants at increased risk of visiting hospital with COVID-19.[27] Pre-existing lung disease and diabetes were consistently associated with a higher risk of requiring respiratory support.[27] A meta-analysis showed that cardiac injury as measured by a high sensitive troponin was associated with higher mortality, higher need for intensive care unit (ICU) care, and severe COVID-19 disease.[28]

2.2.4 Hospitalization of People with COVID-19

Countries and jurisdictions differ in the clinical management of COVID-19 patients. Early in the epidemic, faced with small numbers of infected persons, some resource-rich countries such as Singapore elected to admit all persons with COVID-19 illness regardless of symptom severity to facilitate strict isolation. Admission for reasons of public health or quarantine, rather than medical management, continues to be a requirement in some countries notably in Asia. Elsewhere, it is more common for those with mild illness to be advised to self-isolate at home, while only those severely unwell are admitted for medical management.

Thresholds for ICU management also differ globally and are likely to vary significantly even within individual countries at different stages of the epidemic. For example, at the epidemic peak procedures commonly performed only in ICU may be extended to other care areas, while patients who might otherwise have been considered for ICU admission may be palliated if clinical services are overwhelmed.

Reported mortality rates for those who develop end-organ failure requiring intensive support, including those admitted to ICU, differ widely. Amongst 1591 ICU patients from the Lombardy region in Italy, hardest hit by COVID-19, 88% required mechanical ventilation and 11% noninvasive ventilation.[29] The ICU mortality rate was 26%. Of 1043 patients with available data, 709 (68%) had at least 1 comorbidity and 509 (49%) had hypertension, 21% had cardiovascular disease. Younger patients (≤63 years) compared to older patients, had lower ICU mortality and higher rates of discharge from ICU. The median length of stay in the ICU was 9 days though 58% remained in ICU at time of report.[29] In one report of the Chinese experience in Wuhan, 31 of 32 persons who required mechanical ventilation died.[7] In the United Kingdom, of the 4078 COVID-19 patients admitted into critical care with reported outcomes, 50.7% died in ICU; those requiring advanced respiratory support and renal support had worse outcomes.[30] These data underline the importance of attenuating the disease in its early phase prior to the development of end-organ failure and the requirement of intensive care.

2.2.5 Viral Kinetics of SARS-CoV-2 Infection

Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset.[31] Viral RNA shedding from pharynx gradually wanes as symptom resolve though viral RNA is still detectable weeks after symptom resolution.[31,32,33] Median duration of viral shedding was 20 days in survivors (longest 37 days), but SARS-CoV-2 was detectable until death in non-survivors.[8] Whether this is viable virus with the potential for continued transmission remains uncertain. RNAemia has been reported but is relatively rare.[32,34] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[35] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[36]

The contribution of ongoing viral replication to disease progression in the third most severe stage of COVID-19 (i.e. on ventilator or extra-corporeal membrane oxygenation [ECMO]) is unclear, but likely minor as we hypothesize that any organ damage from the infection has likely occurred already and the predominant drivers of progression to severe disease/ARDS are those of the uncontrolled local and systemic immune response.

2.2.6 Immune Responses to SARS-CoV-2 Infection

Notwithstanding the observed high viral loads, and progression of viral shedding from the upper to lower respiratory tract in those with progressive disease, the humoral immune response to SARS-CoV-2 appears variable and may be slow. While data are still emerging, it appears that in a significant proportion of cases, antibody responses are not yet evident at the time (day 5-7) when disease progression and hospitalization most commonly occur, supporting a role for supplementation of the antibody response at that time point.

Two large series have described antibody responses (IgG and IgM). In the first, samples from 82 confirmed and 58 probable cases of COVID-19 in a cross-sectional analysis demonstrated IgG detection 14 (interquartile range [IQR] 10-18) days after symptom onset, with IgM detected median of 5 days (IQR 3-6) after symptom onset. Antibodies were absent in around 22% of individuals at assessment (IgM), and IgM was most commonly absent in those assessed early (within 7 days of symptom onset)].[37] In the second study of 262 patients who provided 363 samples, antibody levels were examined by days from symptom onset. IgM antibodies were detectable in just under 40% of

patients at day 5-7, rising to 50% at day 8-10, while interestingly IgG was detectable in a slightly higher proportion at those time points: just over 50% at day 5-7, rising to 60% at day 8-10.[38] This series was drawn from hospitalized patients, but the severity of illness and any relationship with disease outcomes were not described. Both studies show considerable individual variation in antibody kinetics. Further longitudinal studies are underway and will better characterize the kinetics of these responses in individuals.

SARS-CoV-2 infection may also induce significant changes in elements of the cellular immune response. As the disease process progresses, the peripheral lymphocyte count typically declines. The depletion of peripheral lymphocytes likely reflects translocation to the pulmonary tissue. The extent that this influx exclusively is helpful to the host, or possibly may contribute adversely to disease severity is currently unclear. In severe cases this decline in CD4+ and CD8+ lymphocytes is also associated with an increase in activated CD4+ and CD8+, increases in key proinflammatory cytokines including interleukin 6 (IL-6), and increases in natural killer (NK) cells.[39,40] Trials assessing the use of various immunomodulatory agents with the aim of dampening this migration and systemic inflammation are underway, and may help to clarify this.

2.2.7 Current Treatment Strategies for COVID-19

There has been no proven therapy for COVID-19, and no international standard of care has been established, though many clinical trials are underway. Approaches include direct anti-virals, including repurposed drugs found in vitro to have activity against SARS-CoV-2; immune modulators especially in patients with advanced disease, and modifiers of other pathophysiological pathways implicated in disease progression, including potentially anticoagulants and anti-platelet agents. In certain regions, local standards of care have been established, generally with agents hypothesized to have clinical activity but where robust comparative data are not yet available. For example, lopinavir, hydroxychloroquine, and favipiravir have all seen widespread use in hospitalized patients in different regions.

The most promising current antiviral agent is remdesivir, a nucleotide analogue previously studied for Ebola.[41] A preliminary report of the National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT) showed that participants receiving remdesivir had a shorter median time to recovery compared with those receiving placebo (11 vs 15 days; p<0.001). There was a trend toward a survival benefit after 14 days; estimates of mortality were 7.1% and 11.9% (hazard ratio [HR]=0.70; 95% CI: 0.47-1.04).[42] In contrast, a smaller randomized study from China did not show a significant benefit for remdesivir in a similar hospitalized population (HR for time to clinical improvement 1.23 [95% CI 0.87–1.75]); however that trial was stopped early due to slow enrollment and power was substantially less than planned (58% instead of 80%).[43] A number of other remdesivir trials are ongoing and may clarify the extent of its therapeutic effect and other issues including optimal dosing and optimal timing of therapy.

Based on the findings of ACTT, remdesivir will be provided to all study participants as SOC unless contraindicated for an individual patient. As in ACTT, remdesivir will be administered as a 200 milligram (mg) IV loading dose following the hIVIG/placebo infusion, followed by a 100 mg once-daily IV maintenance dose while hospitalized up to a 10 day total course. Participants taking remdesivir prior to randomization will continue their daily remdesivir infusions while hospitalized up to a 10 day course.

Other chemotherapeutic agents with hypothesized direct antiviral activity undergoing clinical study include antimalarial agents, hydroxychloroquine and chloroquine, lopinavir-ritonavir (protease inhibitors) and favipiravir (an RNA-dependent RNA polymerase inhibitor). Despite some early trials that did not establish the efficacy of high-dose chloroquine[44] and lopinavir-ritonavir,[45] and uncontrolled studies showing minimal benefit and possible harm with hydroxychloroquine and

azithromycin,[46] these agents along with favipiravir have been incorporated into some local institutional protocols as SOC, especially in patients hospitalized with advanced and progressive disease.

Other agents under exploration modulate pathophysiological pathways implicated in disease progression. Given the apparent role of excessive IL-6 production in patients with advanced disease, tocilizumab and other inhibitors of IL-6 and associated cytokine pathways (such as Janus kinase, JAK, inhibitors) are all under evaluation, and off-label use of tocilizumab in critical illness is common in some settings. Similarly given the apparent role of platelet dysfunction and pro-coagulant effects of SARS-CoV-2 infection, there is interest in the use of antiplatelet agents and anticoagulants especially at the onset of progressive disease.

A further promising line of approach is the use of passive immunotherapies to enhance the host immune response to SARS-CoV-2 infection, potentially enhancing viral control and limiting disease progression. Convalescent plasma, generic intravenous immunoglobulin (IVIG) and hIVIG to COVID-19 are all gaining interest. While their characteristics differ, convalescent plasma and hIVIG are examples of passive antibody therapy involving administration of antibodies against SARS-CoV-2 as prevention or therapy. High doses of standard IVIG have also been hypothesized to be useful for their immunomodulatory effects (as for example in their use in immune thrombocytopenia) and are under evaluation as described below. The concept of passive immunotherapy is based on the historical concept of serotherapy developed in the 1890s where serum from immunized animals containing an antitoxin factor that could neutralize the toxin and be transferred onward to non-immune animals offered protection.[47,48]

The most widely used of these agents at present is convalescent plasma containing COVID-19 antibodies (CCP). CCP is collected by apheresis from individuals who have recovered from COVID-19 and tested for the presence of SARS-CoV-2 antibodies, preferably with a target neutralizing antibody titer. Despite relatively widespread use, data for its efficacy in SARS-CoV-2/COVID-19 is very limited. Convalescent sera were previously evaluated in an uncontrolled study for SARS-CoV-1 illness in Hong Kong. This was shown to be more effective when given early, and in those who were polymerase chain reaction (PCR) positive and seronegative.[49] In a pilot uncontrolled study of CCP in China, one dose of 200 milliliters (mL) of CCP with neutralizing antibody titers ≥ 1:640 dilution was used in 10 patients with severe COVID-19.[50] This was shown to be safe and showed a possible improvement in clinical outcomes. Another study in New York reported that 39 patients given convalescent plasma had improvements in supplemental oxygen requirements and survival compared to retrospectively matched controls.[51] An initial report of the first 5,000 hospitalized patients with COVID-19 given convalescent plasma through an expanded access program in the US reported that SAEs within 4 hours of infusion occurred in less than 1% of patients.[52] This study was not controlled.

2.2.8 Hyperimmune Intravenous Immunoglobulin (hIVIG)

Anti-Coronavirus Hyperimmune IVIG contains polyvalent antibodies with neutralizing specificity for SARS-CoV-2. It has the potential to provide a standardized therapy to augment host immunity to SARS-CoV-2 and prevent disease progression in symptomatic patients. Hyperimmune IVIG differs from standard IVIG in its derivation from donors who have mounted an immune response to the infection of interest (natural infection as undertaken in this protocol, or following vaccination for other disease states), and its standardization as a product based on neutralizing antibody titers or similar assays demonstrating its activity against the infection of interest. Hyperimmune globulin requires plasma from otherwise healthy individuals in the convalescent phase of the infection, and it is clear that there will be many individuals fitting this criterion with most patients recovering from COVID-19 and therefore able to safely provide a plasma donation during convalescence. Therefore,

this resource will be rapidly available and will serve as an accessible therapeutic modality across multiple jurisdictions globally.

In other respects, hyperimmune and standard IVIG have similarities in their production, constituents, and safety profiles. Production of IVIG requires care when selecting donors, optimum screening of collected products for known infective agents, use of virus inactivation methods like fractionation, and physical and chemical treatment including solvent detergent treatment and caprylation (a short-chain saturated fatty acid which results in a product enriched for IgG) and nanofiltration.[47] Stabilizers currently used in IVIG are nonessential amino acids like glycine and L- proline unlike previous sucrose-containing preparations which could predispose to acute renal failure.

Standard IVIG is by far the more widely used product compared with the various hyperimmune globulins, and contributes considerably to our understanding of the safety and administration of hyperimmune IVIG. Standard IVIG became a commercially available product in the early 1980s and remains an important therapeutic agent in those with primary immunodeficiencies, where it replaces absent or deficient immunoglobulins, and in immune thrombocytopenia and other autoimmune conditions, where it acts as an immunomodulator.[47] Collected from large pools of human plasma, polyvalent and highly diverse monomeric IgG is the key product constituent. Very low levels of other plasma constituents such as other immunoglobulins including IgA and IgM and possibly IgE, solubilized membrane components, complement proteins, coagulation factors, and possibly other solubilized receptors, as well as specific antibodies to human leukocyte antigen (HLA) determinants and lymphocyte surface molecules are also present, and in some circumstances may contribute to its mechanism of action.[53]

Standard IVIG is currently being studied as a therapy for COVID-19 illness in small trials, primarily as an immunomodulatory agent. For this purpose, it is given at relatively high doses (in the range of 2 grams (g) per kilogram (kg) divided over 4 to 5 days). Ongoing trials include NCT04261426, NCT04350580, and NCT04264858. Some efficacy for standard IVIG has also been reported in a retrospective comparison[54] and a small case series.[55]

Hyperimmune globulin preparations have been described to have therapeutic utility in varicella zoster, cytomegalovirus (CMV) pneumonitis,[56] parvovirus induced red cell aplasia,[57] and respiratory syncytial virus (RSV) infection[58] in patients with underlying impairments of immunity. In addition, hyperimmune globulins for hepatitis A,[59] hepatitis B,[60] and rabies[61] have proven prophylactic efficacy and their use is recommended in clinical guidelines. The potential utility of this approach has also been explored in severe respiratory infections caused by other pathogens including influenza[62] and severe acute respiratory syndrome (SARS).[63,64,65] However, the evidence for efficacy of hyperimmune globulin in SARS infection is limited because in that disease outbreak, its use was assessed only in small, poorly controlled clinical studies.[66]

While there are some mechanistic similarities between hIVIG and convalescent plasma,[67] individual doses of convalescent plasma are inherently variable from unit to unit. Unlike hIVIG, convalescent plasma cannot be standardized as a therapeutic product at the required scale. In contrast to convalescent plasma where generally, a single unit of plasma obtained from a single ABO compatible donor is used, hIVIG is a highly purified preparation containing high titers of neutralizing antibodies pooled from multiple donors, and would be safer and have higher activity than CCP. Regulatory compliance and availability of assays to detect SARS-CoV-2 in serum and virologic assays to measure viral neutralization are critical.

2.2.9 Study Treatments

Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin (hIVIG)

Anti-Coronavirus hIVIG is a human hyperimmune product of the purified gamma globulin (IgG) fraction of human plasma containing polyvalent neutralizing antibodies to SARS-CoV-2. hIVIG is

prepared from pooled plasma collected from healthy, adult donors who have recovered from SARS-CoV-2 infection.
Multiple hIVIG products will be used in this trial. These hIVIG products are described below. Each hIVIG is labelled with the following name: "Anti-COVID-19 Hyperimmune Globulin (Human)". An aliquot from each lot of hIVIG prepared for this trial will also be tested centrally at the NIAID Integrated Research Facility at Fort Detrick, Maryland. This batched central testing will not form part of the release criteria for hIVIG lots. The test results for each lot will be used in efficacy subgroup analyses by lot.

Emergent BioSolutions

Emergent BioSolutions' Anti-Coronavirus disease hIVIG, is a liquid product containing approximately 100 mg/mL (10g%) protein of which at least 96% is purified human IgG, stabilized with 250 millimoles (mmol) proline and 0.03% PS80 at pH 5.8. The vialed product will be clear to slightly opalescent, and colorless or pale-yellow liquid, essentially free of foreign particles.
The manufacturing process for SARS-CoV-2 hIVIG contains two steps implemented specifically for virus clearance. The solvent and detergent step (using TnBP and TX-100, respectively) is effective in the inactivation of enveloped viruses such as HBV, HCV, and HIV. Virus filtration, using a Planova™ 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses. These two viral clearance steps are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped viruses. In addition to these two specific steps, the process of anion exchange chromatography was identified as contributing to the overall viral clearance capacity for small non-lipid enveloped viruses.

Grifols Therapeutics, Inc.

Grifols Therapeutics' Anti-Coronavirus hIVIG is a ready-to-use sterile, preservative-, pyrogen-, and latex-free solution of human immune globulin for IV administration. The drug product consists of approximately 100 mg/mL (9.0 to 11.0%) protein in 0.16 to 0.24 M glycine. The pH of the drug product is 4.0 to 4.5 and the osmolality is close to the physiologic range. The protein composition consists of not less than 98% purified IgG. The product is clear to opalescent and colorless to pale yellow liquid.

The purification process used to manufacture hIVIG includes multiple segments with virus clearance capacity, such as caprylate-induced precipitation followed by filtration, caprylate incubation, ion-exchange chromatography, 35 nanometers (nm) nanofiltration, and low pH incubation. The capacity of these manufacturing segments to inactivate and/or remove virus was assessed via laboratory experiments in which a test virus was spiked into starting material that was then processed comparably to the commercial scale by means of a small-scale model, and the processed material was assayed for residual viral infectivity. The purification process demonstrated a large overall virus clearance capacity for enveloped and non-enveloped viruses of diverse physico-chemical properties, providing a very high margin of safety from the risk of transmission of infectious viruses.

Takeda Pharmaceuticals

Takeda's anti-COVID-19 Hyperimmune Globulin (Human) is a ready-for-use sterile, liquid preparation of highly purified and concentrated IgG antibodies. The product contains 100 mg/mL protein of which at least 98% is IgG; average IgA concentration is 37 micrograms (µg)/mL and IgM is present in trace amounts. Glycine (0.25 M) serves as a stabilizing and buffering agent. There is no added sugar, sodium, or preservatives. The pH is 4.6 to 5.1; the osmolality is 240 to 300 mOsmol/kg. Only clear or slightly opalescent and pale yellow solutions may be administered. Vials found to contain particles or discoloration must not be used.

The manufacturing process for anti-COVID-19 Hyperimmune Globulin (Human) contains three dedicated virus clearance steps, i.e., S/D treatment,[68,69] nanofiltration (35 nm),[70,71] and low pH incubation at elevated temperature.[72,73] Viral safety studies used virus models and target viruses to evaluate the clearance of lipid enveloped and nonenveloped deoxyribonucleic acid (DNA) and RNA viruses by the manufacturing steps specific for viral reduction. These studies demonstrated that the 3 dedicated virus inactivation/removal steps provide effective and robust clearance of HIV, West Nile virus (WNV), hepatitis A virus (HAV), parvovirus B19 (B19V), as well as of model viruses for HCV, HBV, HAV, and B19V.

CSL Behring

Anti-COVID-19 hyperimmune globulin comes as a ready-for-use sterile, 10% protein liquid preparation in single-use vials. It contains 100 mg/mL protein stabilized with 250 mmol/L L-proline. Anti-COVID-19 hyperimmune globulin has an osmolality of 320 mOsmol/kg (range: 240 to 440 mOsmol/kg) and a pH of 4.8 (range: 4.6 to 5.0), with an IgG purity ≥ 98%. The vialed solution is clear or slightly opalescent and colorless to pale yellow.

Production of Anti-COVID-19 hyperimmune globulin requires sourcing plasma from convalescent donors collected at qualified plasma collection centers, optimum screening of collected products for known infective agents, and use of virus reduction methods like low pH incubation, clarifying depth filtration, and 20 nm nanofiltration, which demonstrated a large overall virus clearance capacity for enveloped and non-enveloped viruses of diverse physico-chemical properties. Stabilizers currently used in IVIG are nonessential amino acids like L-proline unlike sucrose-containing preparations which could predispose to acute renal failure.

Placebo
Participants assigned to the placebo group for hIVIG will be given infusions of a commercially available isotonic saline solution. There are color differences between the infusion preparations for hIVIG and placebo. Therefore, site pharmacists will be instructed to place a colored sleeve or other suitable covering over all infusion bags to mask the color of the contents and reduce the risk of unblinding. The volume used for hIVIG and for placebo will be comparable.

3 RISK/BENEFIT ASSESSMENT

3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with having blood drawn, IV catheterization, possible reactions to hIVIG infusions, thrombosis, the volume of fluid infused, and breach of confidentiality. These risks are discussed below.

3.1.1 Blood Draw and IV Catheterization

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IV catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site of blood draw or at catheterization less likely.

3.1.2 Study Treatments

The hIVIG used in this study is manufactured in the same manner and to the same standards as commercially available IVIG. This includes screening for blood borne pathogens, and manufacturing steps including solvent/detergent to inactivate any viruses. The risks are anticipated to be the risks of standard IVIG preparations. Specific considerations related to the use of hIVIG in COVID-19, including thrombosis and the theoretical risk of antibody-dependent enhancement, are summarized at the conclusion of this section.

As IVIG is made from human plasma, transmittable viral infections like hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) are a potential risk (though steps are taken to screen for and inactivate such pathogens). In addition, there is a theoretical risk, although deemed very low, that hIVIG administration may be capable of transmitting other known or unknown infectious agents other than viruses, such as infectious prions (e.g., the agent of Creutzfeldt-Jakob disease).

Immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella.

The safety of human IV immunoglobulins is well established. As described in the Investigational Brochures (IBs), a number of adverse events have been associated with the use of IVIG in both children and adults. In the range of 1 to 15%, usually less than 5%, of recipients experience some type of reaction, with the severity ranging from mild to severe. Most reactions occur during the initial 30 to 60 minutes of the infusion and are mild and self-limited.

Pyrogenic Reactions

- These reactions are marked by a significant rise in temperature and are usually accompanied by systemic symptoms.

Allergic Reactions

- Allergic reactions often present with an uncomfortable feeling, especially a tightening around the neck, chest, or abdomen. There may be difficulty swallowing, a choking sensation, or difficulty breathing. Other symptoms of anaphylaxis include wheezing, rash, hives, rapid or weak pulse, hypotension, sweating, or an upset stomach with or without nausea, vomiting or diarrhea. Other more serious allergic reactions are rare, and include hemolysis and aseptic meningitis.

Vasomotor Symptoms

- These can occur with or without additional cardiac manifestations.
- Blood pressure can either increase or decrease, and may be accompanied by flushing or tachycardia.
- Patients experiencing such reactions may report shortness of breath or tightness in the chest.

Non-allergic Systemic (Anaphylactoid) Reactions

- These reactions most commonly include headache, dizziness, or lightheadedness.
- Patients can also experience chills, nausea, vomiting, back or hip pain, malaise, myalgia and arthralgias.
- Rigors are a rare infusion reaction that is an extreme form of chills that affects the whole body with vigorous shaking.
- The most frequent cause of such reactions is infusion at an excessively rapid rate.
- These types of reactions are more common in a patient naïve to IgG treatment and/or who harbor chronic infection. These reactions may be marked by flushing and warmth of the skin, chills, headache, dizziness, nausea, vomiting, and muscle aches.
- Frequently the patient reports anxiety and in some cases, “a sense of impending doom.” Often, the patient will have elevated blood pressure rather than hypotension, distinguishing this type of reaction from true anaphylaxis.

Post-infusion Reactions

- These reactions can occur immediately or up to 48 to 72 hours following the infusion.
- Symptoms associated with post-infusion reactions are usually less severe in nature, but can interfere with a patient's quality of life.
- Common post-infusion reactions may include headache, low-grade fever, nausea, arthralgias, and generalized malaise.

Other Reactions

- Renal dysfunction, acute renal failure, and osmotic nephropathy may occur with immune globulin intravenous products in predisposed patients. Renal dysfunction and acute failure occur more commonly in patients receiving IVIG products containing sucrose. The hIVIG products in this study do not contain sucrose.
- Transfusion-related acute lung injury (TRALI), although very rare, may occur and is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever.
- The infused volumes of study product may be as high as 200 mL, so there is the risk of volume overload in the recipient which could cause pulmonary edema. Transfusion-associated circulatory overload (TACO) has been associated with plasma infusion and may be clinically indistinguishable from TRALI even though the physiologic mechanisms differ. TACO is hydrostatic, not permeability, edema and more responsive to diuresis when it occurs. Patients with pre-existing conditions who may not tolerate the volume of hIVIG/placebo to be given will be excluded from this study, but this condition could still occur in recipients.
- There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking.[74] Pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults.[75] Other thrombotic events, including myocardial infarction, cerebral vascular accident, and deep vein thrombosis may also occur.

Specific Considerations in COVID-19

There is potentially a slight elevation in the risk of thrombosis with standard IVIG therapy, and in some cases COVID-19 is associated with thrombotic complications. Hence participants with pre-existing prothrombotic tendencies will not be included and any thrombotic events will form part of the primary endpoint assessment and be monitored during interim safety analyses by the DSMB. There is a theoretical risk the antibody infusion may worsen the disease course of COVID-19 via antigen-dependent enhancement (ADE). It is unclear if this phenomenon is relevant and clinically significant in COVID-19, but to ensure detection of any such phenomenon (which could be manifested by disease progression soon after hIVIG infusion) close monitoring of clinical disease outcomes will be maintained in the randomized groups, including in the days prior to the primary endpoint assessment at Day 7.

3.1.3 Confidentiality and Privacy

Participants will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the participant's PHI. All source records including electronic data will be stored in secured systems in accordance with institutional policies and government regulations.

All study data that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a participant through a code key maintained at the clinical site. Names or readily identifying information will not be released. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify study participants. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, NIAID and applicable regulatory agencies (e.g. US Food and Drug Administration [FDA]).

3.2 Known Potential Benefits

While the trial is conducted to test the hypothesis that hIVIG will reduce the risk of further disease progression, hIVIG may or may not prevent this outcome in any individual who participates in this trial. However, there is benefit to society from their participation in this trial resulting from insights gained about the therapeutic agent under study as well as the natural history of the disease. While there may not be benefits for an individual, there will be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objectives and Primary Endpoint

The primary objective is to compare the clinical status of participants in the hIVIG + SOC and placebo + SOC groups on Day 7 using an ordinal outcome with 7 mutually exclusive categories. On Day 7, the worst of the 7 categories the participant was in that day will constitute the primary outcome. The 7 categories are:

7. Death

6. End-organ failure

5. Life-threatening end-organ dysfunction

4. Serious end-organ dysfunction

3. Moderate end-organ dysfunction

2. Limiting symptoms due to COVID-19

1. No limiting symptoms due to COVID-19

Appendix F provides clinical definitions of each category. In addition to the overall summary odds ratio (OR) that will be estimated as described in Section 11.1, ORs will be estimated for the 6 dichotomized definitions of improvement that can be formulated from the categories of the ordinal outcome.

4.1.1 Rationale for Primary Endpoint at Day 7

The goals of this study are to assess the safety, tolerability and efficacy of a single infusion of hIVIG in preventing further progression and mortality related to COVID-19 when administered at the onset of clinical progression, with the aim of improving the long term outcome of the disease process. There is as yet no consensus on the optimal endpoint for determining clinical benefit from COVID-19 therapies, including the constituent elements of the endpoint and the timing of its assessment after randomization. Both may differ depending on the target population and the nature of the treatment studied.

The primary ordinal outcome captures the range of severity experienced by hospitalized patients with COVID 19, recognizing that end-organ manifestations in addition to pneumonia and ARDS are increasingly emerging as significant contributors to morbidity. The ordinal outcome includes 7 well-

defined mutually exclusive categories that assess further progression of disease as well as recovery from COVID-19.

The ordinal outcome includes both pulmonary manifestations as assessed in prior COVID-19 trials and additional components representing key non-pulmonary outcomes; the latter are highlighted as *"extra-pulmonary"* in the guidance table (Appendix F). The primary endpoint will include both pulmonary and extra-pulmonary components, while the pulmonary manifestation scale only will be reported as a secondary endpoint.

Day 7 was chosen for the timing of the primary endpoint for several reasons based on the following assumptions. The impact of hIVIG on disease progression may not be immediate; a few days may be needed to see the effects on clinical outcomes as measured by the ordinal outcome. Also, transient treatment effects that are no longer present at Day 7 may be clinically less relevant. Assessment of the ordinal outcome at a later time point may result in a diminished treatment difference because spontaneous recovery from COVID-19 may have begun in many participants. Also, antibody differences between the treatment groups, an important biologic mechanism for observing a clinical benefit, are assumed to be greatest during the first week after infusion.

Lastly, use of Day 7 to characterize the clinical severity of participants in 7 categories as studied here, results in a distribution of participants in the placebo group for the ordinal outcome that is sufficiently granular and not overly skewed to the most severe or least severe categories and, therefore, provides good power for comparing the two treatment groups with a feasible sample size given the difficulty in producing large quantities of hIVIG (see Section 5.5).

4.2 Secondary Objectives

Secondary objectives will be assessed by comparing hIVIG + SOC with placebo + SOC over the 28 day follow-up period for outcomes listed below. Because there is no established endpoint for evaluating the clinical efficacy of treatments for COVID-19, other clinically relevant outcomes, including outcomes used in other COVID-19 treatment trials, will be recorded. Thus, the randomized groups can be compared for multiple outcomes, and results can be compared or combined with other trials. Many of the endpoints used in other trials are ordinal outcomes or are defined based on a dichotomy of an ordinal outcome and assessed at a single follow-up time point or as a time-to-event outcome.

19. All-cause mortality through Day 28.

20. The primary ordinal outcome on Days 3, 5, 14 and 28.

21. Change in National Early Warning Score (NEWS) (see Appendix G) from baseline at Day 3.

22. Time to the 3 least favorable categories of the primary outcome measure.

23. Time to the 2 most favorable categories of the primary outcome measure.

24. Hospitalization status (a binary outcome, alive and discharged from the hospital to home or rehabilitation versus dead or hospitalized) at Days 7, 14 and 28.

25. Time to discharge (this is similar to the recovery outcome used in the ACTT-1 trial[42])

26. Days alive outside of a hospital through Day 28

27. Pulmonary only components of the primary outcome measure at Days 3, 5, 7, 14 and 28

28. Thrombotic components of the primary outcome measure (stroke, myocardial infarction, venous and arterial thrombosis or embolism, plus disseminated intravascular coagulation) at Days 3, 5, 7, 14, and 28.

29. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate cross trial comparisons and overviews, e.g., 6-, 7- and 8- category ordinal scales at days 7, 14 and 28; and binary outcomes defined by improvement or worsening based on the primary ordinal outcome and ordinal outcomes used in other trials.

30. Clinical organ dysfunction defined by *new onset* of any one or more of the following conditions (or requirement for the following therapies) through Day 28:
    a. Respiratory:
        1. Extracorporeal membrane oxygenation (ECMO)
        2. Invasive ventilation
        3. Non-invasive ventilation or high flow oxygen
    b. Cardiac and vascular:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. NYHA Class III/IV congestive cardiac failure
        4. Vasopressor therapy
    c. Renal:
        1. Renal replacement therapy (dialysis)
    d. Hepatic:
        1. Hepatic decompensation
    e. Neurological
        1. Cerebrovascular event (stroke)
        2. Encephalitis, meningitis or myelitis
        3. Acute delirium
    f. Hematological:
        1. Disseminated intravascular coagulation
        2. New thrombotic events, including pulmonary embolism, deep venous thrombosis, or arterial thrombosis
    g. Infective:
        1. Microbiologically-proven severe infection (not including SARS-CoV-2)

31. Safety and tolerability will be assessed using outcomes described above (e.g., mortality and thrombotic outcomes) and also assessed by the following outcomes:

    a. A composite of incident grade 3 and 4 events (not limited to a laboratory abnormality), SAEs (see Section10.1.2), or death through Day 7 (primary safety endpoint)
    b. Infusion reactions of any grade severity during the infusion and 2 hours post-infusion, and percentage of participants for whom the infusion was interrupted or stopped prior to completion
    c. SAEs or deaths through Day 28
    d. Prevalence of adverse events of any grade on Days 1, 3, 7 and 28.

32. Change in immunoglobulin levels (IgG, IgG subclasses, IgM, IgA) and neutralizing antibody titers from baseline to Days 1, 2, 3, 7, 28 and 90.

33. The primary endpoint by duration of symptoms at study entry. This is a key subgroup analysis. For those with shorter duration of time since symptom onset, the treatment effect is hypothesized to be greater than among participants who have had symptoms for a longer period of time. This hypothesis assumes that disease progression among those with longer duration of symptoms at study entry will be primarily determined by organ damage that has already occurred instead of ongoing viral replication. In addition, it is assumed that the natural antibody response to SARS-CoV-2 infection is likely to be greater at entry for those with longer symptom duration, and this would diminish the treatment difference between the hIVIG and placebo groups over the week following infusion. Given the inclusion criteria of ≤ 12 days, we anticipate the upper quartile will be 8-10 days (75% of participants will have symptom duration < 8 to 10 days). In ACCT-1, a more severely ill target population than studied here, there was no limit to the duration of symptoms and the median was 9 days (interquartile range, 6 to 12).[42] The quartile definitions for duration of symptoms will be determined following the completion of enrollment, and will be stated in the data analysis plan.

34. The primary endpoint for other subgroups defined by the characteristics measured at baseline will also be assessed:
    - Age
    - Biological sex
    - Race/ethnicity
    - BMI
    - Presence of selected chronic medical conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, cancer)
    - Geographic location
    - hIVIG product administered
    - hIVIG lot potency of administered product
    - Upper respiratory SARS-CoV-2 viral load
    - Neutralizing antibody level
    - Oxygen saturation level
    - Dyspnea severity
    - Organ/respiratory dysfunction category based on ordinal primary outcome
    - NEWS
    - Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the day 7 ordinal outcome: age, gender, duration of symptoms, oxygen saturation level, ordinal outcome category at entry, NEWS, and chronic health conditions).

5 STUDY DESIGN

5.1 Overall Study Design

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of hIVIG in consenting hospitalized patients with COVID-19 who have had COVID-19 symptoms ≤ 12 days, and who do not have life-threatening organ dysfunction or organ

failure. Remdesivir will be provided to participants in both the hIVIG and placebo groups as SOC unless contraindicated for an individual participant.
Participants may co-enroll in INSIGHT observational studies (e.g. INSIGHT 004 Genomics, FLU-003+) or have been previously enrolled in such studies prior to hospitalization (e.g. ICOS).

5.2 Randomization

Randomization will be stratified by site pharmacy (clinical sites may share a pharmacy). Participants will be randomized in a 1:1 ratio to receive a single infusion of hIVIG or placebo.
Hyperimmune IVIG will be manufactured by multiple groups and the specific hIVIG distributed to each site will be determined in a way that considers factors discussed in Section 5.4.
Within each stratum permuted block randomization will be used to generate treatment assignments.

5.3 Blinding

Hyperimmune IVIG or placebo will be prepared by a pharmacist who is unblinded to the treatment assignment.
Blinding of the participant and clinical staff will be achieved by placing a colored sleeve over the infusion bags used for hIVIG and placebo. Placebo will consist of normal saline.
In the event that the blind is broken for safety reasons, this will be recorded, and the protocol co-chair(s) will be notified. In that situation, every attempt will be made to minimize the number of people unblinded.

5.4 Distribution of Anti-Coronavirus hIVIG to Clinical Sites

It is critical to establish whether Anti-Coronavirus hIVIG is safe and effective as rapidly as possible. To accomplish this, hIVIG will be manufactured for use in this trial by 3 different groups. Four hIVIG products, two produced by an Alliance of several companies including Takeda Pharmaceuticals and CSL Behring, and one each produced by Emergent BioSolutions and Grifols Shared Services North America, Inc., will be used. No single group can prepare sufficient quantity of hIVIG product to rapidly complete this trial. Thus, for practical reasons, the primary analysis (see Section 11.1) which compares the hIVIG and placebo groups on Day 7 for the primary ordinal endpoint will pool the outcome results for the 4 different hIVIG products and matching placebos.

To simplify logistics related to the supply of hIVIG to clinical sites and to take advantage of the randomization, which is stratified by site pharmacy, the same hIVIG product will be provided to a given site pharmacy for the duration of the trial to the extent possible. This is illustrated in Figure 2 with an example that assumes that there are 24 site pharmacies and the supply of each of hIVIG products will be the same.

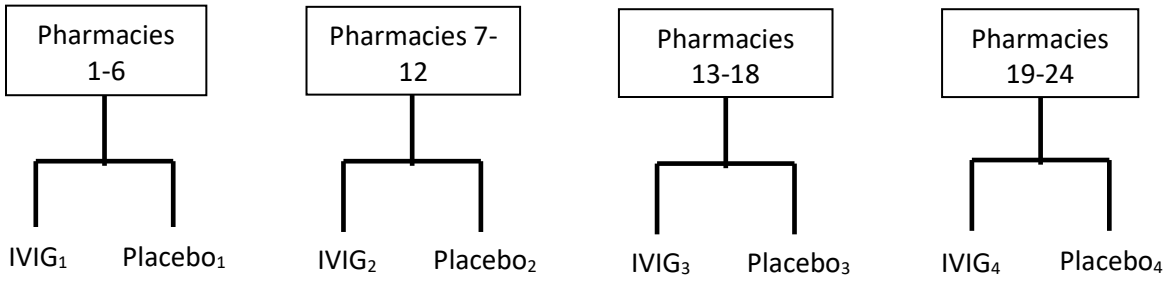
The site pharmacy allocation of hIVIG will take into account estimates of the number of participant doses each manufacturer will provide and estimates of the number of participants to be enrolled by sites using each site pharmacy (i.e., it may not be an equal number of site pharmacies or participants for each hIVIG product).

It is likely that the hIVIG provided by each manufacturer will be from more than one lot during the study. For each individual participant, all hIVIG vials used will come from the same lot. This plan for distributing the hIVIG will simplify the tracking of lots used by each site pharmacy. This plan also simplifies the pharmacy plans prepared for each site pharmacy.

More generally, with this plan, one can consider this as parallel multi-center trials of different hIVIG

products for which planned analyses that compare the hIVIG and placebo groups for primary and secondary outcomes will be pooled across the hIVIG products used. With such a plan, depending on the number of doses of each hIVIG product provided, there may be adequate power to compare each hIVIG product with matching placebo for some outcomes other than the primary efficacy outcome, including potentially change in anti-SARS-CoV-2 IgG levels from baseline (Day 0), safety outcomes, such as AEs and infusion interruptions, and selected secondary efficacy outcomes.

FIGURE 2. EXAMPLE OF ALLOCATION OF HIVIG TO 24 SITE PHARMACIES



5.5 Sample Size Assumptions

5.5.1 Primary Analysis

The planned sample size for the trial is 500 participants (250 in each group). The following assumptions were made in estimating the required sample size.

o. The primary analysis will be intention to treat.
p. A proportional odds model with indicators for the six cut-offs corresponding to using any of categories 1 to 6 as cut-offs for determining clinical improvement, treatment group (hIVIG versus placebo), baseline severity of illness as defined by the ordinal outcome, two-way interactions between baseline severity of illness and the six cut-offs, hIVIG product/matching placebo used, and two-way interactions between hIVIG product/matching placebo used and the six cut-offs will be used to estimate the OR.
q. Type 1 error = 0.05 (2-sided) and power = 0.80.
r. The clinical status (% distribution) of participants in the placebo group at Day 7 is assumed as shown in the 3rd column in Table 2. Since both randomized treatment groups will receive remdesivir as SOC (unless contraindicated), these percentages were estimated using Day 7 data from the ACTT-1 trial for a subgroup of patients similar to ours (the subgroup of participants who entered ACTT-1 in categories 4+5 of their 8-category ordinal outcome for disease severity and were randomized to the remdesivir group).
s. We assumed an OR (hIVIG/placebo) of 1.61 for a more favorable outcome. This corresponds to the % distribution of the clinical status of participants in the hIVIG group at Day 7 shown in the 2nd column in Table 1 below. For example, the percentage of participants in the 2 most favorable categories would be increased to 65.4% in the hIVIG group from 54.0% in the placebo group (an 11.4% increase from the placebo group). Conversely, the percentage of participants in the 4 most severe categories would decrease to 19.4% from 28.1% in the placebo group. The same proportional improvement was assumed across the ordinal scale.
t. Sample size depends on a number of assumptions, including the hypothesized odds ratio, the number of categories in the ordinal outcome, and the distribution of responses for the placebo group.[76] Hypothesized odds ratios closer to 1.0 correspond to a smaller treatment effect, and

require a larger sample size to maintain 80% power. The final sample size was chosen after consideration of a range of odds ratios and of category percentages for the placebo group.

u. Based on the category percentages in Table 1, the estimated sample size is 494. This was increased to 500 to allow for a small number of participants who may be randomized but not receive the study infusion or be lost to follow-up.

We are planning a *blinded* sample size re-estimation using pooled data (both the hIVIG and placebo groups combined) for the primary endpoint that will be made after approximately 150 participants have completed the Day 7 follow-up assessment. The goal of the re-estimation is to retain 80% power to detect the hypothesized summary odds ratio of 1.61. The re-estimation will use the observed (pooled) distribution of the ordinal outcome at day 7, pooled across study arms.

TABLE 2. HYPOTHESIZED PERCENTAGE OF PARTICIPANTS IN EACH CATEGORY ON DAY 7 IN THE HIVIG AND PLACEBO GROUPS BASED ON AFOREMENTIONED ASSUMPTIONS

Category	hIVIG + SOC Group	Placebo + SOC Group
7. Death	0.6	1.0
6. End-organ failure	4.0	6.3
5. Life-threatening end-organ dysfunction	4.2	6.3
4. Serious end-organ dysfunction	10.6	14.5
3. Moderate end-organ dysfunction.	15.1	17.9
2. Limiting symptoms due to COVID-19	57.6	49.0
1. No limiting symptoms due to COVID-19	7.8	5.0
Total	100.0	100.0

5.5.2 Key subgroup analysis

For the key subgroup defined according to duration of symptoms at entry, 375 participants will be in the lower 3 quartiles. Assuming the category percentages in Table 1, with 375 participants, an OR of a more favorable outcome on hIVIG compared to placebo of 1.61 can be detected with 70% power. For this subgroup, an OR of 1.73 can be detected with 80% power and type 1 error = 0.05 (2-sided).

5.5.3 Key secondary outcomes

The study is not powered to detect treatment differences in mortality, because the mortality is expected to be low given the eligibility criteria.

The following outcomes are defined as key secondary outcomes:

Composite of death, end-organ failure, or life-threatening end-organ dysfunction (categories 5-7 of the ordinal outcome) at Day 7: This composite outcome comprises the most severe three categories of the ordinal outcome. Decreasing the probability that a participant enters one of these disease states and remains there through Day 7, has high clinical significance. Comparing the hIVIG+SOC versus the placebo+SOC groups for the proportion of participants in the three worst categories on Day 7, a total sample size of 500 participants is sufficient to detect a decrease to 6.1% in the hIVIG

group compared with 13.6% in the placebo group (difference 7.5%, OR=2.4) with 80% power, under the following assumptions:

a. The analysis will be intention to treat.
b. Type 1 error = 0.05 (2-sided) and power = 0.80.
c. The proportion of participants who are in categories 5-7 of the ordinal outcome on Day 7 in the placebo + SOC group is 13.6% (Table 1). In the ACTT-1 study, the proportion was 10.8%, among participants in baseline categories 4+5 of the ACTT-1 ordinal outcome who were randomized to the remdesivir group (confidential data, personal communication).

A decrease from 13.6% to 8% (OR 1.8) could be detected with power of 47%.

Time to discharge from hospital, time to the 2 most favorable categories of the primary ordinal outcome: We expect that by Day 28, almost all participants will be discharged from the hospital. Similarly, we expect most participants will be in in one of the 2 most favorable categories of the primary ordinal outcome by Day 28. In the ACTT-1 trial, in the subset of participants who entered the trial with disease severity similar to our eligibility criteria (ACTT-1 ordinal outcome categories 4+5), 94.7% had been discharged from the hospital by Day 28. This percentage was similar for the ACTT-1 definition of "recovery" that include a small percentage of participants who were hospitalized but no longer requiring medical care. Comparing the hIVIG versus placebo groups for time to hospital discharge, our study is powered to detect a relative rate ratio (RRR) of 1.3 with 80% power and a significance level of 0.05. The power calculations assume that the RRR is approximately constant to Day 28, the overall cumulative percentage discharged (pooled across treatment groups) by Day 28 is 94% and that between 2.5 and 3% withdraw consent or are lost to follow-up by Day 28. We assume power is similar for time to the 2 most favorable outcomes of the primary ordinal outcome.

Hospitalization status: Comparing the hIVIG versus the placebo+SOC groups for the hospitalization status (a binary outcome, alive and discharged from the hospital to home or rehabilitation versus dead or hospitalized) on Day 7, the total sample size of 500 participants is sufficient to detect an increase in the proportion discharged to 58% in the hIVIG group from 45% in the placebo group (OR=1.7), with 80% power. Similarly, the study has 80% power to detect an increase to 81% in the hIVIG group compared with 70% in the placebo group (OR=1.85) at Day 14. Corresponding estimates from the ACTT-1 trial were 51% discharged on Day 7, and 77% on Day 14, for participants that were similar to ours and randomized to the remdesivir arm (confidential data; personal communication). Our hypothesized percentages are slightly lower, because our eligibility criteria allow for use of high-flow oxygen, in addition to the ACTT-1 ordinal categories 4+5. Power calculations assume that the treatment groups are compared by intent-to-treat.

5.6 Schedule of Assessments

Participants will be randomized and given their infusion of study drug/placebo on Day 0, in addition to standard of care therapy. All participants will be followed through 28 days. Consenting participants at selected sites will return for a visit 90 days after randomization to obtain a blood draw; this subset will comprise all participants at selected sites where return for a later visit is practical for participants. While in the hospital, evaluations will be made each day (Appendix B). SAEs and deaths should be immediately reported. Participants who are discharged will be asked to return to the site at Day 1, 2, 3, 7 and Day 28 (if already discharged) for a blood draw and health status assessment. Additional visits after discharge at Days 5 and 14 can be completed by telephone contact.

5.7 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

In general, the study will take a pragmatic approach to the use of intercurrent, concomitant medications. With the exception of convalescent plasma or IVIG (hyperimmune or standard, other than study drug) which is not permitted prior to entry or through Day 7, there are few restrictions.

Participants will be asked at screening to agree to refrain from participation in other clinical trials until after the assessment of the primary endpoint (Day 7). However, it is recognised that, in the case of progression to life-threatening disease and end-organ failure (broadly categories 5 and 6 of the outcome measure) there will be considerable clinical concern, and participation in an additional clinical trial at that time will not be restricted.

Prior participation in clinical trials (except receipt of IVIG, hIVIG or convalescent plasma) is not restricted, recognising for example that participants may have enrolled in a study for mild disease prior to progression and then may wish to participate in this study at the onset of progression.

The planned analyses are by intention to treat. All participants will be compared at Day 7 irrespective of use of concomitant treatments. Concomitant treatments at baseline and Day 7 will be recorded. The study randomization and site stratification will balance the use of concomitant medications on average at baseline and these will be summarized with other baseline characteristics. Follow-up use of concomitant treatments may differ by treatment group reflecting different efficacy/safety of the study treatments. Use of concomitant treatments will be summarized at Day 7 by treatment group.

6 SCIENTIFIC RATIONALE FOR THE STUDY

The clinical course of SARS-CoV-2-infected individuals tends to diverge around day 3 to 8, with a fraction of patients showing progression (most notably pneumonia) while others recover. A proportion of those progressing then further progress to end-organ failure, including respiratory failure, and in some cases death. Humoral immunity to SARS-CoV-2 is not yet well understood, and may be variable or delayed in some individuals (including potentially those progressing). Augmentation of the antibody response using passive immunotherapy with hIVIG to SARS-CoV-2 around the onset of clinical progression but before end-organ failure has developed may reduce the subsequent risk of further disease progression and death.

7 STUDY POPULATION

The total sample size is projected to be 500 adults ≥18 years of age with COVID-19 and who meet all eligibility criteria. These participants will be enrolled at clinical trial sites globally. Each site pharmacy may supply several clinical sites; approximately 20-30 site pharmacies will participate (see Section 5.4). The estimated time from screening (Day -1 or Day 0) to the end of the study for an individual participant is approximately 28 days. Consenting participants at selected sites will return at Day 90 for a final blood draw.
Patient eligibility must be confirmed by a study clinician named on the delegation log. There is no exclusion for receipt of SARS-CoV-2 vaccine (experimental or licensed).

7.1 Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

8. SARS-CoV-2 infection documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection

9. Symptomatic COVID-19 disease

10. Duration of symptoms attributable to COVID-19 ≤ 12 days

11. Requiring inpatient hospital medical care for clinical manifestations of COVID-19 (admission for public health or quarantine only is not included)

12. Age ≥ 18 years

13. Willingness to abstain from participation in other COVID-19 treatment trials until after study Day 7

14. Provision of informed consent by participant or legally authorized representative

7.2 Exclusion Criteria

10. Prior receipt of SARS-CoV-2 hIVIG or convalescent plasma from a person who recovered from COVID-19 at any time

11. Prior receipt of standard IVIG (not hyperimmune to SARS-CoV-2) within 45 days

12. Current or predicted imminent (within 24 hours) requirement for any of the following:

    - Invasive ventilation
    - Non-invasive ventilation
    - Extracorporeal membrane oxygenation
    - Mechanical circulatory support
    - Continuous vasopressor therapy

13. History of allergy to IVIG or plasma products

14. History of selective IgA deficiency with documented presence of anti-IgA antibodies

15. Any medical conditions for which receipt of the required volume of intravenous fluid may be dangerous to the patient

    - Includes New York Heart Association Class III or IV stage heart failure

16. Any of the following thrombotic or procoagulant disorders:
    - Acute coronary syndromes, cerebrovascular syndromes and pulmonary or deep venous thrombosis within 28 days of randomization
    - History of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome

17. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments

7.3 Costs to Participants

There is no cost to participants for the research tests, procedures/evaluations, and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the participant, participant's insurance or third party.

8 STUDY PRODUCT

8.1 hIVIG and Placebo

8.1.1 hIVIG Description

Summary characteristics of the individual hIVIG products and placebo are summarized in Section 2.2.9, with information on handling and preparation found in the Study Procedure Modules

8.1.2 hIVIG Dose

The hIVIG product is administered as a single dose of 400 mg/kg (or 0.4 g/kg) body weight, to a maximum dose of 40 g or 400 mL (i.e. capped at a body weight of 100kg).
The safety profile of hIVIG is anticipated to be comparable to licensed IVIGs for which doses of well above 400 mg/kg are safe and well tolerated. Licensed IVIGs are used with doses up to 400mg/kg for immune replacement and up to 2 g/kg for immunomodulatory induction, with an established favourable safety profile in which adverse events are not closely dose related.
The selected dose is derived from measures of anti-SARS-CoV-2 neutralizing potency from hIVIG, in comparison with that observed in convalescent plasma pools. Convalescent plasma pools used to produce hIVIG contain approximately 10 mg/mL of IgG immunoglobulin. Analysis of hIVIG shows an expected 10-fold increase in anti-SARS-CoV-2 binding IgG, but a lower than expected (5-fold) enrichment in anti- SARS-CoV-2 neutralizing potency. This suggests that only 50% of anti-SARS-CoV-2 neutralizing potency of plasma pools utilized to produce hIVIG is associated with IgGs. Based on this comparison, the neutralizing potency associated with the selected dose of 400 mg/kg hIVIG is significantly higher than in a fixed dose of 400 mL of convalescent plasma (3.5-5 fold higher than that dose of plasma when administered to 70-100 kg). This dose was therefore selected as providing an appreciable dose margin over convalescent plasma (in addition to the other advantages of hIVIG versus plasma), while remaining well within the accepted safe dose range for other IVIG products, and observing the limitations of hIVIG product supply.
There are no data so far to define target therapeutic titers for anti-SARS-CoV-2 antibody which would support dose derivation from target titers rather than the approach to dose selection described above. Although not considered for dose selection in the present study, the hIVIG products' potencies, and circulating levels of immunoglobulins (IgG, IgG subclasses, IgM, IgA) and neutralizing antibody titers following treatment will be measured. The analysis of the relationship between neutralizing titers and clinical outcomes may help to define a target therapeutic neutralizing titer for hIVIG+SOC and therefore may support dose optimization for future clinical investigations.

8.1.3 hIVIG Administration

The hIVIG product is administered as a single dose of 400 mg/kg (or 0.4 g/kg) current actual (not ideal) body weight, to a maximum dose of 40 g or 400 mL (i.e. capped at a body weight of 100 kg). The product as supplied should not be diluted. The infusion line may be flushed with normal saline. Infusion of hIVIG/placebo should commence at an infusion rate of 0.5 mg/kg/minute 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 as follows: the rate may be increased by doubling the

infusion rate after intervals of not less than 30 minutes, so long as the infusion remains well tolerated. Participants should remain under close clinical observation during the infusion and for at least 60 minutes following completion of the infusion.
For participants judged to be at risk for volume overload (including but not limited to those with pre-existing cardiac failure), or who have for renal dysfunction (estimated creatinine clearance <60ml/min), administer hIVIG at the minimum infusion rate practicable.
For all participants, use of diuretics may be considered as clinically appropriate to avoid or treat fluid overload, with the goal of maintaining participants in a euvolemic state following completion of the infusion.
If adverse events occur, such as flushing, headache, nausea, changes in pulse rate or blood pressure, the rate of infusion should be slowed or infusion should be temporarily stopped. When events resolve, the infusion may be resumed at a rate that is comfortable to the participant (start at half of the last tolerated rate and increase gradually).
The hIVIG treatment should be immediately stopped should new onset or worsening of any of the following occur:
• Profound hypotension (systolic blood pressure < 80 mmHg)
• Severe shortness of breath, wheezing, or sustained (i.e., ≥ 10 seconds) new decrease in oxygen saturation to < 90% on room air
• Severe (Grade ≥ 3) local infusion site reactions, including pain, tenderness, erythema, or swelling as defined in the protocol-specified toxicity grading scale
• Sustained body core temperature exceeding 38.5°C or increase in body core temperature >2.0°C from baseline prior to infusion
• Suspected intercurrent sepsis (not manifestations of COVID-19)
• Severe chest pain
• Suspected anaphylaxis

8.1.4 Preparation/Handling/Storage/Accountability

This information is found in the Study Procedure Modules.

8.2 Remdesivir Background Therapy

8.2.1 Rationale

The antiviral drug remdesivir is being provided to all participants in this study, unless contraindicated. Remdesivir was shown to improve time to recovery in moderately-to-severely ill individuals hospitalized with COVID-19[40]. It is being provided to standardize background therapy in this study; while considered standard of care in hospitalized patients, due to shortages and regulatory status the drug may not be available at some participating sites during the study period.

8.2.2 Description

Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, sulfobutylether-β-cyclodextrin (SBECD), and hydrochloric acid and/or sodium hydroxide.

8.2.3 Administration

Remdesivir will be administered as a 200 mg IV loading dose (100 mL volume) on the first day of its infusion followed by 100mg daily for the course described below; remdesivir may have commenced prior to randomization. For participants starting remdesivir after randomization to hIVIG/placebo, the loading dose should be given immediately after the infusion of hIVIG/placebo, once any infusion reactions from that infusion have resolved; for those who commenced remdesivir prior to

randomization, the usual maintenance dose of 100 mg can be given after the hIVIG/placebo infusion on Day 0 in the same manner. After the first remdesivir infusion, a 100 mg once-daily IV maintenance dose (also 100 mL volume) is given each day while hospitalized for up to a 10 day total course; shorter durations of 5 days may be considered by the clinical investigator as appropriate in patients who are not ventilated. Infusions will not be given to participants after discharge. The total treatment course should not exceed 10 calendar days even if an infusion is missed.
The dose should be given at approximately the same time each day (+/- 2 hours for medication scheduling).
Any dose that is delayed may be given later that calendar day. Any dose that is missed (not given that calendar day) is not made up. The treatment course continues as described above for hospitalized patients even if participants become PCR negative.

8.2.4 Contraindications

Remdesivir is contraindicated in participants with a history of hypersensitivity to remdesivir or any ingredient of the solution for injection.[77] Clinical caution should be exercised in individuals with hepatic or renal dysfunction, and hepatic and renal function should be checked prior to dosing and monitored during therapy.[77] Remdesivir has not been studied in pregnancy, and use in pregnancy should be based on an individual assessment of risk/benefit by the treating physician.

8.2.5 Dose Modification

If the estimated glomerular filtration rate (eGFR) decreases to < 25 mL/min, the remdesivir infusion should not be given on that day. The infusion may be resumed on the next day if the eGFR returns to ≥ 30 mL/min. If the participant's renal function worsens to the point that they require hemodialysis or hemofiltration, remdesivir will be discontinued.
If the ALT and/or AST increases to > than 5 times the upper limit of normal, the dose of remdesivir should be withheld and not be restarted until the ALT and AST reduces to ≤ 5 times the upper limit of normal.

8.2.6 Preparation/Handling/Storage/Accountability

This information is found in the Study Procedure Modules.

8.3 Standard of Care Therapy

8.3.1 Thromboprophylaxis and diagnosis of thrombotic complications

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) in line with local clinical guidelines as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks. Standard approaches to thromboprophylaxis supported by high quality evidence include the use of low molecular weight heparin (for example, enoxaparin 0.5m/kg daily; high quality evidence), which is the preferred agent in some COVID-19 treatment guidelines.[78,79,80] However other standard approaches in accordance with local and institutional guidelines and the medical circumstances of an individual participant may also be considered, including the use of low (prophylactic) dose unfractionated heparin (high quality evidence), or higher doses than prophylactic doses as judged appropriate (low quality evidence). Specialist advice should be sought for participants who are pregnant.
An appropriate degree of clinical suspicion should be maintained for the development of new thrombotic complications, including deep venous thrombosis, pulmonary embolism, and other vascular events. Use of laboratory testing such as D-dimer may be confounded in the presence of acute COVID-19 infection. Consideration should be given to use of definitive imaging strategies for

diagnosis wherever possible (for example, limb ultrasonography, computed tomography pulmonary angiograms), as appropriate for an individual participant.

8.3.2 Other Standard Supportive Care

Participants will be offered supportive care of complications of COVID-19 as clinically appropriate for the individual.
This includes appropriate management of pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Such care includes treatment with anti-bacterial agents for patients believed to have bacterial infection (high quality evidence), and guidelines-compliant management of sepsis when it is present (moderate quality evidence).
For participants requiring intensive care measures, consideration should be given to supportive care measures including lung-protective ventilation for patients who require invasive ventilation (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence).[81,82]
As noted in section 8.1.3, hIVIG administration, use of diuretics may be considered as clinically appropriate to avoid or treat fluid overload.
Links to details of such care can be found in Appendix D.

8.3.3 Cautions and Contraindications

It is not recommended to use high dose chloroquine (600 mg twice daily) due to studies showing excess harm and no demonstrable benefit. (Hydroxy)chloroquine has no documented clinical benefit, and hence should not be used as part of SOC for COVID-19. Of note, the effectiveness of remdesivir may also be reduced if combined with (hydroxy)chloroquine, and hence it is not advisable to combine these two drugs; in patients who are on pre-existing hydroxychloroquine for therapy of other diseases such as systemic lupus erythematosus, specialist advice should be sought.[83]

8.3.4 Infection Control Measures

Minimum standards of protection to *reduce the risk of SARS-CoV-2 transmission* from trial participants to research personnel, participants in other trials, or patients treated in the same facility can be found in links displayed in Appendix D.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening/Baseline, Follow-up and Endpoint Assessments

Data collection at each visit is outlined below and summarized in Appendix B. Day 0 refers to the day on which randomization occurs and on which the hIVIG/placebo infusion is given. Screening and baseline assessments can be done on the same day. The term “baseline” refers to data that are collected prior to randomization.

9.1.1 Screening/Baseline Assessments

After obtaining informed consent, the following assessments are performed within 24 hours prior to randomization to determine eligibility and to collect baseline data:

- Confirm EITHER:
  - the positive SARS-CoV-2 test result (PCR or other NAT) was performed within 3 days prior to randomization or,
  - if more than 3 days prior to randomization, the prospective participant demonstrates progressive disease suggestive of ongoing SARS-CoV-2 infection

- Take a focused medical history, including the following information:
  - Demographics including age, biological sex
  - Day of onset of COVID-19 signs and symptoms
  - History of chronic medical conditions, including targeted conditions for outcome analysis
  - Medication allergies
  - Current use of targeted concomitant medications
  - Prior use of monoclonal antibody treatment or SARS-CoV-2 vaccine trial participation

- Perform a focused physical examination:
  - Height and weight;
  - Vital signs: Blood pressure, heart rate
  - Respiratory rate, oxygen requirements and saturation

- Obtain blood for local laboratory evaluations:
  - White blood cell count
  - Hemoglobin
  - Platelets
  - Lymphocytes
  - C-reactive protein (CRP)
  - Serum creatinine
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)

- Determine disease status at entry (includes SpO2, oxygen requirements) for the constituents of the ordinal outcome categories.

- Plasma and serum specimens for central testing for immunoglobulin levels, SARS-CoV-2 neutralizing antibody determination and storage for future COVID-19 related research (four [4] 1 mL aliquots of serum and four [4] 1 mL aliquots of plasma). Two 9mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

- Mid-turbinate swab for determination of SARS-CoV-2 viral load in central laboratory

- Urine or serum pregnancy test (in women of childbearing potential) (not an exclusion criterion but performed to ensure any pregnancy is recognized at entry)

Note: If a woman is either postmenopausal (i.e., is age ≥ 45 years and has had ≥12 months of spontaneous amenorrhea) or surgically sterile (i.e., has had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation), she is not considered to be of childbearing potential.

The overall eligibility of the patient for the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.
Participants who qualify will be randomized within 24 hours of obtaining the baseline assessments.
Post-randomization on Day 0 the following will be recorded:

- Adverse events of any grade severity prior to starting the infusion
- Start and stop times of the infusion of hIVIG/placebo and remdesivir
- Infusion related reactions

- Whether the completion of the infusion was as planned
- Medication used prophylactically or therapeutically to manage infusion-related reactions
- Adverse events (AEs) of any grade severity during and for 2 hours after the infusion

9.1.2 Follow-up assessments

Participants will be followed through Day 28 following randomization for collection of study data. Clinical data targeted to components of the primary and secondary endpoints will be collected daily during hospitalization, and at scheduled visits to day 28 after discharge. This will include discharge status, development of key medical conditions, vital signs including SpO_2. On Day 7, interim targeted physical exam and concomitant medications will be collected along with the results of blood tests for serum creatinine, ALT or AST, white blood cell count, hemoglobin, platelets, lymphocytes, and C-reactive protein (CRP).

AEs of any grade severity will be collected on Day 0 prior to infusion and on Days 1, 3, 7, and 28 (AEs present on those days). Incident AEs of grade 3 or 4 severity will be collected through Day 7 and all SAEs will be collected through Day 28.

The primary ordinal outcome measure will be assessed daily while the participant is hospitalized and on Day 3, 5, Day 7 (primary endpoint), Day 14 and Day 28 for all participants. Items necessary for determination of NEWS will be collected on Day 3. The Borg dyspnea score will be evaluated at baseline and day 7.

For participants who are no longer hospitalized, in-person visits will be done on study days where blood is collected (Days 1, 2, 3, 7, and 28). For other visits (Day 5 and Day 14), contact with the participant for the purpose of study data collection may be performed by telephone, recognizing that certain components of the endpoints (e.g. SpO_2) are not likely available from outpatients. Other information as possible will be gathered.

On Days 1, 2, 3, 7, and 28, plasma and serum samples (four 1 mL aliquots of both plasma and serum at each visit) will be obtained for central testing of antibody levels (including neutralizing antibodies) to SARS-CoV-2 and for storage for future related research. Two 9 mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

In consenting participants at selected sites (determined at site level prior to opening; selected sites will endeavor to follow all participants to day 90), plasma and serum samples (four 1 mL aliquots of both plasma and serum) will be obtained at Day 90 for central testing of antibody levels (including neutralizing antibodies) to SARS-CoV-2 and for storage for future related research. Two 9mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

For patients co-enrolled on INSIGHT 004 Genomics, where genomics samples have not already been collected prior to enrollment in this protocol they may be collected at any time during follow-up.

9.1.3 Stored Samples and Future Research

The plasma and serum specimens collected as outlined above and the inoculum from the baseline mid-turbinate nasal swab will be stored at a central specimen repository in the US. In addition to the specified testing to be done per protocol, the specimens will be available for later use in research concerning COVID-19, SARS-CoV-2, and the impact of the study treatment. Proposed research utilizing these specimens will be reviewed and approved by the trial oversight committee. Results of research tests on individual specimens will not be given to participants or their clinicians. Aggregate research results will be made available.

10 SAFETY REPORTING

The safety evaluation of the study intervention includes several components, all of which will be regularly reviewed by the independent DSMB. For this protocol, the term "study intervention" refers to the hIVIG/placebo and to remdesivir.

With the exception of infusion related reactions of any grade, which are only collected for the hIVIG/placebo, all other AEs are collected for the study intervention (either the hIVIG/placebo or study-provided SOC treatment). Selected events will be reported to regulators and IRBs/ethics committees in addition to being regularly reviewed by the DSMB.

The following information will be collected to evaluate safety:

- Infusion-related reactions of any grade severity during and within 2 hours post-infusion of the hIVIG/placebo.
- Clinical AEs of any grade severity will be collected on Days 0, 1, 3, 7, and 28 (AEs present on those days).
- Targeted laboratory abnormalities of any grade severity at Day 7.
- Incident grade 3 and 4 clinical adverse events occurring through Day 7 (isolated laboratory abnormalities that are not associated with signs or symptoms are not recorded).
- Clinical events that are collected as part of the primary ordinal outcome or as secondary outcomes through Day 28. These are protocol exempt events and are not reported as SAEs unless they are considered as related to the study intervention.
- Serious adverse events, including laboratory-only serious events, considered related to the study intervention (either the hIVIG/placebo or a study-provided SOC treatment) through Day 28.
- Serious adverse events that are not collected as part of the primary ordinal outcome or as a secondary outcome through Day 28.
- Unanticipated problems through Day 28.
- Deaths through Day 28.

An overview of safety data collected during the study is given in Table 2.

Table 3. Adverse Event Data Collection Overview

	Day 0*	Infusion +2 hrs	Day 1	Day 3	Day 5	Day 7	Day 14	Day 28
Infusion-related reactions and symptoms		X						
Incident Grade 3 and 4 clinical AEs**			Collected through day 7					
Clinical AEs of any grade severity	X	X	X	X		X		X
Targeted laboratory abnormalities of any grade						X		
Targeted clinical events collected as study endpoints***				Collected through Day 28				
Serious clinical AEs not reported as a study endpoint***				Collected through Day 28				
Unanticipated problems				Collected through Day 28				
Any serious adverse event related to study-provided treatment				Collected through Day 28				

* pre-infusion AE collection
** Incident grade 3 and 4 AEs are *new* (not present at baseline) AEs or AEs that have *increased in grade*
*** see section 10.2.5 for specific events

Definitions and methods of reporting each type of event are given below.

10.1 Definitions

10.1.1 Adverse Event (AE)

An adverse event is any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE. AEs are reported on the appropriate case report form (CRF) when prompted.

10.1.2 Criteria for Seriousness

Events are serious if they lead to one of the following outcomes:

- Death
- Life-threatening (i.e., an immediate threat to life)
- Hospitalization or prolongation of hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical evens that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

10.1.3 Unanticipated Problems

An unanticipated problem (UP) is any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure (IB) or other study documents; and
   b. the characteristics of the population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Furthermore, a UP could be an expected event that occurs at a greater frequency than would be expected based on current knowledge of the disease and treatment under study. The DSMB providing oversight to the study may make such an assessment based on an aggregate analysis of events.

10.1.4 Severity

The investigator will evaluate all AEs with respect to both seriousness (results in outcomes as above) and **severity** (intensity or grade). AEs will be graded for severity according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, (also known as the DAIDS AE Grading Table; see Appendix D for the URL).
For specific events that are not included in the DAIDS AE Grading Table, the generic scale below is to be used:

TABLE 4. GENERIC AE GRADING SCALE

Grade 1	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Symptoms causing inability to perform usual social and functional activities
Grade 4	Symptoms causing inability to perform basic self-care functions, or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Events resulting in death

10.1.5 Causality

Causality refers to the likelihood that the event is related to the study intervention. It will be assessed for SAEs and UPs. This assessment will be made for both the agent under investigation (hIVIG) and the study-provided background therapy of remdesivir using the following guidelines:

- Reasonable possibility – There is a clear temporal relationship between the study intervention and the event onset, and the AE is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- No reasonable possibility – There is no evidence suggesting that the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

The causality assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.1.6 Expectedness

Expectedness will be assessed for SAEs using the Reference Safety Information section of the IBs for the hIVIG and remdesivir.
The expectedness assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.2 Schedule for Data Collection and Reporting of Specific Events

10.2.1 Infusion-related reactions

Infusion related signs/symptoms of any grade that are new or have increased in grade compared to their pre-infusion level are reported for the hIVIG/placebo if they occur during or within 2 hours post infusion. Any infusion related reaction assessed as meeting SAE criteria will be reported as an SAE. Similarly, any grade 3 or 4 infusion related reaction will be reported as an AE.

10.2.2 Targeted Laboratory abnormalities

Selected laboratory tests are performed prior to infusion and on Day 7. These values are associated with a severity grade centrally using the laboratory test results reported on the eCRFs with normal ranges, and with the DAIDS AE Grading Table.

Other laboratory abnormalities identified in the course of the participant's clinical care are not reported as AEs (e.g., an isolated elevated glucose level) unless they are associated with a specific clinical diagnosis/syndrome, in which case they are reported if they meet the reporting criteria of one of the other safety outcomes. In addition, if an isolated laboratory test result meets SAE reporting criteria (e.g., a serious event related to the study intervention), it should be reported as an SAE.

10.2.3 Clinical adverse events of any grade severity on Days 0, 1, 3, 7 and 28

On Day 0 prior to infusion and on Days 1, 3, 7 and 28 the prevalence of AEs of any grade severity that the participant reports that day will be collected. This information supplements the information on grade 3 and 4 events through Day 7 that is collected.

10.2.4 Incident Grade 3 and 4 clinical adverse events through Day 7

From the time of randomization on Day 0 through Day 7, clinical events reaching Grade 3 or 4 severity level will be reported as AEs unless they are a protocol-specified exempt event (see below).

Any medical condition of grade 1 and 2 that is present at Day 0 will be reported as an AE if it increases to Grade 3 or 4 by Day 7.

Isolated laboratory abnormalities will not be recorded on the eCRF for grade 3 and 4 events. However, as noted above, if an isolated laboratory result meets SAE criteria, it should be reported as an SAE.

10.2.5 Protocol-specified exempt events

These events are listed in sections 4.1 and 4.2 and are collected systematically during study follow-up on eCRFs. These events will not be reported as Grade 3 or 4 AEs even if they occur at that severity grade. They also will not be reported as SAEs, even if they meet one or more of the criteria for seriousness, ***unless the investigator considered that there was a reasonable possibility that the study intervention caused the event***. These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.
The following are **protocol-specified exempt events**:

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)

- Arterial or deep venous thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, noninvasive ventilation, or invasive ventilation
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Acute delirium
- Disseminated intravascular coagulation
- Microbiologically-proven severe infection (not including SARS-CoV-2)

10.2.6 Reportable SAEs

Reportable SAEs for this study are:

- Serious clinical AEs not reported as a study endpoint; and
- Any serious AE related to the study intervention

Deaths, life-threatening events, and others SAEs considered related to the investigational agent, irrespective of whether the event is mentioned above as a protocol-specified exempt event, that occur from the time of infusion of the hIVIG/placebo begins through the Day 28 visit must be reported by sites on the SAE eCRF to the sponsor via the INSIGHT Safety Office. These events must be reported **within 24 hours of site awareness.** All other SAEs must be reported within 3 days of site awareness.

SAEs are followed until the outcome of the SAE is known. If the outcome of an SAE is still unknown at the time of the final follow-up visit (Day 28), the outcome will be entered in the database as "unknown."

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are assessed as related to a study-provided treatment and are unexpected per the Reference Safety Information of the IB for that treatment. SUSARs are reported from the INSIGHT Safety Office to applicable regulators in an expedited fashion. SUSARs that result in death or are immediately life-threatening are reported to regulators within 7 calendar days of receipt. All other SUSARs are reported to regulators within 15 calendar days. The INSIGHT Safety Office will generate a Safety Report for each SUSAR for distribution to investigators and other parties. Investigators are responsible for submitting Safety Report summaries that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

Safety reports for SUSARs indicate the study intervention (i.e., are unblinded).

SAEs that are not protocol-specified exempt events and that are not related to the study intervention (investigational agent or treatment provided as SOC) must be reported on the SAE eCRF within 3 days of site awareness.

10.2.7 Unanticipated Problems (UPs)

UPs must also be reported via the appropriate eCRF to the INSIGHT Safety Office no later than 7 calendar days after site awareness of the event. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

10.2.8 Deaths

Deaths that are considered unrelated to the study intervention are reported on the eCRF for deaths. Deaths considered related to the study intervention (investigational agent or study-supplied SOC) must also be reported as an SAE.

10.3 Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs, making an independent assessment of causality and expectedness, preparing sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder.

10.4 Treatment Interruption or Discontinuation

An infusion may be interrupted or discontinued at any time at the participant's request or at the discretion of the Investigator or Sponsor. Reasons for interruption or discontinuation and the total volume administered will be recorded.

10.5 Halting Rules

The sponsor medical monitor or the DSMB may request that enrollment be halted for safety reasons (e.g., unacceptably high rate of infusion-related reactions or other unanticipated AEs). As a guideline, the DSMB will be asked to consider halting enrollment if more than 5% of participants experience a grade 3 or 4 infusion AE or if more than 10% do not complete the infusion due to an AE(s). This will be informed by the lower bound of the confidence interval. If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed.
The IND holder and sponsor, in collaboration with the protocol chair and the DSMB will determine if it is safe to resume the study. The sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRBs/ethics committees of the decision to resume the study.

11 EVALUATION

11.1 Data Analysis

A brief summary of the statistical considerations is provided here, full details will be described in a statistical analysis plan (SAP) that will be finalized prior to unblinding of the data. Data unblinding will either occur after a recommendation from the independent DSMB or after all participants complete the Day 28 follow-up visit.
The primary analysis will be by intention to treat comparing all participants randomized to hIVIG with those randomized to placebo. The different hIVIG products will be pooled for this analysis.
This analysis plan applies to the primary efficacy and safety outcomes, and important secondary outcomes.
For the primary endpoint, the percent of participants in the 7 categories of the ordinal outcome will be compared. A proportional odds model will be used to estimate a summary OR.[84] The model will include a single indicator for treatment, indicators for the participant's clinical state at entry (categories of ordinal outcome), and its two-way interactions with the six cut-offs. The model will also include indicators for which of the four hIVIG product/matching placebo product was used and their two-way interactions with the six cutoffs for each of the six cumulative odds of improvement. A test for the proportional odds assumption will be carried out. Even if the proportional odds assumption is violated, the overall summary OR will be the basis for inference based on the primary

analysis. In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for each of the six dichotomized definitions of improvement that can be formulated from the components of the ordinal outcome.

For the primary endpoint analysis only, multiple imputation based on baseline and follow-up data will be used to estimate participant status at day 7 for participants with missing follow-up data. For this imputation the following baseline covariates will be considered in addition to an indicator for treatment group: age, geographic region, clinical status based on the ordinal outcome at enrollment, presence of comorbidities, NEW score, and oxygen saturation. In addition to these baseline covariates, the last NEW score and the last value of the ordinal outcome measured will be used in the imputation.

We will impute ten data sets; parameter estimates (e.g., the summary odds ratio) from the 10 multiply imputed datasets will be combined using Rubin's combining rules. The imputation will take into account whether partial information concerning the ordinal outcome at Day 7 is known (e.g., it is known that the patient is alive and no longer hospitalized and receiving supplemental oxygen and only which of the best 2 categories the patient is in is unknown).

Categories 3 and 4 of the primary ordinal outcome differ in part by the amount of supplemental oxygen required, and a single cut point (4 liters/minute) defines the difference. Since, together, these 2 categories of the ordinal outcome are expected to include approximately 30% of participants, an analysis that combines these two categories (a 6-category ordinal outcome) will be carried to supplement the primary analysis using the same methods described above.

SAEs and grade 3 and 4 events (excluding isolated laboratory abnormalities) will be classified by system organ class according to MedDRA®. The composite of incident grade 3 or 4 events, an SAE or death over 7 days of follow-up will be summarized with Mantel Haenszel chi-square tests stratified by hIVIG/matched placebo group. Time to event methods (e.g., Kaplan-Meier estimates and Cox regression) will be used to summarize deaths and SAEs through Day 28.

Safety analyses will also include infusion reactions collected during or within 2 hours after the infusion of hIVIG/placebo. Percentages of participants who experience infusion reactions or prematurely terminated infusions will be summarized by treatment groups, and Cochran Mantel Haenszel tests will be used to compare groups.

For secondary endpoints such as time to discharge and time to the 2 most favorable categories of the primary ordinal outcome, time to event methods that take into account the competing risk of death will be used. Specifically, Gray's test with rho=0, the Fine-Gray model, and the Aalen-Johansen estimator for the cumulative incidence curve are the competing risk equivalents to the log-rank test, Cox proportional hazards model, and the Kaplan-Meier estimator for the cumulative proportion of participants with the event, respectively.[85,86,87]

Longitudinal random effects models will be used to summarize log-transformed antibody level differences between the hIVIG and placebo groups at Days 1, 3, 7 and 28 of follow-up. Baseline antibody levels will be included as a covariate in these models. For the subset of participants for whom blood is collected at Day 90, antibody levels will be compared.

Subgroup analyses for the primary 7-category ordinal outcome (primary efficacy outcome), as well as for the primary safety outcome (Grade 3 and 4 events, SAE or death through Day 7) will be performed to determine whether the treatment effect (hIVIG versus placebo) differs across baseline-defined subgroups. The key subgroup analysis is by duration of symptoms at study entry. For the subgroup of participants in the lower 3 quartiles, the OR for the primary ordinal outcome at Day 7 is hypothesized to be greater than the overall result and those in the upper quartile (longest duration of symptoms at study entry). The difference in ORs will be compared for those in the lower 3 quartiles versus the upper quartile. In addition, the trend across the four quartiles will be assessed.

The following other baseline-defined subgroups will be considered: age, gender, race/ethnicity, BMI, history of chronic conditions, geographic region, hIVIG product administered, neutralizing antibody level, baseline upper respiratory SARS-CoV-2 viral load, oxygen saturation level, ordinal outcome category at entry, NEWS, dyspnea severity, and a disease progression score. *A priori* we have no reason to believe the clinical efficacy or safety of hIVIG compared to placebo will be substantially different in any of the subgroups considered. These analyses will be approached cautiously because random differences can occur (type 1 error is inflated due to the number of subgroups examined), confounding due to other factors in defining each subgroup is possible, and power is limited. To partially control the inflation of type 1 error and to guide the interpretation of subgroup summaries, an overall test of heterogeneity of treatment effect (treatment by subgroup interaction) will be constructed to assess how strong the evidence is that the treatment effect varies across the baseline subgroups.

In addition to these subgroup analyses, a subgroup analysis by lot potency will be carried out. The aim of this analysis will be to determine if the primary outcome varies by range in potency among the various lots of hIVIG used. The potency of each lot will be measured by a central laboratory. Participants in the placebo group will be classified according the lot potency they would have received had they been randomly assigned to the hIVIG group. The methods used for this subgroup analysis will be as described above.

If there is a beneficial effect of hIVIG compared to placebo, in order to support regulatory claims for each hIVIG product used, sensitivity analyses comparing each hIVIG product to its matched placebo will be carried out for key efficacy and safety endpoints. These analyses will consider that each hIVIG product will be used by a different group of clinical sites (i.e., each comparison will represent a small multi-center trial), and that power will likely be very low for all of the outcomes. These analyses are referred to as sensitivity analyses because overall therapeutic efficacy and safety will be based on the pooled analysis of the four hIVIG products with placebo.

If the hIVIG and placebo groups differ for the primary ordinal outcome at Day 7, the extent to which a favourable treatment difference for hIVIG can be explained by antibody levels measured at baseline and Days 1, 3, 7, and 28 of follow-up will be investigated.

11.2 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

11.3 Data Monitoring by an Independent DSMB

An independent DSMB will review the study prior to initiation and at frequent intervals during the trial. The DSMB will review safety data for first 20 to 30 participants randomized after they have been followed for 7 days. Thereafter, the DSMB will review safety data at 30 day intervals. Safety summaries will include the safety outcomes in section 4.2. The DSMB may also convene additional reviews as necessary. After each meeting they will recommend continuing the study as planned, modifying the study, or terminating the study.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. As a guideline, asymmetric boundaries will be

provided to the DSMB to monitor the primary endpoint comparison. For monitoring early benefit of hIVIG, the Lan-DeMets spending function analogue of the O'Brien-Fleming boundary will be used[88,89]; a Haybittle-Peto type boundary using a 2.5 standard deviation (SD) difference for the first 100 participants enrolled and 2.0 SD afterwards will used as a guideline for harm.[90] The Lan-DeMets boundary used will be chosen to preserve a 1-sided 0.025 level of significance. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the number of participants who have completed 7 days of follow-up divided by the target sample size (currently 500). With this guideline for early termination, less evidence will be required for crossing a boundary for harm than benefit.

Futility analyses will also be presented to the DSMB for the primary endpoint comparison by the unblinded statisticians based on conditional power estimates. Conditional power incorporates the observed results by treatment group thus far (and uses the originally assumed treatment effect for future data) to calculate the conditional probability of obtaining a significant result by the end of the trial. If conditional power, given the observed data and assuming the originally hypothesized treatment effect thereafter, is less than 20% after 50% of information (primary endpoints) is available, consideration should be given to stopping the trial.

A SAP will be developed to guide DSMB interim analyses. The SAP will include recommended analyses for the DSMB to consider in addition to the primary endpoint analysis in the event early termination for efficacy or futility is considered. For example, the primary endpoint at Day 7 for the key previously defined subgroup of those in the lower 3 quartiles of symptom duration at entry will be routinely summarized in the closed interim report to the DSMB.

All of these analyses will consider the timeliness of reporting primary outcome data, secondary efficacy and safety outcomes, and subgroups.

12 PROTECTION OF HUMAN SUBJECTS AND ETHICAL CONSIDERATIONS

12.1 Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). It is anticipated that potential participants will be recruited by the site investigators and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care providers in these settings.

Prior to the initiation of the study at each clinical research site, the protocol, informed consent form and any participant information materials will be submitted to and approved by a central/national IRB or EC and/or the site's local IRB/EC. Likewise, any future amendments to the study protocol will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register for this study before screening potential participants and must register for any protocol amendments. Specific protocol registration information can be found in the Study Procedure Modules.

12.2 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. For patients who are incapacitated, informed consent may be obtained from a legally authorized representative. Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated. Should the individual regain capacity during the study, their direct consent should be obtained at the earliest opportunity. Electronic consent methods may be used if

approved by the IRB/EC. Procedures for recording of written consent may be modified for infection control purposes as approved by the IRB/EC.

12.3 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

12.4 Regulatory Oversight

Sites in the US will conduct this trial under the terms of the IND and will adhere to FDA regulations found in 21 CFR 312, Subpart D. Sites in countries other than the US will not conduct the trial under the IND. All sites will conduct the trial in accordance with the requirements of GCP as codified in their local law and regulation, under the oversight of their institution and competent regulatory authority.

A specific protocol monitoring plan will be developed. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

APPENDIX A-1 SAMPLE INFORMED CONSENT FORM (follow-up ending Day 28)

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

Sponsored by: The University of Minnesota

A Multicenter Study of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Full Title of the Study: **An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19**

CONSENT FOR PARTICIPATING IN A NATIONAL INSTITUTES OF HEALTH (NIH)-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

OHRP Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

oin.

This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question?

We are trying to find out if giving anti-coronavirus hyperimmune intravenous immunoglobulin (hIVIG) can help people in the hospital with COVID-19 have fewer bad effects from COVID-19, get better faster, and get out of the hospital faster. Anti-coronavirus hIVIG contains antibodies against the virus that causes COVID-19.

We think this will help your body fight COVID-19 better, but we are not sure and so we are doing this study. We are asking you to join the study because you are in the hospital with COVID-19.

What do you have to do if you decide to be in the study?

The study staff at your hospital will make sure it is safe for you to be in the study. They will check your medical history. They will look at routine medical test results that you are probably already having done regularly in the hospital.

If you agree to be in the study, we will randomize you to one of two study groups. It will be up to chance, like flipping a coin, and you will have an equal chance (50/50) of getting either hIVIG or a saline placebo (a salt solution). Your doctor will not decide which of these you will get, and neither you nor your doctor or study staff will know what treatment you are getting.

You will get the usual supportive care for COVID-19 recommended by your hospital, just as you would if you do not join the study. In addition, the study will supply an antiviral drug called remdesivir, unless there is a medical reason that you should not get remdesivir. Remdesivir has been shown in other studies to improve recovery from COVID-19 in persons who have been hospitalized.

You will get the study treatment (hIVIG or placebo) once, on the day you join the study. You will get it by a drip through a tube attached to a needle in your arm (intravenously). It will take about 1-2 hours, though it may sometimes take longer depending on how your body reacts to the infusion. This is the only thing in the study that is experimental. Everything else is part of routine medical care for someone in the hospital with COVID-19.

You will get remdesivir once a day intravenously for up to 10 days while you are in the hospital, as part of standard care for your COVID-19.

You will also need to agree not to participate in any other COVID-19 study for the first 7 days you are in this study.

You will be in the study for 28 days. We will check on your health every day while you are in the hospital, and at regular intervals once you leave the hospital.

We will collect the following information at these times:

Up to 1 day before you get study treatment	Day 0 (the day you get study treatment)	Day 1, Day 2, and Day 3	Day 5 and Day 14	Day 7	Day 28
• Informed consent • Blood tests to check your health • Check to see how you are feeling • Pregnancy test • Your medical history	• Infusion of study treatment • If you are taking certain medicines • Blood for future research (18 mL, about 2 tablespoons) • Nasal swab for future research	• How you are feeling • Blood for future research (18 mL, about 2 tablespoons)	• How you are feeling	• How you are feeling • If you are taking certain medicines • Blood tests to check your health • Blood for future research (18 mL, about 2	• How you are feeling • Blood for future research (18 mL, about 2 tablespoons)

				tablespoons)	

Day 28 is the last day you will be in the study.
We may need to get some information from your medical record. By signing this consent, you also agree to let us get information for this study from your medical record.

We will send the information we collect to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that you or the study staff chooses will be used on your information. We never give information that could identify you, such as your name, address, birth date, or medical record number, to anyone outside this site. The study staff at this site is responsible for keeping your identifying information safe from anyone who should not see it. We will send the blood samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we hope will be many years. We will use the samples in the future for tests to help understand more about COVID-19 and how people respond to treatment for COVID-19. You and your doctor will not get any results from these tests. We will not test your DNA (your genes). We will not sell your samples and they will not be used for research aimed at making money (commercial research). The samples will not have any information connected to them that could identify you.

Why would you want to be in the study?

If you get the hIVIG, it may help you get better faster, although we do not know that for sure. Remember that half (50%) of the people in this study will not get the hIVIG.

By being in this study, you help doctors know more about how to treat COVID-19 in people in the hospital. Because so many people are getting hospitalized with COVID-19, this could be a big impact if a treatment proves to be effective.

Why would you NOT want to be in the study?

Only half (50%) of the people in this study will get the hIVIG. You may not get the hIVIG. If hIVIG turns out to be a good treatment, you would not get that benefit. It's also possible that if you do get hIVIG, it may turn out not to be useful, or may cause side effects that are harmful to you.

What are the side effects of the study hIVIG treatment?

hIVIG is usually very safe to give. Similar immunoglobulin preparations have been used in many different diseases over many years, but immunogloblin prepared solely from individuals who have recovered from COVID-19 has not been studied before. In an earlier study of influenza hIVIG in people in the hospital with the flu, over 150 people got hIVIG. There were no serious problems that occurred in people because they got hIVIG.

All treatments cause side effects, and you may have some side effects from hIVIG. About 1% to 10% (1 in 100 people to 1 in 10 people) who get hIVIG get a fever, chills, nausea, vomiting, dizziness, shortness of breath, rash, hives, or headache, but these are usually not serious. These can happen during the infusion or afterwards and usually go away on their own or with short-term treatment. Although IVIG has been very safe for people with other diseases, less than 0.1% (less than 1 in 1,000) of people taking other types of IVIG for other illnesses have had very serious reactions to it, including a kind of lung injury called TRALI.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

In some laboratory studies, infusions of antibodies have made infections with viruses similar to the virus that causes COVID-19 worse. This is a very unlikely but possible side effect of the treatment infusion in this study, and you will be closely monitored for any signs of this effect.

It is also possible that getting the study treatment infusions could cause problems with your health because of the amount of fluid given to you for the study treatment if you have some other health condition that affects how your body handles fluids. You will get up to about 400 mL of fluid for hIVIG or placebo, and about 100mL each day for remdesivir if you receive it

Some people may have some side effects after the hIVIG infusions. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the benefits and risks or side effects of remdesivir treatment?

Remdesivir was recently shown to help people who are in the hospital with COVID-19 to get better faster than people who got a placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study. If your doctor considers that remdesivir is not a suitable treatment for you, you can still join this study, and you will receive hIVIG or placebo without remdesivir. For example, remdesivir might be unsuitable for you if you have serious liver or kidney problems or an allergy to it.

The most common side effects of remdesivir include abnormal liver function test results, abnormal kidney function test results, fever, elevated blood sugar, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver and kidney function tests may last a few days or longer but came back to normal levels over time.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

Some people may have some side effects after the infusion of remdesivir. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the side effects of the other study procedures?

As shown in the table of what will happen at each visit, you will have some extra blood drawn for laboratory testing and storage. You will also have an extra swab of your nose and throat that would not be done if you are not in the study. The risks and discomforts of these extra blood draws and swab are no different than what you would have if they were performed as part of your regular hospital care for COVID-19.

Additional information:

Here is some additional information about the study that may help you make your choice about whether you want to be in the study.

The US National Institutes of Health (NIH), an agency of the US Federal government, is paying for this study. Because public money is paying for the study, we are required to comply with all rules and regulations about research. We are doing this study according to internationally recognized standards of research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 500 people around the world.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time by telling someone on the study team that you want to stop being in the study. If you choose not to join or to stop, your regular medical care will not change.

If we get any new information that might change whether you want to join or stay in the study, we will tell you right away.

Your study participation may be stopped without your consent if:

- The groups overseeing the study decide the study should be stopped;
- Your study team believes that being in the study is no longer in your best interests.

If your participation is stopped, you will still get the usual care given at your hospital for COVID-19.

If you do not want to be in this study, you will still get the usual care to treat COVID-19. However, you cannot get the hIVIG treatment, because it is experimental.

What are the costs to you?
We will give you the study treatment (hIVIG or placebo) at no cost. We will also give you remdesivir at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

THE NEXT PARAGRAPH IS FOR UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location

Will you be paid to be in the study?
We will compensate you for your time and inconvenience participating in the study. *[Specific details to be completed by site.]*
What if you are hurt as part of this study?
If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.

What happens to the blood samples and respiratory swabs?
We will send the blood and respiratory swab samples to a central laboratory in the United States of America. You and your doctor will **not** get the results of any tests done on these samples.
The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The nasal swab will measure how much virus you have in your respiratory system.
Any blood samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19. You and your doctor will **not** get any results from these tests. Some of the blood will also be given to the company that made the hIVIG to help them learn more about its effects.
How do we protect your privacy?
We will take every reasonable step to keep your health information private and to keep anyone from misusing it.
Your information (data) and samples will not be identified by name, or in any other way, in anything published about this study.
We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.
These people may see your medical and research information at your site:

- the *[insert the name of the hospital/clinic]* ethics committee (institutional review board [IRB]);
- the sponsor, other study research staff, and study monitors
- US and other participating countries' health regulatory agencies
- the US National Institutes of Health which is funding the study

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we are required to make sure that people not involved with this study cannot see your research and medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the UMN in the US through a secure application. By signing this consent, you agree to have your data sent to UMN. No information that could directly identify you is sent to UMN. This is called "pseudonymized data." Access to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

Your study data will be shared with the regulators that oversee the studies, as required by law. Your study data will also be shared with the drug company that provides the hIVIG to help them develop the drug.

UMN may share your data and specimens with other people who study COVID-19. UMN will remove any information that could possibly be used to identify you before sharing. This is called "anonymizing the data." We will not ask you for additional consent for this sharing. UMN will only share data and specimens for research projects that are approved by the group that is conducting this study.

This study has a Certificate of Confidentiality from the US Federal government. This means that UMN cannot share any data it has about you with national, state, or local civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov as required by U.S. law, and on the EudraCT website (https://eudract.ema.europa.eu/). These websites will not include your name or any other direct identifiers such as your contact information. These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

[Note for US sites: The following brief HIPAA authorization is provided. Your site-specific consent should be modified to reflect the HIPAA authorization language requirements at your site.]

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

____**Yes**, I agree to the collection and processing of my personal data.

____**No**, I do not agree to the collection and processing of my personal data.
It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this research and have a chance to get the experimental treatment if we cannot collect and use your data.
[The following section (up to "What if you have problems or questions?") is for countries subject to the General Data Protection Regulation (GDPR) or similar legislation requiring this information. It should only be included in consents for sites subject to such legislation. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced to meet the requirements of a particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]
What are your rights regarding your data?
The UMN is a public research university, and this study is funded primarily by a grant from the US Federal government. UMN and the study funding source require the sponsor (UMN) to follow regulations and policies that are meant to protect your privacy. UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from people in Europe.

There is no specific independent supervisory authority overseeing the processing of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

The GDPR gives you additional rights which we would like to inform you about below.

Right to Information
You have the right to know what data about you is being processed. You can also get a free copy of this data provided.

Right to Correction
You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization
The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

Right to Restriction of processing
Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study physician or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability

You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction
You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

Right to Withdrawal of this consent
You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your investigator. If you withdraw your consent this will not affect the lawfulness of the data processing that has been or will be done with data collected until you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:

Person responsible for data collection at the study center:	
Name:	
Address:	
Phone:	
Email	

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:

Data protection authority responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

<u>What if you have problems or questions?</u>
If you ever have questions about this study, or about the storage or use of your data or samples, or if you are hurt by being in the study, contact:

- *[name of the investigator or other study staff]*
- *[telephone number of the above]*

If you have questions about your rights as a research participant, you can call:

- *[name or title of person on the ethics committee (IRB) or other organization appropriate for the site]*
- *[telephone number of the above]*

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 013 STUDY (Inpatient Treatment with Anti-Coronavirus Immunoglobulin, ITAC)

I have read the consent or have had it explained to me. I am satisfied that I understand the information. By signing this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

If you agree to be in this study, please sign below.

_____ Date: _____
Signature of participant

_____
Printed name of participant

_____ Date: _____
Signature of investigator/designee

_____
Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____
Signature of Legally Authorized Representative (LAR)

_____
Printed name of LAR

_____
Relationship of LAR to Participant
(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law)

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the subject, and the subject indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____
Signature of witness

_____
Printed name of witness

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

If no-touch / electronic consent is used, the participant must be provided with a copy of the consent in a manner appropriate to the method used to obtain it. A record of the act of consent must also be appropriately retained in the participant's medical record.

APPENDIX A-2 SAMPLE INFORMED CONSENT FORM for sites collecting Day 90 Samples

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

Sponsored by: The University of Minnesota

A Multicenter Study of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Full Title of the Study: **An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19**

CONSENT FOR PARTICIPATING IN A NATIONAL INSTITUTES OF HEALTH (NIH)-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

OHRP Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

oin.

This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question?

We are trying to find out if giving anti-coronavirus hyperimmune intravenous immunoglobulin (hIVIG) can help people in the hospital with COVID-19 have fewer bad effects from COVID-19, get better faster, and get out of the hospital faster. Anti-coronavirus hIVIG contains antibodies against the virus that causes COVID-19.

We think this will help your body fight COVID-19 better, but we are not sure and so we are doing this study. We are asking you to join the study because you are in the hospital with COVID-19.

What do you have to do if you decide to be in the study?

The study staff at your hospital will make sure it is safe for you to be in the study. They will check your medical history. They will look at routine medical test results that you are probably already having done regularly in the hospital.

If you agree to be in the study, we will randomize you to one of two study groups. It will be up to chance, like flipping a coin, and you will have an equal chance (50/50) of getting either hIVIG or a saline placebo (a salt solution). Your doctor will not decide which of these you will get, and neither you nor your doctor or study staff will know what treatment you are getting.

You will get the usual supportive care for COVID-19 recommended by your hospital, just as you would if you do not join the study. In addition, the study will supply an antiviral drug called remdesivir, unless there is a medical reason that you should not get remdesivir. Remdesivir has been shown in other studies to improve recovery from COVID-19 in persons who have been hospitalized.

You will get the study treatment (hIVIG or placebo) once, on the day you join the study. You will get it by a drip through a tube attached to a needle in your arm (intravenously). It will take about 1-2 hours, though it may sometimes take longer depending on how your body reacts to the infusion. This is the only thing in the study that is experimental. Everything else is part of routine medical care for someone in the hospital with COVID-19.

You will get remdesivir once a day intravenously for up to 10 days while you are in the hospital, as part of standard care for your COVID-19.

You will also need to agree not to participate in any other COVID-19 study for the first 7 days you are in this study.

You will be in the study for 90 days. We will check on your health every day while you are in the hospital, and at regular intervals once you leave the hospital.
We will collect the following information at these times:

Up to 1 day before you get study treatment	Day 0 (the day you get study treatment)	Day 1, Day 2, Day 3, Day 28	Day 5 and Day 14	Day 7	Day 90
• Informed consent • Blood tests to check your health • Check to see how you are feeling • Pregnancy test • Your medical history	• Infusion of study treatment • If you are taking certain medicines • Blood for future research (18 mL, about 2 tablespoons) • Nasal swab for future research	• How you are feeling • Blood for future research (18 mL, about 2 tablespoons)	• How you are feeling	• How you are feeling • If you are taking certain medicines • Blood tests to check your health • Blood for future research (18 mL, about 2 tablespoons)	• Blood for future research (18 mL, about 2 tablespoons)

We may need to get some information from your medical record. By signing this consent, you also agree to let us get information for this study from your medical record.

We will send the information we collect to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that you or the study staff chooses will be used on your information. We never give information that could identify you, such as your name, address, birth date, or medical record number, to anyone outside this site. The study staff at this site is responsible for keeping your identifying information safe from anyone who should not see it. We will send the blood samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we hope will be many years. We will use the samples in the future for tests to help understand more about COVID-19 and how people respond to treatment for COVID-19. You and your doctor will not get any results from these tests. We will not test your DNA (your genes). We will not sell your samples and they will not be used for research aimed at making money (commercial research). The samples will not have any information connected to them that could identify you.

Why would you want to be in the study?

If you get the hIVIG, it may help you get better faster, although we do not know that for sure. Remember that half (50%) of the people in this study will not get the hIVIG.

By being in this study, you help doctors know more about how to treat COVID-19 in people in the hospital. Because so many people are getting hospitalized with COVID-19, this could be a big impact if a treatment proves to be effective.

Why would you NOT want to be in the study?

Only half (50%) of the people in this study will get the hIVIG. You may not get the hIVIG. If hIVIG turns out to be a good treatment, you would not get that benefit. It's also possible that if you do get hIVIG, it may turn out not to be useful, or may cause side effects that are harmful to you.

What are the side effects of the study hIVIG treatment?

hIVIG is usually very safe to give. Similar immunoglobulin preparations have been used in many different diseases over many years, but immunogloblin prepared solely from individuals who have recovered from COVID-19 has not been studied before. In an earlier study of influenza hIVIG in people in the hospital with the flu, over 150 people got hIVIG. There were no serious problems that occurred in people because they got hIVIG.

All treatments cause side effects, and you may have some side effects from hIVIG. About 1% to 10% (1 in 100 people to 1 in 10 people) who get hIVIG get a fever, chills, nausea, vomiting, dizziness, shortness of breath, rash, hives, or headache, but these are usually not serious. These can happen during the infusion or afterwards and usually go away on their own or with short-term treatment. Although IVIG has been very safe for people with other diseases, less than 0.1% (less than 1 in 1,000) of people taking other types of IVIG for other illnesses have had very serious reactions to it, including a kind of lung injury called TRALI.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

In some laboratory studies, infusions of antibodies have made infections with viruses similar to the virus that causes COVID-19 worse. This is a very unlikely but possible side effect of the treatment infusion in this study, and you will be closely monitored for any signs of this effect.

It is also possible that getting the study treatment infusions could cause problems with your health because of the amount of fluid given to you for the study treatment if you have some other health condition that affects how your body handles fluids. You will get up to about 400 mL of fluid for hIVIG or placebo, and about 100mL each day for remdesivir if you receive it

Some people may have some side effects after the hIVIG infusions. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the benefits and risks or side effects of remdesivir treatment?

Remdesivir was recently shown to help people who are in the hospital with COVID-19 to get better faster than people who got a placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study. If your doctor considers that remdesivir is not a suitable treatment for you, you can still join this study, and you will receive hIVIG or placebo without remdesivir. For example, remdesivir might be unsuitable for you if you have serious liver or kidney problems or an allergy to it.

The most common side effects of remdesivir include abnormal liver function test results, abnormal kidney function test results, fever, elevated blood sugar, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver and kidney function tests may last a few days or longer but came back to normal levels over time.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

Some people may have some side effects after the infusion of remdesivir. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the side effects of the other study procedures?

As shown in the table of what will happen at each visit, you will have some extra blood drawn for laboratory testing and storage. You will also have an extra swab of your nose and throat that would not be done if you are not in the study. The risks and discomforts of these extra blood draws and swab are no different than what you would have if they were performed as part of your regular hospital care for COVID-19.

Additional information:

Here is some additional information about the study that may help you make your choice about whether you want to be in the study.

The US National Institutes of Health (NIH), an agency of the US Federal government, is paying for this study. Because public money is paying for the study, we are required to comply with all rules and regulations about research. We are doing this study according to internationally recognized standards of research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 500 people around the world.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time by telling someone on the study team that you want to stop being in the study. If you choose not to join or to stop, your regular medical care will not change.

If we get any new information that might change whether you want to join or stay in the study, we will tell you right away.

Your study participation may be stopped without your consent if:

- The groups overseeing the study decide the study should be stopped;
- Your study team believes that being in the study is no longer in your best interests.

If your participation is stopped, you will still get the usual care given at your hospital for COVID-19.

If you do not want to be in this study, you will still get the usual care to treat COVID-19. However, you cannot get the hIVIG treatment, because it is experimental.

What are the costs to you?
We will give you the study treatment (hIVIG or placebo) at no cost. We will also give you remdesivir at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

THE NEXT PARAGRAPH IS FOR UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location

Will you be paid to be in the study?
We will compensate you for your time and inconvenience participating in the study. *[Specific details to be completed by site.]*
What if you are hurt as part of this study?
If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.

What happens to the blood samples and respiratory swabs?
We will send the blood and respiratory swab samples to a central laboratory in the United States of America. You and your doctor will **not** get the results of any tests done on these samples.
The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The nasal swab will measure how much virus you have in your respiratory system.
Any blood samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19. You and your doctor will **not** get any results from these tests. Some of the blood will also be given to the company that made the hIVIG to help them learn more about its effects.
How do we protect your privacy?
We will take every reasonable step to keep your health information private and to keep anyone from misusing it.
Your information (data) and samples will not be identified by name, or in any other way, in anything published about this study.
We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.
These people may see your medical and research information at your site:

- the *[insert the name of the hospital/clinic]* ethics committee (institutional review board [IRB]);
- the sponsor, other study research staff, and study monitors
- US and other participating countries' health regulatory agencies
- the US National Institutes of Health which is funding the study

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we are required to make sure that people not involved with this study cannot see your research and medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the UMN in the US through a secure application. By signing this consent, you agree to have your data sent to UMN. No information that could directly identify you is sent to UMN. This is called "pseudonymized data." Access to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

Your study data will be shared with the regulators that oversee the studies, as required by law. Your study data will also be shared with the drug company that provides the hIVIG to help them develop the drug.

UMN may share your data and specimens with other people who study COVID-19. UMN will remove any information that could possibly be used to identify you before sharing. This is called "anonymizing the data." We will not ask you for additional consent for this sharing. UMN will only share data and specimens for research projects that are approved by the group that is conducting this study.

This study has a Certificate of Confidentiality from the US Federal government. This means that UMN cannot share any data it has about you with national, state, or local civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov as required by U.S. law, and on the EudraCT website (https://eudract.ema.europa.eu/). These websites will not include your name or any other direct identifiers such as your contact information. These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

[Note for US sites: The following brief HIPAA authorization is provided. Your site-specific consent should be modified to reflect the HIPAA authorization language requirements at your site.]

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

____**Yes**, I agree to the collection and processing of my personal data.

____**No**, I do not agree to the collection and processing of my personal data.
It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this research and have a chance to get the experimental treatment if we cannot collect and use your data.
[The following section (up to "What if you have problems or questions?") is for countries subject to the General Data Protection Regulation (GDPR) or similar legislation requiring this information. It should only be included in consents for sites subject to such legislation. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced to meet the requirements of a particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]
What are your rights regarding your data?
The UMN is a public research university, and this study is funded primarily by a grant from the US Federal government. UMN and the study funding source require the sponsor (UMN) to follow regulations and policies that are meant to protect your privacy. UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from people in Europe.

There is no specific independent supervisory authority overseeing the processing of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

The GDPR gives you additional rights which we would like to inform you about below.

Right to Information
You have the right to know what data about you is being processed. You can also get a free copy of this data provided.

Right to Correction
You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization
The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

Right to Restriction of processing
Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study physician or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability

You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction
You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

Right to Withdrawal of this consent
You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your investigator. If you withdraw your consent this will not affect the lawfulness of the data processing that has been or will be done with data collected until you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:

Person responsible for data collection at the study center:	
Name:	
Address:	
Phone:	
Email	

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:

Data protection authority responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

<u>What if you have problems or questions?</u>
If you ever have questions about this study, or about the storage or use of your data or samples, or if you are hurt by being in the study, contact:

- *[name of the investigator or other study staff]*
- *[telephone number of the above]*

If you have questions about your rights as a research participant, you can call:

- *[name or title of person on the ethics committee (IRB) or other organization appropriate for the site]*
- *[telephone number of the above]*

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 013 STUDY (Inpatient Treatment with Anti-Coronavirus Immunoglobulin, ITAC)

I have read the consent or have had it explained to me. I am satisfied that I understand the information. By signing this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

If you agree to be in this study, please sign below.

_____ Date: _____
Signature of participant

_____
Printed name of participant

_____ Date: _____
Signature of investigator/designee

_____
Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____
Signature of Legally Authorized Representative (LAR)

_____
Printed name of LAR

_____
Relationship of LAR to Participant
(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law)

Witness to Consent Interview

On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the subject, and the subject indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____
Signature of witness

_____
Printed name of witness

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

If no-touch / electronic consent is used, the participant must be provided with a copy of the consent in a manner appropriate to the method used to obtain it. A record of the act of consent must also be appropriately retained in the participant's medical record.

APPENDIX B SCHEDULE OF ASSESSMENTS

	Screen or Day 0	Day 0	Follow-up Study Day Shaded columns denote in-person visits								
Day	**−1/0[1]**	**0[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+3**	**+4**
ELIGIBILITY & BASELINE DATA											
Informed consent	X										
Height and weight	X										
Baseline medical history (including day of illness from symptom onset)	X										
Baseline medications	X										
Symptom-directed physical exam	X										
Review SARS-CoV-2 test results	X										
Mid-turbinate swab for central SARS-CoV-2 viral load testing	X										
Urine pregnancy test or other documentation of pregnancy status	X										
STUDY INTERVENTION											
Randomization		X									
Study Drug/Placebo Administration		X									
Assess infusion completion and AEs		X									
STUDY PROCEDURES											
Clinical assessment for ordinal outcomes[2]		X	X	X	X	X	X	X	X	X	X
Vital signs for NEW score assessment[3]	X				X						
Hospitalization status					X		X		X	X	X
Interim medical history									X	X	X
Interim medications									X		
Borg dyspnea scale	X								X		
Clinical adverse events of any grade (present on day of assessment)		X	X		X				X		X
Incident grade 3 and 4 adverse events (all through Day 7)		X	X	X	X		X		X		
Local laboratory testing	X								X		
Research sample storage (plasma and serum) and central testing for immunoglobulin levels and neutralizing antibody titers[4]	X		X	X	X				X		X
SAEs and unanticipated problems	Report as they occur										
Deaths	Report as they occur										
Hospitalization Summary	Report upon hospital discharge										

[1] Screening and randomization can be done in same session.

[2] Collected every day for inpatients and at Days 7, 14 and 28 for outpatients.

[3] Collected while hospitalized only

[4]Consenting participants at selected sites will also be seen at Day 90 (+10 days) to obtain a blood sample for central testing and storage

APPENDIX C INSIGHT 013 PROTOCOL TEAM

To oversee the implementation of this treatment study, membership on the protocol team will include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Collaborating laboratory representatives
- Collaborating hIVIG manufacturers
- Site investigators
- Study biostatisticians
- Community representative

A core team consisting of the co-chair(s), ICC leaders, NIAID representatives, study statisticians and other representatives and the INSIGHT Principal Investigator (PI) will also regularly convene to review study progress and address study conduct and administrative issues that arise.

APPENDIX D REFERENCES ON THE INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 013 protocol and to other information pertinent to the study:

- DAIDS toxicity table: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

- INSIGHT Publications and Presentations Policy ((http://insight.ccbr.umn.edu/resources/P&P_policy.pdf)

- CDC and ECDC guidance on how to handle infection control measures (https://www.cdc.gov/sars/guidance/i-infection/healthcare.html) and https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings)).

- Treatment guidelines from NIH and WHO (https://www.covid19treatmentguidelines.nih.gov/, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, and https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory)

APPENDIX E LIST OF ACRONYMS

µL	microliter
ADE	Antibody-dependent enhancement
AE	adverse event
ACTT	Adaptive COVID-19 Treatment Trial
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
B19V	parvovirus B19
BMI	body mass index
CCP	convalescent plasma containing COVID-19 antibodies
CDC	Centers for Disease Control and Prevention (US)
CI	confidence interval
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CVA	cerebrovascular accident
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DVT	deep vein thrombosis
EC	ethics committee
ECMO	extra-corporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
EU	European Union
FDA	US Food and Drug Administration
g	gram(s)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hIVIG	hyperimmune intravenous immunoglobulin
HR	hazard ratio
IB	investigator's brochure
ICC	International Coordinating Center
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee
IgA, IgE, IgG, IgM	immunoglobulin A, E, G, M
IL-6	interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board
IVIG	intravenous immunoglobulin
kg	kilogram
mg	milligram

MI	myocardial infarction
mL	milliliter
mmol	millimole(s)
NEWS	National Early Warning Score
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
nm	nanometer(s)
OHRP	Office for Human Research Protections (US)
OR	odds ratio
PCR	polymerase chain reaction
PHI	personal health information
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
UMN	University of Minnesota
UP	unanticipated problem
US	United States of America
WHO	World Health Organization
WNV	West Nile virus

APPENDIX F CLINICAL CATEGORICAL DEFINITIONS FOR ORDINAL OUTCOME

Each participant is categorized in the highest applicable category.

Ordinal Category	Categorical Description	Categorical Definition*
7	Death	Death
6	End-organ failure	Currently requiring invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy
5	Life-threatening end-organ dysfunction	Currently requiring non-invasive assisted ventilation or high-flow oxygen or Extra-pulmonary: Symptoms and signs of an acute stroke (NIHSS > 14)
4	Serious end-organ dysfunction	Currently requiring supplemental oxygen (≥ 4 liters/min, or ≥ 4 liters/min above premorbid requirements**) but not high-flow oxygen or Any of symptoms or signs of the following extra-pulmonary conditions: Stroke (NIH Stroke Scale/Score [NIHSS] ≤ 14), meningitis, encephalitis, or myelitis, myocardial infarction, myocarditis, pericarditis, or New York Heart Association Class III or IV congestive heart failure, arterial or deep venous thrombosis including pulmonary embolism.
3	Moderate end-organ dysfunction	Requiring supplemental oxygen < 4 liters/min, or < 4 liters/min above premorbid requirements**
2	Limiting symptoms due to COVID-19	Symptomatic and currently unable to independently undertake usual activities
1	No limiting symptoms due to COVID-19	Can independently undertake usual activities with minimal or no symptoms

***Continued hospitalization or presence in a particular category of inpatient facility (e.g. intensive care or high dependency) is not used to divide these categories, as indication for continued hospitalization among recovering COVID patients is intrinsically subjective, in part determined by social and financial factors, and varies markedly across the globe.*

*** Premorbid requirement refers to requirements prior to the development of COVID-19, for example in patients with chronic obstructive pulmonary disease, other chronic pulmonary diseases, or oxygen requirements related to altitude.*

APPENDIX G NATIONAL EARLY WARNING SCORE (NEWS)

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.

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