octapharma

CLINICAL STUDY PROTOCOL

GAM10-10

EFFICACY AND SAFETY OF *OCTAGAM 10%* THERAPY IN COVID-19 PATIENTS WITH SEVERE DISEASE PROGRESSION

Investigational Product:	*Octagam 10%* - Intravenously Administered Immunoglobulin
Indication:	Immunomodulation in patients with severe Coronavirus disease to prevent deterioration of clinical status
Study Design:	Randomized, double-blind, placebo controlled
Sponsor:	Octapharma USA 117 West Century Blvd Paramus, NJ 07652
Study Number:	GAM10-10
EudraCT and/or IND Number:	IND Number 022051
Development Phase:	Phase 3
Planned Core Clinical Start:	2nd Quarter 2020
Planned Core Clinical End:	4th Quarter 2020
Planned Follow-up Registry Start:	3rd Quarter 2020
Planned Follow-up Registry End:	4th Quarter 2021
Date of Protocol:	27-January-2021
Version:	08
Coordinating Investigator:	[redacted]

STUDY OUTLINE

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: *Octagam® 10%*	**Protocol Identification Code:** GAM10-10
Name of Active Ingredient: Intravenously Administered Immunoglobulin	**Date of Final Protocol:** 27-January-2021

Title of Study:

Efficacy and safety of *Octagam 10%* therapy in COVID-19 patients with severe disease progression

Indication:

Immunomodulation in patients with severe Coronavirus disease to prevent deterioration of clinical status.

Number of Study Center(s):

Approximately 20 sites in the USA, Russia, and Ukraine.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine if high-dose *Octagam 10%* therapy will stabilize or improve clinical status in subjects with severe COVID-19 during the first seven days following treatment commencement.	• Proportion of subjects with stabilized or improved clinical status at Day 7 of at least one category of the following 6-point clinical status scale: 1. Hospital discharge or meet discharge criteria, defined as clinical recovery, ie, no fever, respiratory rate, oxygen saturation return to normal, and cough relief 2. Hospitalization, not requiring supplemental oxygen 3. Hospitalization, requiring supplemental oxygen (but not non-invasive mechanical ventilation [NIV]/high-flow nasal cannula [HFNC]), as defined by A-a Gradient <150 mmHg

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	4. Intensive care unit (ICU)/hospitalization, requiring NIV/HFNC therapy, as defined by A-a Gradient ≥ 150 mmHg 5. ICU, requiring Extracorporeal Membrane Oxygenation (ECMO) and/or Invasive Mechanical Ventilation (IMV) 6. Death
Key Secondary Efficacy	
• To compare the length of hospital stay in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.	• Length of hospital stay (time to discharge) from randomization through Day 33.
• To determine if high-dose *Octagam 10%* therapy will stabilize or improve clinical status in subjects with severe COVID-19 during the 14 days following treatment commencement.	• Proportion of subjects with stabilized or improved clinical status of at least one category on the 6-point clinical status scale on Day 14.
• To compare the cumulative duration of IMV in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.	• Cumulative duration of IMV from randomization through Day 33.
• To compare the cumulative incidence of severe progression in subjects treated with *Octagam 10%* compared to those that received placebo at Day 33.	• Proportion of subjects with severe progression defined as requiring ECMO, IMV and/or have died through Day 33.
• To compare the length of time in ICU for subjects treated with Octagam 10% compared to those that received placebo through Day 33.	• Length of time in ICU from randomization through Day 33.

• To compare cumulative mortality in subjects treated with *Octagam 10%* compared to those that received placebo at Day 33.	• Mortality rate through Day 33.
Other Secondary Efficacy	
• To determine if high-dose *Octagam 10%* affects severe acute respiratory syndrome from Coronavirus 2 (SARS-CoV-2) infection status at Day 7.	• Results of reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nares/throat swab and/or sputum and/or lower respiratory tract sample on Day 7.
• To compare the cumulative incidence of new ICU admittance in subjects treated with *Octagam 10%* compared to those that received placebo at Day 33.	• Proportion of subjects admitted to the ICU from randomization through Day 33
• To determine if high-dose Octagam 10% therapy will improve clinical status in subjects with severe COVID-19 during the 14 days following treatment commencement.	• Proportion of subjects with improvement on Days 7, 14, 21, and 33.
• To compare the cumulative incidence of IMV in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.	• Proportion of subjects requiring IMV by Day 33.
• To compare the time to recovery in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.	• Time to recovery through Day 33 where recovery is defined as a clinical status of 1 or 2.
• To compare the time to first improvement in clinical status in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.	• Time to first improvement in clinical status through Day 33.
Secondary Safety	
• To describe the safety of *Octagam 10%* compared to placebo when administered to subjects with severe COVID-19.	• Incidence of all adverse events (AEs) • Incidence of AEs considered related to the Investigational Medicinal Product (IMP) • Incidence of serious adverse events (SAEs)

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	• Clinical laboratory parameters • Vital sign parameters • Radiological findings (chest computerized tomography [CT]/chest X-ray)
Exploratory	
• To compare changes in SpO_2 on room air from Baseline (Day 1) to all available on-study time points up to Day 33 in subjects treated with *Octagam 10%* compared to those that received placebo.	• Improvement of SpO_2 on room air from Baseline (Day 1) to Day 33 using trend from all available observed data.
• To compare changes in the Modified Borg Dyspnea Scale from Baseline (Day 1) to Days 7, 14, 21, and 33 in subjects treated with *Octagam 10%* compared to those that received placebo.	• Modified Borg Dyspnea Scale score at Baseline (Day 1) and on Days 7, 14, 21, and 33.
• To compare changes in Quality of Life (McGill Quality of Life Single-Item Scale, MQoL-SIS) score from Baseline (Day 1) to Days 7, 14, 21 and 33 in subjects treated with *Octagam 10%* compared to those that received placebo.	• MQoL-SIS score at Baseline (Day 1) and on Days 7, 14, 21 and 33.

Study Design:

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to evaluate if high-dose *Octagam 10%* therapy can stabilize or improve clinical status in subjects with severe Coronavirus disease.

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Number of Subjects:

Maximum 208 subjects will be recruited to achieve a study sample of 104 subjects each in the treatment and placebo groups (1:1 randomization in both arms), allowing for a 15% drop-out rate.

Subject Selection Criteria:

Inclusion Criteria:

1. Adult aged ≥ 18 years old
2. Provide voluntary, fully informed written and signed consent before any study-related procedures are conducted
3. Able to understand and comply with the relevant aspects of the study protocol
4. Laboratory (RT-PCR) confirmed COVID-19 infection on nares/throat swab and/or sputum and/or lower respiratory tract samples at Screening or within 7 days prior to Screening
5. Hospitalized, requiring supplemental oxygen with a resting room-air SpO_2 of ≤93% or arterial oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ratio < 300 mmHg. Measurement can be taken from documented source records within the 24 hours prior to Screening
6. Chest imaging confirming lung involvement

Exclusion Criteria:

1. Existence of other evidence that can explain pneumonia including but not limited to: Influenza A virus, influenza B virus, bacterial pneumonia (as suggested by the combined clinical picture, radiological findings and known laboratory results [eg, elevated procalcitonin >0.5ng/mL and concomitant neutrophilia]), known fungal pneumonia, suspected fungal pneumonia based on compromised immune system with a history of past fungal infections, noninfectious causes, etc.
2. Known history of serious allergic reactions, including anaphylaxis to intravenous immunoglobulin (IVIG) or its preparation components
3. Subjects with a history of thromboembolic event (TEE) within the last 12 months, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV)
4. Subjects with an underlying medical condition that can lead to hypercoagulable states and hyperviscosity such as antithrombin III deficiency, Factor V Leiden, Protein C deficiency, antiphospholipid syndrome, and malignancy

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5. Known history of selective IgA deficiency with antibodies against IgA
6. Subjects with conditions such as human immunodeficiency virus (HIV) infection, known acute or chronic hepatitis B or C (HBsAg positive or HCV ribonucleic acid (RNA) PCR positive or currently treated with antivirals), pulmonary fibrosis, elevated procalcitonin (> 0.5) with concomitant neutrophilia (elevated polys), heparin induced thrombocytopenia (HIT), and moderate to severe renal dysfunction (per investigator discretion based on estimated glomerular filtration rate [eGFR] <59 mL/min/1.73 m^2, as defined by KDIGO Clinical Practice Guideline):
    - Moderately reduced GFR (G3a): GFR = 45 to 59 ml/min/1.73 m^2
    - Moderately reduced GFR (G3b): GFR = 30 to 44 ml/min/1.73 m^2
    - Severely reduced GFR (G4): GFR = 15 to 29 ml/min/1.73 m^2
    - Kidney failure (G5): GFR <15 ml/min/1.73 m^2
7. Currently requiring IMV or having received IMV during the last 30 days
8. Known clinically significant preexisting lung, heart, or neuromuscular disease that, in the investigator's opinion, would impact subject's ability to complete study or may confound the study results
9. Body weight >125 kg
10. Women who are pregnant or breast-feeding
11. Subjects who received COVID-19 convalescent plasma, IVIG products, anti-interleukin agents (eg, Tocilizumab), or interferons for their COVID-19 disease before enrollment or plan to receive this treatment during the course of the study
12. Enrolled in other experimental interventional studies or taking experimental medications (ie, convalescent plasma). Diagnostic studies can be allowed if the anticipated total blood volume to be drawn across both studies and for therapeutic purposes does not exceed 450 mL over any 8-week period.

Test Product, Dose, and Mode of Administration:

Octagam 10%, 2 g/kg divided by 4 days (0.5 g/kg/day), administered by intravenous infusion over approximately 2 hours per day over 4 consecutive days.

Duration of Treatment:

The duration of treatment is 4 days. The duration of the entire study for each subject will be approximately 33 days:

- Screening period: 1 day
- Treatment period: 4 days

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- Follow-up period: 29 days

Reference Therapy, Dose, Mode of Administration:

Placebo (saline), equivalent volume as test product, administered by intravenous infusion over approximately 2 hours per day over 4 consecutive days.

Efficacy Parameters:

Efficacy assessments include clinical status, oxygenation and ventilator status, SARS-CoV-2 RT-PCR results, oxygen saturation, modified Borg Dyspnea Scale and MQoL-SIS.

Safety Parameters:

Safety assessments include AEs and SAEs, vital signs including SpO_2, clinical laboratory evaluations and chest CT/chest X-ray findings.

Study Procedures:

Investigators will enroll subjects into the study only after written informed consent has been obtained from subject or legally authorized representative (LAR). The Flow Chart of Assessments includes full details of all the procedures that will be performed at each study visit. Below is a brief summary of the procedures that will be performed during the study.

Screening Visit:

After written informed consent has been obtained from subject or LAR, subjects will be evaluated for study eligibility according to the inclusion/exclusion criteria. These evaluations will include confirmation of a COVID-19 diagnosis (including RT-PCR for SARS-CoV-2 if not available from the 7 day period prior to Screening), demographics, medical history, physical examinations, body weight, current medication use, vital signs including SpO_2 saturation, clinical status and oxygenation/ ventilator status, blood sample collection (for evaluation of clinical safety parameters and serum pregnancy test, if appropriate), urine sample for legionella and pneumococcal antigens, chest CT/chest X-ray and completing the MQoL-SIS.

Infusion Visits (Days 1 to 4):

Following the completion of all Screening procedures including confirmation of eligibility criteria and medical history, the subject will be randomized to receive either *Octagam 10%* or placebo. The subject will receive either *Octagam 10%* medication in the dose of 2 g/kg administered over 4 days (0.5 g/kg/day), or an equivalent volume

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of placebo (saline), infused slowly over approximately 2 hours per day over 4 consecutive days. Other evaluations will include clinical status and oxygenation/ventilator status, vital signs including SpO_2 saturation and A-a Gradient (A-a Gradient collected on Day 1 only), completion of the MQoL-SIS, and the modified Borg Dyspnea scale, physical examinations, blood sample collection, AE monitoring, and concomitant medication use.

Primary Endpoint Visit (Day 7)

On Day 7, the following evaluations will be performed, including the primary endpoint evaluation: clinical status (confirmed by A-a gradient if clinical status of 3 or 4) and oxygenation/ventilator status; and secondary endpoint evaluations: vital signs including SpO_2 saturation, swab for RT-PCR detection of SARS-CoV-2 infection status, completion of the MQoL-SIS and the modified Borg Dyspnea scale, blood sample collection, chest CT/chest X-ray, AE monitoring, and concomitant medication use.

Follow-up Visits (Days 14 and 21)

The subject will have 2 safety follow-up visits at which the following procedures will be performed: clinical status and oxygenation/ventilator status, vital signs including SpO_2 saturation, completion of the MQoL-SIS and the modified Borg Dyspnea scale, AE monitoring, and concomitant medication use.

End of Study Visit (Day 33)

At Day 33, the following End of Study evaluations will be performed: clinical status and oxygenation/ventilator status, vital signs including SpO_2 saturation, completion of the MQoL-SIS and the modified Borg Dyspnea scale, physical examination, blood sample collection, AE monitoring, and concomitant medication use. After Day 33, the core clinical study is considered completed for the subject. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs) require follow-up.

Telephone Visits:

If a subject is discharged from the hospital at any time during the course of their participation in the study, a pulse oximeter will be provided to them to monitor their oxygen saturation at home. The Research Coordinator or other qualified research team member will contact the subject at Day 14 and Day 21 to collect data points. Data collection will also include the Modified Borg Dyspnea Scale, MQoL-SIS, AE recording, and concomitant medication review.

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One Year Registry Follow-up:

After completion of the core 33-day trial, all subjects will be followed for a one-year follow-up registry. Subjects will be contacted by telephone or electronically by the Principal Investigator or the Sponsor (or its designee) every three months (±14 days) for one year to obtain data on health status and any residual health effects from COVID-19 or the study treatment. There will not be any additional in-person site visits required. The responsibility for the oversight of this registry follow-up period will be managed by a central Coordinating Principal Investigator (not the enrolling Investigator responsible for the 33-day core trial), unless the local Investigator elects to continue to oversee their subjects directly during this one-year follow-up period. The data recorded during this registry follow-up period will be submitted as a supplement to the core study data once all subjects have completed the year of follow-up.

Statistical Analysis Plan:

Assuming that the proportions of subjects who successfully achieve the primary endpoint are 0.6 for placebo arm and 0.8 for IVIG arm, with additional assumptions of normality approximation of difference of two proportions, the maximum sample size needed is 208 to provide at least 80% power assuming a drop-out rate of 15%. That is, 176 subjects will provide at least 80% of statistical power with overall type I error of 0.05.

Final Analysis

For this study, the primary population for analysis is defined as:

- **Enrolled Population (EP)**

All subjects who are enrolled in the study will be included in the enrolled population (EP).

- **Intent-To-Treat Analysis Population (ITT)**

All subjects who are randomized will be included in the intent-to-treat (ITT) analysis population and analysis will be conducted according to the study arm in which subjects are randomized, regardless of randomization errors or protocol violations.

- **Safety Analysis Population (SAF)**

All subjects who are randomized and received any amount of IVIG or placebo will be included in the modified safety analysis set (SAF) and analysis will be conducted according to the treatment which subjects actually received.

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- **Per-Protocol Analysis Population (PP)**

Per protocol (PP) analysis set includes subjects who receive at least 80% of planned dose (IVIG or placebo) without major protocol deviations.

Efficacy Analysis Plan

Descriptive statistics, including mean, standard deviation, median, maximum, and minimum will be provided for baseline age, weight, vital signs, physical exam, laboratory results, oxygen saturation. Gender, race and ethnicity, and other demographic information will be tabulated. Medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 23.0 and tabulated with start date, ongoing status, and end date, if applicable.

The ITT set will be used for primary analysis set to analyze the primary endpoint. The handling of missing data is described in the body of the protocol. A subject is randomized to either IVIG group or placebo group. A subject is determined to be a success (ie, reached the primary endpoint) if the clinical status category on Day 7 is not worse than the clinical status category at Baseline (Day 1 prior to IMP infusion). Null hypothesis of no difference in proportion of subjects who reach success in two treatment groups will be tested versus the alternative hypothesis that there is a difference between proportions of subjects who reach success in two groups. Hypothesis testing will be performed using Cochran-Mantel-Haenszel (CMH) stratified by age category (≤65 versus >65) at a two-sided 0.05 significance level. The difference in proportion of subjects between both groups with standard deviation, and 95% confidence interval will also be provided.

Subgroup analysis of the primary endpoint will include sex (male/female), age (>65, ≤65), race, ethnicity, and disease severity (according to the definitions of the electronic Case Report Form [eCRF]).

Sensitivity analysis using different alternative analysis population and additional analysis methods will also be performed. More details will be provided in the Statistical Analysis Plan (SAP).

The analysis for key secondary endpoints will be based on the ITT population. The hypothesis testing with p-value assessments for key secondary efficacy endpoints at designated timepoints will be implemented for confirmatory purpose after statistical significance is claimed from the primary endpoint. The following secondary endpoints will be analyzed by hierarchical procedure in the order specified below with overall two-sided type I error of 0.05:

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1. Length of hospital stay (time to discharge) through Day 33
2. Proportion of subjects with stabilized or improved clinical status of at least one category on the 6-point clinical status scale on Day 14.
3. Cumulative duration of IMV through Day 33
4. Proportion of subjects with severe progression defined as requiring ECMO, IMV and/or have died through Day 33
5. Length of time in ICU from randomization through Day 33
6. Mortality rate through Day 33

Hypothesis testing for proportions will be conducted as described for the primary endpoint. Stratified log-rank tests will be performed to compare treatment effects between arms for time to event data using age category as a stratification variable. Kaplan-Meier plots will also be provided. ANOVA or Van Elteren tests will be performed for continuous endpoints.

Secondary endpoints which demonstrate statistical significance will be analyzed by subgroups including sex (male/female), race, ethnicity, and disease severity (according to the definitions in the eCRF).

A detailed SAP describing missing data handling and further details with respect to testing for each endpoint will be compiled as a separate document.

Safety Analysis Plan

Safety data analysis will be based on the SAF. Descriptive statistics will be provided for imaging assessments, clinical laboratory parameters, AEs, SAEs, and vital signs, including physical examination, concomitant medicines, concomitant procedures, and safety laboratory test results.

AEs observed will be classified using the MedDRA classification system version 23.0. AEs will be summarized by MedDRA system organ class and preferred terms. Separate tabulations will also be produced for related AEs, SAEs, discontinuations due to AEs, and AEs of at least Grade 3 severity. A summary of the number and severity of treatment-emergent AEs and study drug related AEs will also be produced.

Laboratory results will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 whenever

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possible. Laboratory parameters will be summarized for changes across study using descriptive statistics including shifts relative to NCI-CTCAE criteria for laboratory abnormalities. Laboratory measures will also be compared with their corresponding normal ranges, and the incidence of abnormally high and abnormally low laboratory values will be summarized.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments Performed Throughout the Study

ASSESSMENTS	Screening Visit (Day 0)	Baseline/Infusion Visit 1 (Day 1) [1]	Infusion Visits 2-4 (Days 2-4)	Primary Endpoint Visit 5 (Day 7 or at discharge if prior to Day 6) [2]	Safety Follow-up Visits 6 & 7 (Days 14 & 21) [3]	End of Study Visit (Day 33) [3]	Registry follow-up: every three months for one year [4]
Informed consent	x						
Eligibility criteria [5]	x	x					
Demographics/Baseline Characteristics	x						
Medical history (including COVID-19 diagnosis date)	x	x					
Diagnosis confirmation [5]	x			x			
Clinical Status and Oxygenation/Ventilator Status Evaluation [6]	x	x	x	x	x	x	
Body weight	x	x (if not performed at Screening)					
Vital Signs [7]	Collected throughout the study						
SpO_2 and A-a Gradient [7]	Collected throughout the study						
McGill Quality of Life Single Item Scale	x	x	x	x	x	x	
Modified Borg Dyspnea Scale		x	x	x	x	x	
Physical examination[8]	x	x (if not performed at Screening or available in hospital admission notes)				x (performed at Day of Discharge)	
Chest CT/Chest X-ray [9]	x	x (if not available at Screening)		x			
Laboratory Sample Collection [10]	x	x	x	x	x [11]		
Urine sample for legionella, pneumococcal antigens	x						

ASSESSMENTS	Screening Visit (Day 0)	Baseline/Infusion Visit 1 (Day 1) [1]	Infusion Visits 2-4 (Days 2-4)	Primary Endpoint Visit 5 (Day 7 or at discharge if prior to Day 6) [2]	Safety Follow-up Visits 6 & 7 (Days 14 & 21) [3]	End of Study Visit (Day 33) [3]	Registry follow-up: every three months for one year [4]
Serum Pregnancy Test, if applicable	x						
Randomization		x					
Administration/Infusion of IMP		x	x				
Post-infusion site assessment		x	x				
AE monitoring		Collected from first administration of IMP until End of Study (Day 33)					
Prior/Concomitant medication[3]	Collected throughout the study						
Health Status[12]							x

1. First day of Baseline/Infusion, labeled as Visit 1/Day 1, must fall within 24 hours of Screening Visit.
2. Assessments done on day of discharge if prior to Day 6 will not be repeated if already performed as part of the assessments for that day.
3. Can be done via telehealth/telephone call.
4. Health status questions will record COVID-19 status including, relapse or new COVID-19 infection, hospitalization(s) and cause(s) of hospitalization, and death.
5. See Section 7.1.4 and 7.2.3.
6. See Sections 7.2.1 and 7.2.2.
7. See Section 7.3.5 for details. Vital signs will not be collected if the visit is conducted by telephone or telehealth.
8. Physical Exam is only done at Baseline if not done at Screening. Screening physical exam can be assessed from hospital chart notes.
9. Chest computerized tomography/Chest X-ray from within +/-1 day will be accepted for Screening and Day 7.
10. See Section 7.3.4 for a list of safety laboratory evaluations. All laboratory samples should be drawn prior to IMP infusions at Visits 1 through 4. If the Day 1 infusion commences within 8 hours of the blood collection for the Screening laboratory parameters, only those parameters not assessed at Screening need to be performed prior to the Day 1 infusion.
11. Final blood sample will be drawn on day of discharge (if after Day 7) or Day 33, whichever is sooner.
12. Can be delegated to the Sponsor / contract research organization.

PROTOCOL SIGNATURES

Sponsor's Representatives

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted]

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In-Text Tables

LIST OF ABBREVIATIONS

Abbreviation	Description
ABG	Arterial blood gas
aCL	Anticardiolipin Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AKI	Acute Kidney Injury
ANOVA	Analysis of Variance
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMH	Cochran-Mantel-Haenszel
CMP	Comprehensive Metabolic Panel
CoV	Coronaviruses
COVID-19	Coronavirus disease-2019
CRO	Contract Research Organisation
CRP	C-reactive protein
CT	Computerized Tomography
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EP	Enrolled Population
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	Fractional Inspired Oxygen
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HFNC	High-Flow Nasal Cannula
HIT	Heparin Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
hsCRP	high-sensitivity C-reactive protein
IB	Investigators' Brochure
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobin
IL	Interleukin

IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
ITT	Intent-To-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KDIGO	Kidney Disease Improving Global Outcomes
LAR	Legally Authorized Representative
LDH	Lactic acid dehydrogenase
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MIS	Multisystem Inflammatory Syndrome
MMN	Multifocal Motor Neuropathy
MQoL-SIS	McGill Quality of Life Single-Item Scale
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
NIV	Non-Invasive Mechanical Ventilation
PaO_2	Arterial Oxygen Partial Pressure
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RNA	Ribonucleic acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Coronavirus 2
SDV	Source Data Verification
SID	Secondary immune deficiency
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SOP	Standard Operating Procedure
TACO	Transfusion-associated circulatory overload
TEE	Thromboembolic Event
TRALI	Transfusion-related acute lung injury

1 INTRODUCTION

Coronaviruses (CoV) are enveloped ribonucleic acid (RNA) viruses capable of causing acute respiratory distress in humans (1). Previous outbreaks have caused Middle East Respiratory Syndrome (MERS/MERS-CoV) and Severe Acute Respiratory Syndrome (SARS/CoV). In December of 2019, a highly infectious coronavirus designated 2019-nCoV causing the severe acute respiratory syndrome from Coronavirus 2 (SARS-CoV-2) was found to be present in a cluster of patients linked via a seafood and wet animal wholesale market in Wuhan, China (2).

Following the initial outbreak in Wuhan, the spread of Coronavirus disease-2019 (COVID-19) via human to human transmission forced the World Health Organization to declare a global pandemic on March 11, 2020 (3).

In an early description of 41 patients admitted to a hospital in Wuhan and found to be COVID-19 positive, the clinical manifestations showed men were affected three times as often as women. Furthermore, diabetes (20%), hypertension (15%) and other cardiovascular disease (15%) were found to be the most commonly associated diseases (4). Common initial symptoms were fever (98%), dry cough (76%), shortness of breath (55%), and myalgia or fatigue (44%) (4). Median time from symptom onset to dyspnea is 8 days. All patients had lymphopenia and abnormal chest computerized tomography (CT) findings. Adult Respiratory Distress Syndrome occurred in 29%; 15% of all patients died (4).

Risk of death is highest in patients with advanced age, with approximately 80% of deaths occurring among adults older than 60 years of age (5). The main cause of death is massive alveolar damage and progressive respiratory failure caused by inflammatory infiltration of the pulmonary interstitials resulting in pulmonary fibrosis (6).

The proximate cause of death implicates an abnormal pulmonary immune response associated with multiple respiratory viral infections in which there is an elevation of cytokine and chemokine production often associated with poor clinical outcomes, referred to as a “cytokine storm” (7, 8). In patients with severe COVID-19, there is increased interleukin (IL-2, IL-7), granulocyte colony stimulating factor, interferon gamma, inducible protein 10, monocytes chemoattractant protein 1, macrophage inflammatory protein 1-alpha, and tumor necrosis factor-alpha. Elevated IL-6, C-reactive protein (CRP) and myoglobin are significantly associated with patients who die compared to those who are ultimately discharged (7).

There is no known effective treatment for patients infected with COVID-19. Many therapies have been proposed based on anecdotal reports including hydroxychloroquine and azithromycin (9), corticosteroids (10), broad spectrum antiviral agents (11), convalescent plasma (12), and intravenous immunoglobulin (IVIG) (6). IVIG, which consists of pooled IgG preparations from thousands of donors and has

been used to treat patients with immune mediated diseases for almost 40 years (13), is an attractive possible treatment. The adverse effect profile is well understood, as is its most efficacious dose (2 g/kg over 4-5 days) and expected time efficacy (2 to 10 days; personal communication; after 2-3 doses) (14). The mechanism by which IVIG modulates the immune system is uncertain, but among possibilities includes blocking and modulation of Fc expression and signaling, increased autoantibody clearance by FcRn saturation, suppression of immunoglobulin production, modulation of antigen presenting cell activation, blockade of complement proteins, induction of regulatory T cells, and inhibition of differentiation and maturation of dendritic cells (14). Recent studies in patients with idiopathic thrombocytopenia purpura and Guillain-Barre syndrome show that IVIG significantly modulates inflammatory cytokines (15, 16).

Side effects of IVIG include increased blood viscosity, thromboembolic phenomena, acute renal failure, increased blood pressure, and anaphylaxis (14, 17, 18).

The published cases of IVIG showing an effect in patients with COVID-19 infection showed an almost immediate impact on disease progression after receiving a standard loading dose of IVIG (2 g/kg over 5 days), enabling discharge within 10 days of IVIG initiation (6). None were intubated, but all were treated while being observed to have increasing dyspnea and decreasing oxygen saturation levels. All had markedly elevated high sensitivity CRP (hsCRP) and abnormal CT scan (6).

1.1 Rationale for Conducting the Study

In early 2020, several case studies were published which showed the successful use of IVIG in treating COVID-19 patients (6, 19, 20, 21, 22). A retrospective, multicenter cohort study that included 325 adult critical patients from 8 centers, demonstrated that early high-dose IVIG administration (<7 days following admission) improves the prognosis of critical COVID-19 patients (19). In addition, a retrospective chart review of 58 patients with severe COVID-19 pneumonia compared outcomes in those receiving high-dose IVIG treatment ≤48 hours versus >48 hours after admission to the intensive care unit (ICU). Results demonstrated that high-dose IVIG received ≤48 hours after admission to the ICU resulted in reductions in the use of mechanical ventilation, hospital/ICU stay, and 28-day mortality in patients with severe COVID-19 pneumonia (20). An observational study was conducted in 10 COVID-19 patients, and results demonstrated that short-term moderate-dose corticosteroid combined with high-dose IVIG effectively reversed severe, deteriorating COVID-19 patients who failed initial low-dose therapy (21). It's notable that researchers were motivated to employ this therapeutic regimen as it was preliminarily shown to reduce the risk of death in 12 patients with SARS. The authors postulate that corticosteroid use at an early deterioration stage has a timely effect on the suppression of the inflammatory response. More importantly, the combination use of IVIG is believed to strengthen

immune function to prevent a potential delay in viral clearance caused by the corticosteroid.

Another study conducted in three deteriorating patients with severe COVID-19 who received high-dose IVIG (0.3 to 0.5 g/kg/day for 5 days) demonstrated that all experienced a successful recovery with significant improvement in symptoms within 24 to 48 hours. They also observed that “the first few days of deterioration may present a critical point when potent suppression of the inflammatory cascade could save patients from fatal immune-mediated injuries.” (6).

More recently, Sakoulas et al. have performed a prospective randomized controlled pilot study in 34 COVID-19 patients (22). Sixteen patients received IVIG (0.5 g/kg/day for 4 days) plus standard of care (SOC) versus 17 patients SOC alone. Among subjects with A-a gradient of >200 mm Hg at enrollment, the IVIG group showed i) a lower rate of progression to requiring mechanical ventilation (2/14 vs 7/12, p=0.038 Fisher exact test), ii) shorter median hospital length of stay (11 vs 19 days, p=0.01 Mann Whitney U), iii) shorter median ICU stay (2.5 vs 12.5 days, p=0.006 Mann Whitey U), and iv) greater improvement in PaO_2/FiO_2 at 7 days (median [range] change from time of enrollment +131 [+35 to +330] vs +44·5 [-115 to +157], p=0.01, Mann Whitney-U) than SOC. No safety signals including thrombo-embolic events were detected.

The benefits of IVIG in COVID-19 was further demonstrated in pediatric patients who developed Kawasaki-like disease, also called MIS (Multisystem Inflammatory Syndrome) (23, 24, 25, 26) In Feldstein et al., which documents the largest cohort of patient, 186 patients with MIS were treated in 26 states in the United States and 77% were treated successfully with IVIG (23).

There are documented case studies of IVIG being used in patient care for various viral infections affecting the upper respiratory system (27). In both the United States and Saudi Arabia, varying levels of IVIG were used in the treatment of patients who had been diagnosed with MERS (28). Additionally, various forms of IVIG have been related to symptom improvement in patients diagnosed with SARS (29). Namely, delayed administration of pentaglobin, an IgM-enriched IVIG serum, led to improved radiological appearance and overall improved symptoms in 12 severe SARS patients (30).

Furthermore, IVIG has been seen to have therapeutic effects in a variety of patients with influenza. A 2016 study carried out on immunocompromised children diagnosed with 2009 Influenza (H1N1) concluded that high-dose IVIG could be useful as an ancillary therapy for the influenza virus (31). Likewise, IVIG given at 0.4g/kg over a period of 4 hours, was shown to contribute to decreasing viral loads in adult patients diagnosed with the H1N1 virus (32). In non-human populations, a 2017 study carried out in ferrets demonstrated that IVIG administered at exposure to the influenza virus

(H1N1/H5N1) led to a significant reduction in lung viral load. The study went on to conclude that IVIG administered before the onset of a pandemic had the potential to modulate serious influenza infection-associated mortality and morbidity, and that it could be used as a prophylactic to protect vulnerable populations in the event of a pandemic (33).

IVIG was first introduced in the US for the treatment of primary immune deficiency in the early eighties, it has increasingly been recognized not only for its ability to fight infections but also for its anti-inflammatory and immunomodulatory effects. Other US Food and Drug Administration (FDA) approved indications for IVIG include SID (secondary immune deficiency) CIDP (Chronic inflammatory demyelinating polyneuropathy), MMN (Multifocal Motor Neuropathy), Kawasaki disease and ITP (Immune Thrombocytopenia). IVIG has been studied for decades in numerous different diseases and has a good safety profile.

The mechanism of action of IVIG is not completely understood, but it may modulate the immune response via multiple mechanisms, including blocking a wide array of proinflammatory cytokines that potentially lead to severe inflammatory responses, including cytokine storm, as well as Fc-gamma receptor binding of activated macrophages and other antigen presenting cells.

Recently convalescent plasma was approved for Emergency Use Authorization in COVID-19 patients, although the National Institutes of Health (NIH) has stated that convalescent plasma should not be considered as SOC. There are no randomized prospective trials for convalescent plasma available and no control group was included in these studies. There are potential safety issues of convalescent plasma such as transmission of viruses, TACO and TRALI unlike IVIG which has been pathogen inactivated. One other difference between IVIG and convalescent plasma is the much higher Ig levels in IVIG as compared to convalescent plasma (~40 fold higher) which could result in greater benefits. In conclusion, the preliminary positive IVIG data warrants a larger prospective double-blind, placebo controlled to show efficacy and safety of *Octagam 10%* therapy in COVID-19 patients with severe disease progression.

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), US FDA Code of Federal Regulations (CFR), and other local regulatory requirements.

1.2 Benefit-Risk Statement

The risks of IVIG administration are well documented. In general, the incidence of adverse events (AEs) associated with IVIG tends to increase with the rate of infusion, and thus the recommended dosage, infusion rates, and monitoring procedures should

be adhered to. Patients that are naïve to IVIG are more at risk than those that are well-maintained and on regular therapy.

Patients with pre-existing risk factors for thrombotic events (such as advanced age, obesity, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, and patients with diseases which increase blood viscosity) may be at increased risk of developing thromboembolic events (TEEs) (34). Overdose is possible in overweight and elderly patients and in those who have impaired renal function. In patients with signs of cerebral or cardiac ischemia, the increase in viscosity caused by an immunoglobulin infusion may be a risk (34).

The safety profile of *Octagam 10%* based on clinical studies and long-term post-marketing experience is well-documented and detailed in the European Summary of Product Characteristics (SmPC) (35). Adverse drug reactions (ADRs) such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain occur occasionally. These adverse effects are mostly transient and mild. However, some very rare adverse effects, including renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury, are serious (36). AEs are rarely disabling or fatal, treatment involves supportive measures, and the majority of affected patients have a good prognosis. Reactions to IVIGs tend to be related to the dose and the rate of infusion. Rarely, human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible hemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB.

For *Octagam 10%*, the same type of adverse reactions has been seen as for other IVIG products. No new or unknown safety problems are expected to emerge which are not already described in the SmPC. In the very limited number of COVID-19 cases treated with IVIG, no new or unknown safety concerns were reported (6).

Based on the severe conditions of COVID-19 patients, we postulate that *Octagam 10%* treatment in COVID-19 patients outweighs potential disadvantages of IVIG.

This trial will be conducted in accordance with local and national COVID-19 safety guidelines. This trial was designed with flexibility for remote telemedicine visits where possible to minimize the risk of exposure of patients and healthcare professionals to COVID-19.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To determine if high-dose *Octagam 10%* therapy will stabilize or improve clinical status in subjects with severe COVID-19 during the first seven days following treatment commencement.

2.2 Secondary Objectives

Key Secondary Efficacy Objectives

- To compare the length of hospital stay in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.
- To determine if high-dose *Octagam 10%* therapy will stabilize or improve clinical status in subjects with severe COVID-19 during the 14 days following treatment commencement.
- To compare the cumulative duration of invasive mechanical ventilation (IMV) in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.
- To compare the cumulative incidence of severe progression in subjects treated with *Octagam 10%* compared to those that received placebo at Day 33.
- To compare the length of time in ICU in subjects treated with *Octagam 10%* compared to those that received placebo at Day 33.
- To compare cumulative mortality in subjects treated with Octagam 10% compared to those that received placebo at Day 33.

Other Secondary Efficacy Objectives

- To determine if high-dose *Octagam 10%* affects severe acute respiratory syndrome from Coronavirus 2 (SARS-CoV-2) infection status at Day 7.
- To compare the cumulative incidence of new ICU admittance in subjects treated with *Octagam 10%* compared to those that received placebo at Day 33.
- To determine if high-dose Octagam 10% therapy will improve clinical status in subjects with severe COVID-19 during the 14 days following treatment commencement.
- To compare the cumulative incidence of IMV in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.
- To compare the time to recovery in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.

- To compare the time to first improvement in clinical status in subjects treated with *Octagam 10%* compared to those that received placebo through Day 33.

Secondary Safety Objective

- To describe the safety of *Octagam 10%* compared to placebo when administered to subjects with severe COVID-19.

2.3 Exploratory Objectives

- To compare changes in SpO_2 on room air from Baseline (Day 1) to all available on-study time points up to Day 33 in subjects treated with *Octagam 10%* compared to those that received placebo.
- To compare changes in the Modified Borg Dyspnea Scale from Baseline (Day 1) to Days 7, 14, 21, and 33 in subjects treated with *Octagam 10%* compared to those that received placebo.
- To compare changes in Quality of Life (McGill Quality of Life Single-Item Scale, MQoL-SIS) score from Baseline (Day 1) to Days 7, 14, 21, and 33 in subjects treated with *Octagam 10%* compared to those that received placebo.

3 INVESTIGATIONAL PLAN

This is a Phase 3 randomized, double-blind, placebo-controlled, study of *Octagam 10%* in COVID-19 subjects.

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

- Proportion of subjects with stabilized or improved clinical status at Day 7 of at least one category on a 6-point clinical status scale.

Clinical status categories will be defined as:

1. Hospital discharge or meet discharge criteria (discharge criteria are defined as clinical recovery, ie, no fever, respiratory rate, oxygen saturation return to normal, and cough relief).
2. Hospitalization, not requiring supplemental oxygen.
3. Hospitalization, requiring supplemental oxygen (but not non-invasive mechanical ventilation (NIV)/high-flow nasal cannula [HFNC]) as defined by A-a Gradient <150 mmHg.
4. ICU/hospitalization, requiring NIV/HFNC therapy, as defined by A-a Gradient ≥150 mmHg.
5. ICU, requiring extracorporeal membrane oxygenation (ECMO) and/or IMV.
6. Death.

A subject meets the success criteria of stabilization or improvement if the clinical status category on Day 7 is not worse than the clinical status category at Baseline (Day 1 prior to IMP infusion).

3.1.2 Secondary Endpoints

3.1.2.1 Key Secondary Efficacy Endpoints

The following key secondary endpoints will be included in formal hypothesis testing procedures as described in the statistical section of this protocol.

- Length of hospital stay (time to discharge) from randomization through Day 33
- Proportion of subjects with stabilized or improved clinical status of at least one category on the 6-point clinical status scale on Day 14

- Cumulative duration of IMV from randomization through Day 33
- Proportion of subjects with severe progression defined as requiring ECMO, IMV and/or have died through Day 33
- Length of time in ICU from randomization through Day 33
- Mortality rate through Day 33

3.1.2.2 Other Secondary Efficacy Endpoints

- Results of reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nares/throat swab and/or sputum and/or lower respiratory tract sample on Day 7.
- Proportion of subjects admitted to the ICU from randomization through Day 33
- Proportion of subjects with improvement on Days 7, 14, 21, and 33
- Proportion of subjects requiring IMV by Day 33
- Time to recovery through Day 33 where recovery is defined as a clinical status of 1 or 2
- Time to first improvement in clinical status through Day 33

3.1.2.3 Safety Endpoints

- Incidence of all AEs
- Incidence of AEs considered related to the investigational medicinal product (IMP)
- Incidence of serious adverse events (SAEs)
- Clinical laboratory parameters
- Vital sign parameters
- Radiological findings (chest CT/chest X-ray)

3.1.3 Exploratory Endpoints

- Improvement of SpO_2 on room air from Baseline (Day 1) to Day 33 using trend from all available observed data.
- Modified Borg Dyspnea Scale score at Baseline (Day 1) and on Days 7, 14, 21, and 33.
- MQoL-SIS score at Baseline (Day 1) and on Days 7, 14, 21, and 33.

3.1.4 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, two-arm adaptive Phase 3 study designed to evaluate if high-dose *Octagam 10%* therapy can stabilize or improve clinical status in subjects with severe COVID-19.

Following Screening procedures, subjects that meet eligibility criteria will be randomized to receive either *Octagam 10%* in a dose of 2 g/kg over 4 days (0.5 g/kg/day), or an equivalent volume of placebo (saline). The infusion will be

administered over a period of 2 hours per day over a total of 4 consecutive days. The first dosing will take place within 24 hours of the Screening Visit.

Approximately 208 male or female adult subjects will be recruited so that approximately 104 subjects in each treatment arm will complete the study. Each subject's participation will last a total of approximately 33 days, including 29 days for safety follow-up, followed by a one-year registry follow-up.

This study is planned to start in Q2 2020 and to be completed by Q4 2020, resulting in a maximal overall duration of 7 months. The planned follow-up registry will begin in Q3 2020 and to be completed in Q4 2021.

3.2 Discussion of Study Design and Choice of Control Group(s)

3.2.1 Study Design

Given that this is an efficacy and safety study with the objective of determining if high-dose *Octagam 10%* therapy will stabilize or improve clinical status in subjects with severe COVID-19, a randomized, double-blind, placebo-controlled, multicenter study design is considered standard for this type of research (ie, the evaluation of the safety and efficacy of active versus placebo).

3.2.2 Control Group(s)

A placebo control has been chosen given the objectives of the study to determine the effects of active treatment with *Octagam 10%.* Choosing placebo as a control has a long history of being the standard for clinical investigations of new therapies for a given indication.

3.2.3 Study Parameters

Efficacy assessments include clinical status, ventilator status/means to maintain oxygen status, SARS-CoV-2 RT-PCR results, oxygen saturation, modified Borg Dyspnea Scale and MQoL-SIS. Safety assessments include AEs and SAEs, vital signs including SpO_2, clinical laboratory evaluations and CT/chest X-ray findings. The efficacy and safety assessments used in this study are consistent with those widely used, generally recognized as reliable, accurate, and relevant in this type of research, and are adequate to form the primary basis for the determination of safety and efficacy.

4 STUDY POPULATION

4.1 Population Base

Approximately 208 male or female adult subjects with laboratory-confirmed COVID-19 will be eligible for inclusion in this clinical study.

4.1.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study:

1. Adult aged ≥ 18 years old.
2. Provide voluntary, fully informed written and signed consent before any study-related procedures are conducted.
3. Able to understand and comply with the relevant aspects of the study protocol.
4. Laboratory (RT-PCR) confirmed COVID-19 infection on nares/throat swab and/or sputum and/or lower respiratory tract samples at Screening or within 7 days prior to Screening.
5. Hospitalized requiring supplemental oxygen with a resting room-air SpO_2 of ≤ 93% or arterial oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ratio < 300 mmHg. Measurement can be taken from documented source records in the 24 hours prior to Screening.
6. Chest imaging confirming lung involvement.

4.1.2 Exclusion Criteria

Subjects who meet any of the following criteria are *not* eligible for the study:

1. Existence of other evidence that can explain pneumonia including but not limited to: Influenza A virus, influenza B virus, bacterial pneumonia (as suggested by the combined clinical picture, radiological findings and known laboratory results [eg, elevated procalcitonin >0.5ng/mL and concomitant neutrophilia]), known fungal pneumonia, suspected fungal pneumonia based on compromised immune system with a history of past fungal infections, noninfectious causes, etc.
2. Known history of serious allergic reactions, including anaphylaxis, to IVIG or its preparation components.
3. Subjects with a history of thromboembolic event (TEE) within the last 12 months, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV).

4. Subjects with an underlying medical condition that can lead to hypercoagulable states and hyperviscosity such as antithrombin III deficiency, Factor V Leiden, Protein C deficiency, antiphospholipid syndrome, and malignancy.
5. Known history of selective IgA deficiency with antibodies against IgA.
6. Subjects with conditions such as human immunodeficiency virus (HIV) infection, known acute or chronic hepatitis B or C (HBsAg positive or HCV RNA PCR positive or currently treated with antivirals), pulmonary fibrosis, heparin induced thrombocytopenia (HIT), and moderate to severe renal dysfunction (per investigator discretion based on estimated glomerular filtration rate [eGFR] <59 mL/min/1.73 m^2, as defined by KDIGO Clinical Practice Guideline):
    - Moderately reduced GFR (G3a): GFR = 45 to 59 ml/min/1.73 m^2
    - Moderately reduced GFR (G3b): GFR = 30 to 44 ml/min/1.73 m^2
    - Severely reduced GFR (G4): GFR = 15 to 29 ml/min/1.73 m^2
    - Kidney failure (G5): GFR <15 ml/min/1.73 m^2.
7. Currently requiring invasive mechanical ventilation or having received invasive mechanical ventilation in the last 30 days.
8. Known clinically significant preexisting lung, heart, neuromuscular or other disease that, in the investigator's opinion, would impact the subject's ability to complete study or may confound the study results.
9. Body weight > 125kg.
10. Women who are pregnant or breast-feeding.
11. Subjects who received COVID-19 convalescent plasma, IVIG products, anti-interleukin agents (eg, Tocilizumab), or interferons for their COVID-19 disease before enrolment or plan to receive this treatment during the course of the study.
12. Enrolled in other experimental interventional studies or taking experimental medications (ie, convalescent plasma). Diagnostic studies can be allowed if the anticipated total blood volume to be drawn across both studies and for therapeutic purposes does not exceed 450 mL over any 8-week period.

4.2 Prior and Concomitant Therapy

Concomitant medication includes all pharmaceutical agents, vitamins, nutritional supplements, and herbal medicines used by the subject with the exception of *Octagam 10%* or placebo. Details on medications taken within 1 week prior to Screening and any concomitant medications taken during the study must be recorded in the electronic Case Report Form (eCRF). This includes off-label use of any drugs, devices, or interventions that have been used to manage COVID-19. Use of antivirals

(eg, remdesivir), corticosteroids, chloroquine or hydroxychloroquine, antibiotics, anticoagulants, or antiplatelet agents is allowed and must be documented in eCRF.

The use of medications being administered as part of other experimental studies or the use of experimental non-IVIG products, COVID-19 convalescent plasma, or interferons are forbidden. Should a circumstance arise where it is considered to be in the best interests of a subject to administer such a product, the subject should not receive further study infusions (*Octagam 10%* or placebo) if these are still ongoing. The other medications administered should be documented as concomitant medications, and the subject should continue to be followed up per protocol.

4.3 Withdrawal and Replacement of Subjects

4.3.1 Premature Subject Withdrawal

Subjects have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw subjects in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study non-interpretable, any unnecessary withdrawal of subjects should be avoided.

In addition to the ongoing safety monitoring and periodic Independent Data Monitoring Committee (IDMC) data review, the following rule will be implemented to apply temporary suspension of study drug administration, pending a safety investigation, for an unacceptable increased venous TEE or acute renal failure risk in the *Octagam 10%* group compared to the placebo group:

- For both venous TEEs or acute renal failures, the event risk will be calculated separately as (number of events reported)/(number of daily infusions) in both treatment groups, and the 90% confidence interval (CI) for the resulting risk ratio (ROctagam/RPlacebo) will be determined by means of the / relrisk option of the SAS procedure FREQ. In case no events are observed in the placebo group, 1 will be added to each cell in the 2X2 table to enable this risk ratio evaluation. The stopping rule will be triggered if the lower confidence limit is greater than 1.0.
- This stopping rule will be applied whenever an unblinded evaluation is done, and a total of 40 daily infusions or more have been administered.
- For the first 40 daily infusions (ie, first 10 subjects that complete infusion cycle per protocol) a fixed rule will be applied by the IDMC to temporarily suspend study drug administration in case the number of related serious TEEs or acute renal failures as assessed by IDMC in the *Octagam 10%* group is triple the number in the placebo group. If no TEE or acute renal failure is observed in the

placebo group during this initial study phase, temporary suspension of study drug administration and safety investigation will be initiated if three related serious TEEs as assessed by IDMC or acute renal failures have been reported in the *Octagam 10%* group.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a subject is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

Other reasons for premature termination of subjects may be:

- Withdrawal of subject's consent.
- Pregnant and lactating subjects will be immediately excluded from the study.
- Investigator's opinion that the subject may be severely harmed if he/she continues study participation, namely by the treatment and procedures requested by the study protocol.
- Occurrence of a condition or disease that interferes with the study treatment or represents an exclusion criterion.
- Administration of IVIG other than *Octagam 10%*.
- Subjects do not comply with the study protocol.

4.3.2 Treatment Failures

Treatment failures will be offered SOC therapy.

4.3.3 Subject Replacement Policy

Subjects withdrawn from the study for any reasons will not be replaced.

4.4 Assignment of Subjects to Treatment Groups

The Investigator will enter a unique identifier of each subject in both the eCRF and the confidential subject identification list. The randomization numbers will be allocated sequentially in the order in which the subjects are enrolled. The Investigator will inform the monitor of new subjects enrolled.

Subjects who withdraw from the study or complete the study are not permitted to re-enroll.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the subject in this study after having discussed all relevant aspects.

A list of all included subjects with all deviations from the intended study procedures and other criteria that may affect the validity of subject data for statistical analysis will be prepared after the clinical phase of the study is completed. The list will be discussed prior to study unblinding by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager, and the study statistician. This panel will decide upon the inclusion of each subject in the analysis populations.

4.6 Subsequent Therapy

If a subject decides to withdraw from the study or is withdrawn by the Investigator, she/he will continue to receive SOC therapy.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

Octagam is a 10% IVIG ready for intravenous administration. *Octagam 10%* is produced from a pool of at least 1000 donations of human fresh frozen plasma per batch. The large donor pool ensures that the product contains a broad range of antibodies directed against pathogens and foreign antigens, which is far more diverse than that of plasma from an individual donor. Donor plasma sampling, the manufacturing of the product and the measures to ensure the product's viral safety are subject to strict regulations laid down by regulatory authorities. Octapharma exclusively uses plasma which has been tested by nucleic acid testing techniques.

During the manufacturing process of *Octagam 10%*, significant viral reduction is obtained via a combination of 3 validated manufacturing steps: cold-ethanol fractionation, solvent/detergent treatment with tri-n-butyl phosphate and Octoxynol (Triton X100), and pH 4 treatment. The efficacy of the virus inactivation procedures has been extensively validated according to relevant international guidelines. The composition with the most important ingredients and the biochemical characteristics are summarized in the Investigators' Brochure (IB).

For placebo, saline for intravenous infusion will be used.

5.2 Packaging and Labelling

5.2.1 For the US sites

Octagam 10% delivered as ready-to-use solution in glass bottles; commercially labeled product will be provided to the clinical study sites. Appropriately trained study staff may over-label the commercial supplies with an investigational product label, provided by the Sponsor, that will meet all FDA requirements under 21 CFR 312.6 and shall include the statement: **Caution: New Drug—Limited by Federal (or United States) law to investigational use**, as permitted in accordance with local Standard Operating Procedures (SOPs). Investigational product labels will also be provided for placebo supplies that will be sourced from the site pharmacy's commercial supplies.

After transfer and pooling into Polyvinyl Chloride-free, Diethylhexylphthalate-free and latex–free, infusion bags, the medication (*Octagam 10%* or placebo) will be blinded with an over pouch and re-labeled (both the infusion bag [as permitted in accordance with local SOPs] and the over pouch). The over-label for the infusion bags and over pouches will also include the 21 CFR 312.6 required statement: **Caution: New Drug—Limited by Federal (or United States) law to investigational use**.

Instructions for over-labeling both *Octagam 10%* and saline with investigational product labels will be provided in a study-specific pharmacy manual.

US Master Label – Octagam 10%:

Caution: New Drug-Limited by Federal (or United States) law to investigational use
Study: **GAM10-10**

Octagam 10% Unit size: _____ **mL**

1 mL contains: 100 mg protein of which 96% is human normal immunoglobulin.
Infusion solution for intravenous administration.

To be stored at +2°C (36°F) to +8°C (46°F) and protected from light. Must not be frozen.

Must be inspected visually for particulate matter and discoloration prior to administration.
Do not use non-homogenous solutions or those that have a deposit.

To be warmed up to room or body temperature before use.
Dosage: refer to Clinical Study Protocol, Section 5.4
Patient no.: |__|__|__|__|__| Visit no.: |____| Infusion Day: |____|

Sponsor: Octapharma USA, INC. 117 West Century Road, Paramus, NJ, 07652 [redacted]

Batch no.: _____ Expiration date: _____

US Master Label – Saline:

Caution: New Drug-Limited by Federal (or United States) law to investigational use
Study: **GAM10-10**

Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**

Sterile solution for intravenous infusion
1000 mL of solution contain
Sodium chloride 9.00 g
Electrolyte concentrations mmol per 1000 mL (approx):
Sodium 154 mmol
Chloride 154 mmol

Do not store above +25°C (+77°F) *[depending on product purchased]*

Only to be used if solution is clear and container undamaged

Dosage: refer to Clinical Study Protocol, Section 5.4

Sponsor: Octapharma USA, INC. 117 West Century Road, Paramus, NJ, 07652 [redacted]

Batch no.: _____ Expiration date: _____

US Master Label – Blinded label for infusion bags and over pouch:

Caution: New Drug-Limited by Federal (or United States) law to investigational use
Study: **GAM10-10**

Octagam 10% OR Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**

1 mL contains either 100 mg protein of which 96% is human normal immunoglobulin **OR** sodium chloride 0.9% w/v solution.

Infusion solution for intravenous administration.

Patient no.: |__|__|__|__|__| Visit no.: |____| Infusion Day: |____|

Investigator: _____

Date and time of preparation: _____

If not infused immediately, to be stored at +2°C (36°F) to +8°C (46°F) until
Expiration date and time: _____

Must not be frozen.

To be warmed up to room or body temperature before use.

Sponsor: Octapharma USA, INC. 117 West Century Road, Paramus, NJ, 07652 [redacted]

5.2.2 For the Russia and Ukraine Sites

Octagam 10% will be delivered as ready-to-use solution in glass bottles; labeled and packed as clinical kits will be provided to the clinical study sites.

Marketed saline solution for intravenous infusion, that can be used in the respective countries, will be purchased by Sponsor or designee and provided to the local pharmacies or sites. Saline should be stored and transported at +0°C to 30°C.

Instructions for over-labeling both *Octagam 10%* and saline with investigational product labels will be provided in a study-specific pharmacy manual.

After transfer and pooling into Polyvinyl Chloride-free, Diethylhexylphthalate-free and latex–free, infusion bags, the medication (*Octagam 10%* or placebo) will be blinded with an overpouch and blinded labels will be applied on the infusion bag and the overpouch.

EU Master Label – Octagam 10%:

FOR CLINICAL TRIAL USE ONLY Study: **GAM10-10**
Octagam 10% Unit size: _____ **mL**
1 mL contains: 100 mg protein of which ≥ 95% is human normal immunoglobulin.
Infusion solution for intravenous administration.
To be stored at +2°C to +8°C and protected from light. Must not be frozen.
Must be inspected visually for particulate matter and discoloration prior to administration.
Do not use non-homogenous solutions or those that have a deposit.
To be warmed up to room or body temperature before use.
Dosage: refer to Clinical Study Protocol, Section 5.4
Patient No.: _____ Visit Day.: ____
Investigator: _____
Sponsor: Octapharma USA, INC. 117 West Century Road, Paramus, NJ, 07652 [redacted]
Batch no.: _____ Expiration date: _____

EU Master Label – Saline:

FOR CLINICAL TRIAL USE ONLY Study: **GAM10-10**
Sodium Chloride 0.9% w/v solution Unit size: _____ **mL**
Sterile solution for intravenous infusion
1000 mL of solution contain
Sodium chloride 9.00 g
Electrolyte concentrations mmol per 1000 mL (approx):
Sodium 154 mmol
Chloride 154 mmol
To store this product below 30°C. Do not freeze.
Only to be used if solution is clear and container undamaged
Dosage: refer to Clinical Study Protocol, Section 5.4
Patient No.: _____ Visit Day.: ____
Investigator: _____
Sponsor: Octapharma USA, INC. 117 West Century Road, Paramus, NJ, 07652 [redacted]
Batch no.: _____ Expiration date: _____

EU Master Label – Blinded label for infusion bags and over pouch:

FOR CLINICAL TRIAL USE ONLY Study: **GAM10-10**

Octagam 10% OR Sodium Chloride 0.9% w/v solution Volume:_____ **mL**

1 mL contains: 100 mg protein of which ≥ 95% is human normal immunoglobulin OR sodium chloride 0.9% w/v solution.

Infusion solution for intravenous administration.

To be stored at +2°C to +25°C. Must not be frozen.

To be warmed up to room temperature before use.

Dosage: see study protocol Section 5.4

Patient No: _____ Visit Day.: ____

Bag number: __ of __

Date and time of preparation: _____

Infusion to be completed latest by (Date and time):_____

Investigator: _____

Any unused solution residues or waste material to be disposed according to local requirements at the study site.

Sponsor: Octapharma USA, INC. 117 West Century Road, Paramus, NJ, 07652 [redacted]

5.3 Conditions for Storage and Use

Octagam 10% should be stored and transported light-protected at +2°C to +8°C (36°F to 46°F) and must not be frozen. *Octagam 10%* must not be used after its expiration date.

Saline should be stored and transported according to its product information. Storage conditions will be stated on the IMP label.

The authorized personnel at the individual pharmacies will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

Octagam 10% is available in glass bottles with different volumes of human immunoglobulin. Glass bottles of different volume should be combined in order to reach the required amount of IgG.

Octagam 10% or placebo will be administered by intravenous infusions on 4 consecutive days. The amount of *Octagam 10%* calculated on the dosage delivery schedule is 2 g/kg divided evenly over 4 days (0.5 g/kg/day).

If a subject is randomized to receive placebo, the same volume with the same infusion rate as would have been applied in case the subject would have been randomized to

2.0 g/kg *Octagam 10%* will be used. Therefore, they will receive an equal dose of placebo given over 4 days.

Body weight is to be measured at Screening or within 24 hours of first IMP administration and reported to the pharmacist or designee as it is needed for the preparation of the following study medication dosages.

All subjects should be clinically assessed for being adequately hydrated prior to IMP administration. TEE prophylaxis should be considered.

The initial infusion rate for each infusion episode will be:

- 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes (± 5 minutes)
- if tolerated, advanced to 0.02 mL/kg/min (120 mg/kg/h) for the next 30 minutes (± 5 minutes)
- if tolerated, advanced to 0.04 mL/kg/min (240 mg/kg/h) for the remainder of the infusion

The interval of 30 minutes may be prolonged as per discretion of the investigator.

In subjects at risk for thromboembolic adverse reactions and acute renal failure (such as advanced age, hypertension, history of thrombotic episodes, subjects with prolonged periods of immobilization, concomitant nephrotoxic medication, diabetes mellitus, overweight, hypovolemia), *Octagam 10%* should be administered at the minimum rate of infusion practicable.

If AEs occur during the infusion, the rate is to be reduced to half the rate at which the event occurred, or the infusion is to be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the subject. In case of severe hypersensitivity or anaphylaxis, the infusion will not be restarted and all treatment with the IMP will be withdrawn. The subject will continue to be followed up in accordance with study-specific procedures as specified in the protocol with the exception that no further administrations of IMP will be performed. The subject will receive ongoing treatment in accordance with local SOC.

Events that will prevent the scheduled administration of study drug will include but not limited to:

- Uncontrolled blood pressure elevation (ie, systolic is ≥ 160 mmHg or diastolic is ≥ 90 mmHg)
- Chest pain with or without electrocardiogram changes
- Thrombotic events
- New onset seizures

- Acute Kidney Injury (AKI) as defined by KDIGO Clinical Practice Guideline for AKI as any of the following:
  - Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours
  - or Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
  - or Urine volume < 0.5 ml/kg/h for 6 hours
- Stroke
- Myocardial infarction.

5.5 Preparation and Method of Administration

Each bottle of *Octagam 10%* must be examined visually by the pharmacist or designee for particulate matter and discoloration prior to pooling. Non-homogenous solutions or those that have a deposit must not be pooled. The same procedures should be performed also for placebo.

The preparation of IMP should be performed under aseptic conditions preferably using a sterile bench, as described in the manual handed out to the hospital pharmacist or designee. IMP administration should be completed no later than 8 hours after preparation.

The *Octagam 10%* must be allowed to warm to room or body temperature prior to IMP administration. The same holds true for placebo for subjects in the placebo arm.

Subjects must be monitored before infusion and carefully observed for any symptoms at least once throughout the infusion period and at least 1 hour thereafter.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

The Investigators will be provided with an unblinding procedure to disclose the actual treatment of a particular subject in case of medical emergency; this can be a sealed envelope or its electronic equivalent.

To maintain blinding, infusions will be administered using blinded infusion over pouches and sites may opt to also use opaque or covered infusion lines. The blinded label will be fixed onto the infusion bag as well as to the opaque over pouch by the unblinded hospital pharmacist or designee. An over pouch (normally used for light protection) will be put over the infusion bag to maintain blinding. The new labels will be identical for both *Octagam 10%* and placebo, so that the content of the bags is only known to the unblinded hospital pharmacist or designee.

The unblinded pharmacist or designee will prepare and send the blinded infusion bag(s) per subject (and potentially with the opaque infusion line) to infusion center for administration.

To further assure the double-blind character of this study, the Investigator or designee who administers the medication to the subject will not be involved in any other evaluations other than drawing blood samples or checking for vital signs.

Breaking the blind in individual subjects during the double-blind study is permitted only in case of a SAE or unexpected ADR when knowing the type of the administered IMP is required for therapeutic decisions regarding this event to be taken.

A designated unblinded statistical team not otherwise involved in the study is unblinded to create randomization materials and provide the IDMC with unblinded study results as described in the IDMC charter and Statistical Analysis Plan (SAP).

Additional information on analysis timing and unblinded analyses can be found in Section 9.2.1.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site and IMP dispensed to subjects. A Drug Inventory and Dispensing Log will be kept current by the unblinded staff, detailing the dates and quantities of IMP received and dispensed to each subject and the remaining quantity.

The inventory and dispensing log will be available to the unblinded monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor depot for destruction. Destruction can be initiated only after accountability has been verified and fully reconciled by the unblinded monitor and after the Sponsor has granted written approval of destruction. IMP that was already used for preparation of the infusion can be destroyed after preparation.

5.7.2 Assessment of Treatment Compliance

All subjects will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the batch number(s) in the source data and eCRF.

6 STUDY CONDUCT

The flow chart of assessments by study visit is given in Table 1. Details regarding each assessment are provided in Section 7.

6.1 Observations by Visit

It is anticipated that all study visits will occur while subjects are hospitalized. If a subject is discharged from the hospital prior to the End of Study Visit (Day 33), final safety blood samples (see Section 7.3.4) will be taken on day of discharge, and study data for follow-up visits thereafter will be collected by telephone or telehealth (see Section 6.1.6).

6.1.1 Screening Visit

The following assessments will be performed during the Screening Visit, which should take place within 24 hours (1 day) before the first administration of IMP, unless otherwise indicated:

1. Obtaining voluntarily given, written (signed and dated) informed consent prior to any Screening procedures being performed. Consent can be given by legally authorized representative (LAR) if subject is not able to give consent.
2. Inclusion and exclusion criteria and diagnosis confirmation (including swab for RT-PCR confirmation of SARS-CoV-2 infection or review of results from swab performed during the 7 days prior to Screening)
3. Demographic, baseline characteristics, and medical history (including COVID-19 diagnosis date (see Section 7.1.4) and infection symptoms)
4. Body weight
5. Prior medication use
6. Vital signs including SpO_2 saturation (see Section 7.2.4) or arterial blood gas to confirm eligibility
7. MQoL-SIS
8. Physical examination

   Note: may be extracted from hospital admission information
9. Clinical Status and Oxygenation/Ventilator Status Evaluation
10. Blood sampling for clinical laboratory evaluations (specified in Section 7.3.4)

    Note: clinical laboratory samples taken within 7 days before Screening may be used for Screening assessments
11. Serum pregnancy test for females of child-bearing potential

12. Urine sample for legionella and pneumococcal antigens
13. Chest CT/Chest X-ray

    Note: may be performed within ± 1 day of Screening Visit

6.1.2 Baseline/Infusion, Visits 1 to 4 (Day 1 to Day 4)

After screening and confirmation of eligibility, subjects will be randomized to receive either placebo or Octagam 10% (blinded). Administration of the first infusion must be started within 1 day (24 hours) after the screening visit. In this acute disease setting, the clinical status of patients can change rapidly. If a patient's eligibility status changes (eg, they require intubation and mechanical ventilation or meet other exclusion criteria) between initial confirmation of eligibility and randomization, they will not be randomized and will be considered a screening failure.

The first infusion of IMP should be initiated as soon as possible after randomization. Eligibility will not be re-assessed again between randomization and dosing. All randomized patients will therefore be dosed irrespective of changes in their clinical condition between randomization and dosing unless the Investigator decides that administration of the IMP would place the patient at additional risk.

The following activities/assessments will be performed ***before*** the IMP infusion on Day 1:

1. Confirmation of inclusion and exclusion criteria
2. Body weight (if not performed at Screening)
3. Vital signs
4. Physical Examination (if not performed at Screening or available from hospital admission notes, see Section 6.1.1)
5. Confirm medical history
6. Chest CT/Chest X-ray (at Day 1 if not available at Screening, see Section 7.3.6)
7. A-a Gradient (see Section 7.2.4)
8. Clinical Status and Oxygenation/Ventilator Status Evaluation
9. Blood sampling for clinical laboratory evaluations (specified in Section 7.3.4)
10. Randomization

The following activities/assessments will be performed ***before*** the IMP infusion on Days 2 through 4:

- Vital signs

- Clinical Status and Oxygenation/Ventilator Status Evaluation
- Blood sampling for clinical laboratory evaluations (specified in Section 7.3.4)

All blood sampling (Section7.3.4) will be done ***before*** IMP infusion on all dosing days. If the Day 1 infusion commences within 8 hours of the blood collection for the Screening laboratory parameters, only those parameters not assessed at Screening need to be performed prior to the Day 1 infusion. Physical examination and body weight will be performed at Baseline (Day 1) only if it is not performed at Screening.

During and after IMP administration (Day 1 through Day 4):

The subject will receive either *Octagam 10%* medication in the dose of 2 g/kg administered over 4 days (0.5 g/kg/day), or an equivalent volume of placebo (saline), infused slowly over approximately 2 hours per day over 4 consecutive days. Note: Subjects must be monitored before infusion and carefully observed for any symptoms at least once throughout the infusion period and at least 1 hour thereafter.

The following activities/assessments will be performed on **Day 1 through Day 4**:

1. Infusion of IMP according to randomization code: *Octagam 10%* or placebo
2. Vital signs (taken once during and again after infusion)
3. SpO_2 saturation (see Section 7.2.4)
4. Post-infusion site assessment
5. Modified Borg Dyspnea Scale
6. MQoL-SIS
7. AE monitoring
8. Concomitant medication use review and documentation

6.1.3 Endpoint Visit 5 (Day 7)

The following assessments will be performed 3 days after the end of daily infusions (Day 7 or on day of discharge if prior to Day 6 and restrictions prevent inpatient Day 7 visit and not already performed as part of the assessments for that day):

1. Vital signs
2. SpO_2 saturation and A-a Gradient (see Section 7.2.4) (for subjects discharged prior to Day 6, telephone contact will be made with the subject on Day 7 to ascertain SpO_2)
3. Swab for RT-PCR detection of SARS-CoV-2 to determine infection status
4. Clinical Status and Oxygenation/Ventilator Status Evaluation

5. Modified Borg Dyspnea Scale
6. MQoL-SIS
7. Chest CT/Chest X-ray
8. Blood sampling for clinical laboratory evaluations (specified in Section 7.3.4)
9. AE monitoring
10. Concomitant medication use

6.1.4 Follow-up Visits 6 and 7 (Day 14 and Day 21)

The following safety assessments will be performed at Day 14 and Day 21 (see Section 6.1.6. if subject has been discharged):

1. Vital signs
2. SpO_2 saturation (see Section 7.2.4)
3. Clinical Status and Oxygenation/Ventilator Status Evaluation
4. Modified Borg Dyspnea Scale
5. MQoL-SIS
6. AE monitoring
7. Concomitant medication use

6.1.5 End of Study (Final Examination) Visit (Day 33)

An End of Study Visit will be performed and include the following assessments (see Section 6.1.6 if subject has been discharged):

1. Vital signs
2. Physical examination

   Note: may be extracted from daily physical examinations in hospital chart
3. SpO_2 saturation (see Section 7.2.4)
4. Clinical Status and Oxygenation/Ventilator Status Evaluation
5. Modified Borg Dyspnea Scale
6. MQoL-SIS
7. Blood sampling for clinical laboratory evaluations (specified in Section 7.3.4)
8. AE monitoring
9. Concomitant medication use

After Day 33, the core clinical study is considered completed for the subject. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs) require follow-up. After completion of the core 33-day trial, all subjects will be followed for a one-year follow-up registry. Subjects will be contacted by telephone or electronically by the Principal Investigator or the Sponsor (or its designee) every three months (± 14 days) for one year to obtain data on health status and any residual health effects from COVID-19 or the study treatment. There will not be any additional in-person site visits required. The responsibility for the oversight of this registry follow-up period will be managed by a central Coordinating Principal Investigator (not the enrolling Investigator responsible for the 33-day core trial), unless the local Investigator elects to continue to oversee their subjects directly during this one-year follow-up period. The data recorded during this registry follow-up period will be submitted as a supplement to the core study data once all subjects have completed one year of follow-up.

6.1.6 Telephone Visits

If a subject is discharged from the hospital at any time during the course of their participation in the study, a pulse oximeter will be provided to them to monitor their oxygen saturation at home. The Research Coordinator or other qualified research team member will contact the subject on Day 7 (if discharge took place on Day 5 or earlier), Day 14, Day 21, and Day 33 (if discharge took place prior to Day 33) at approximately the same time (± 2 hours) as the pre-infusion SpO_2 measurement recorded at Baseline (Day 1), to collect the following data points:

1. Clinical Status
2. SpO_2 saturation taken on resting room-air
3. AE and Concomitant medication review
4. Modified Borg Dyspnea Scale
5. MQoL-SIS

6.1.7 Subject Early Discontinuation

A study subject has a right to refuse study treatment and study visits at any time and for any reason. A subject can also withdraw from the study or study drug treatment for AEs, in which case the subject will be followed until resolution of the AE. Every effort will be made to assess the effect and outcome of the AE.

6.1.8 Time Windows Used in this Study, Including Tolerances

In this study, the following time windows and tolerances apply:

Table 2: Time Windows Used in this Study

Time point	Time stated	Tolerance
Screening Visit	24 hours before Visit 1	Max of 26 hours
Visits 1 to 4	Day 1 to 4	None
Visit 5	Day 7 or discharge day	± 1 day
Visit 6 and 7	Days 14 and 21	± 2 days
End of Study Visit	Day 33	± 3 days
Q3 month post-study follow-up	Every 3 months after completion of core trial or early termination	± 14 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Subject

The duration of the core study for each subject will be approximately 33 days: 1 day for Screening, 4 days for the treatment, and 29 days for safety follow-up and end of study assessments. Subsequently, subjects will be followed remotely for an additional year to record any new COVID-19 safety developments.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all subjects have completed the planned observation period/End of Study Visit.

The estimated start of the study (enrollment of first subject) is Q2 2020 and the estimated end of the study (last visit of last subject) is Q4 2020.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigators will ensure that adequate consideration is given to the protection of the subjects' interests.

Regulatory authorities and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be informed in accordance with national regulations.

Early termination of the study as a whole or by center may apply for the following reasons:

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.
- Any other reason rendering the continuation of the study impossible for the Sponsor.

6.2.3.2 Early Termination at an Individual Study Center

At any time, the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

The following information will be recorded during the Screening Visit:

7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics will include sex, age, race/ethnic origin, and weight.

7.1.2 Medical History

The medical history will be obtained by interviewing the subject and/or review of hospital charts. Records of past diseases and treatments (eg, hospital discharge letters) will be obtained for the study files, if available.

7.1.3 Prior and Concomitant Medication Use

Prior and concomitant medication use will be obtained by interview and/or review of hospital charts. Prior medications are defined as any taken within 1 week of the Screening Visit until the start of IMP infusion. Concomitant medications are defined as any with a start date and time after the start of the Day 1 infusion and their use will be collected throughout the study. Data collected will include the dose, route, and dates and times of administration, the identity of the concomitant medication, the reason for administration, as well as any changes in therapy during the course of the study.

7.1.4 Diagnosis Confirmation

COVID-19 infection will be confirmed using RT-PCR evaluated on nares/throat swab and/or sputum and/or lower respiratory tract samples. A positive result taken in the 7 days prior to Screening is acceptable.

7.2 Efficacy Assessments

7.2.1 Clinical Status

Clinical status categories will be defined according to the following 6-category clinical status scale:

1. Hospital discharge or meet discharge criteria (discharge criteria are defined as clinical recovery, ie, no fever, respiratory rate, oxygen saturation return to normal, and cough relief).
2. Hospitalization, not requiring supplemental oxygen.
3. Hospitalization, requiring supplemental oxygen (but not NIV/HFNC), as defined by A-a Gradient < 150 mmHg.

4. ICU/hospitalization, requiring NIV/HFNC therapy, as defined by A-a Gradient ≥ 150 mmHg.
5. ICU, requiring ECMO and/or IMV.
6. Death.

7.2.2 Oxygenation/Ventilator Status

Oxygenation status and/or ventilation status will be recorded at each scheduled visit, and in between visits if there is a change in status. The following will be captured:

Supportive measure required to maintain oxygen saturation:

- Nasal canula ≤ 4 L/min
- Nasal canula > 4 L/min
- Face mask
- Non-breather face mask
- Non-invasive ventilation
- Invasive mechanical ventilation.

Data will be used to calculate the incidence of invasive mechanical ventilation, duration of invasive mechanical ventilation and other changes in oxygenation status as required.

7.2.3 Viral Clearance

COVID-19 infection status will be re-assessed on Day 7 using an RT-PCR assay to evaluate viral clearance. A nares/throat swab and/or sputum and/or lower respiratory tract sample will be taken for the assessment. If the initial Day 7 RT-PCR test is negative, a repeat test will be performed as soon as possible and no later than at the Day 14 visit.

7.2.4 SpO_2 Saturation and A-a Gradient

SpO_2 will be recorded throughout the study, at a similar time each day, on room-air if possible. Measurements on Days 1 to 4 will be taken *prior to* infusion. Readings on Days 7, 14, 21, and 33 should be taken at approximately the same time each day as the pre-infusion measurements (± 2 hours). The pre-infusion value on Day 1 will serve as the baseline value. If a subject is discharged from the hospital at any time during the course of their participation in the study, a pulse oximeter will be provided to them to monitor their oxygen saturation at home. A call will be made to the subject at approximately the same time as the Day 1 pre-infusion SpO_2 measurement was taken (± 2 hours).

A-a Gradient will be recorded at Baseline (predose on Day 1) and Day 7 only if patient remains at a clinical status of 3 or 4 (see Section 7.2.1) using arterial blood gas (ABG) results. ABGs on Day 7 should be drawn at approximately the same time as the Baseline (Day 1) draw (± 2 hours).

7.2.5 Modified Borg Dyspnea Scale

Dyspnea will be measured by the modified Borg Dyspnea Scale which assesses dyspnea on a numerical scale from 0 (representing no dyspnea) to 10 (maximal dyspnea).

Table 3: Modified Borg Dyspnea Scale

Patient Instructions The Borg scale is used to help us understand the intensity or severity of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal.	
How much difficulty is your breathing causing you right now?	
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Source: https://scholarblogs.emory.edu/buddterrace/files/2016/03/Modified-Borg-Dyspnea-Scale.pdf

7.2.6 McGill Quality of Life

Quality of Life (QoL) will be measured by the McGill Quality of Life Single-Item Scale. The MQoL-SIS (see below) is a validated 1-item multidimensional tool designed to measure physical well-being, physical symptoms, psychological symptoms, existential well-being and support, as well as overall quality of life.

Considering all parts of my life – physical, emotional, social, spiritual, and financial – over the past two (2) days the quality of my life has been:

0	1	2	3	4	5	6	7	8	9	10
Very bad										Excellent

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

The following drug safety information shall be collected:

- AEs and SAEs temporally associated with the administration of IMP or placebo (for definitions and reporting requirements, see Sections 7.3.2, 7.3.3, and 7.3.3.1)
- Vital signs including SpO_2
- Clinical laboratory evaluations
- Radiological findings as reported on Chest CT or Chest X-ray
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see Section7.3.7).

7.3.2 Adverse Events (AEs)

7.3.2.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study subject receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase ‘response to an IMP’ means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, ie, the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the subject is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

The condition of the subject will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as “How have you been since the last visit/during the previous study

period?" In addition, the Investigator will check the subject diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the subject reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Sections 7.3.2.3, 7.3.3, and 7.3.2.4. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed, and the subject followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Abnormal laboratory results will only be recorded as AEs in the following circumstances:

- The abnormality requires medical intervention or concomitant therapy, and/or
- The abnormality suggests a disease and/or organ toxicity which is assessed as having developed or evolved since Screening.

In all cases, diagnoses should be documented, if possible.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

Mild: an AE, usually transient, which causes discomfort but does not interfere with the subject's routine activities

Moderate: an AE which is sufficiently discomforting to interfere with the subject's routine activities

Severe: an AE which is incapacitating and prevents the pursuit of the subject's routine activities

The grading of an AE is up to the medical judgment of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

Probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the subject's clinical state.

Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

Unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the subject's clinical state or by environmental factors or other therapies administered.

Not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

Unclassified: reports which for one reason or another are not yet assessable, eg, because of outstanding information (can only be a temporary assessment).

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

Expected: an ADR that is listed in the current edition of the IB or other reference safety information.

Unexpected: an ADR that is not listed in the current edition of the IB or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs will be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae

5. Fatal
6. Unknown

NOTE: A subject's **death** per se is not an event, but an outcome. The event which resulted in the subject's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) Taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available on site for anaphylaxis or other emergencies to ensure the best possible treatment. In case of anaphylaxis, the infusion will be stopped, and the subject will be withdrawn from the study.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (eg, physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the subject has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

NOTE: The term 'life-threatening' refers to an event in which the subject was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the subject. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.3.1 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee with the contact details provided to each site in the Investigator Site Binder. The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

[redacted]

[redacted]

24 hours emergency telephone numbers:

[redacted]

[redacted]

The Investigator must update the Octapharma Serious Adverse Event Report as soon as any additional information becomes available. The Investigator must also report SAEs to the IRB/IEC as required by local and national laws. The Investigator must maintain documentation of all communications to and from the IRB/IEC.

In accordance with 21 CFR 312.32 and local authorities, the Sponsor will submit to the FDA unexpected adverse reactions within 15 calendar days. Unexpected fatal or life-threatening adverse reactions will be submitted within 7 calendar days.

7.3.3.2 Waivers from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.3.4 Laboratory Safety Evaluations

The following laboratory parameters will be investigated during the study at the time points specified in Table 1: Flow Chart of Assessments and below.

All laboratory assessment will be performed at the local laboratories for each study site. In Russia and Ukraine, a central local laboratory could be used for all or part of the tests depending on the site facilities. Samples will be drawn prior to IMP infusions on Day 1 through Day 4, if appropriate:

Laboratory Measures at Screening:

- Comprehensive Metabolic Panel (CMP)
- Complete blood count (CBC) with differential
- D-Dimer
- Fibrinogen
- Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
- hsCRP
- Erythrocyte sedimentation rate (ESR)
- Ferritin, lactic acid dehydrogenase (LDH)
- Cytokines (IL-1Beta, IL-6, TNF-alpha, IFN-gamma)
- C3, C4, CH50
- Total CK, CK-MB fraction, myoglobin
- High sensitivity Troponin I (hs-cTnI) or cTnI-ultra
- Serum pregnancy
- Blood culture
- Urine legionella, pneumococcal antigens

Laboratory measures for Day 1 through Day 3 (If less than 8 hours between Screening lab draw and Baseline Day 1, Baseline labs do not need to be redrawn):

- BUN
- Serum creatinine
- Sodium
- Potassium
- D-Dimer
- Arterial Blood Gases (Day 1 only)

Laboratory measures for Day 4:

- BUN
- Creatinine
- Sodium
- Potassium
- PT, PTT, INR
- CBC with differential
- D-Dimer

Laboratory measures for Day 7:

- CMP
- ESR
- Fibrinogen
- PT, PTT, INR
- CBC with differential
- hsCRP
- D-Dimer
- Ferritin, LDH
- Arterial Blood Gases (for patients with a clinical status of 3 or 4)

Laboratory measures for Day of Discharge (only if discharge is after Day 7) or Day 33, whichever is sooner:

- CMP
- CBC with differential

- hsCRP
- Cytokines (IL-1Beta, IL-6, TNF-alpha, IFN-gamma)
- C3, C4, CH50
- Total CK, CK-MB fraction, myoglobin
- D-Dimer
- Ferritin, LDH
- High sensitivity Troponin I (hs-cTnI) or cTnI-ultra
- PT, PTT, INR
- Fibrinogen

The methods of determination and normal ranges for each parameter will be provided in the clinical study report.

7.3.5 Vital Signs and Physical Examination

Vital signs measurements, blood pressure, pulse, respiration rate, and body temperature (°C) will be recorded as indicated in Table 1: Flow Chart of Assessments.

Routine complete physical examination will be performed at the visits specified in Table 1: Flow Chart of Assessments. Any clinically significant worsening, as deemed by Principal Investigator, or new abnormality found during the exam will be documented as an AE.

7.3.6 Chest CT/Chest X-ray

A non-contrast Chest CT or Chest X-ray will be performed at Screening and Day 7 to assess clinically significant changes from Baseline (Day 1) as determined by the Investigator.

7.3.7 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs up to 4 weeks after the last IMP administration should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and state the relation to the clinical study in the report.

Deaths occurring within 4 weeks after the last IMP administration should also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

Every effort will be made to avoid pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported.

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the Clinical Project Manager or designee (see Section 7.3.3.1).

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

c) Overdose, interaction, medication error, and lack of efficacy

The following safety relevant information should be reported as AE or, if the reaction fulfills one of the criteria for seriousness, as SAE.

d) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

e) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, ie, increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

f) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

g) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected.

7.4 Appropriateness of Measurements

Efficacy evaluations, including assessing clinical status, measuring the modality required to maintain oxygen levels, measuring SpO_2 saturation, A-a Gradient, and ventilator status, are standard methods to evaluate maintenance or improvement of clinical status and respiratory deterioration. These evaluations are widely used, generally recognized as reliable, accurate, and relevant in this type of research, and are adequate to form the primary basis for the determination of efficacy. The 6-category

clinical status scale has recently been used in COVID-19 Remdesivir clinical studies (37).

Monitoring AEs, vital signs, laboratory safety tests, and physical examinations are standard procedures used to evaluate the safety of investigational products in clinical studies. The MQoL-SIS is a standardized, validated instrument that has been used in clinical studies.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (eg, case histories or subject files for each subject enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each subject enrolled, the Investigator will indicate in the source record(s) that the subject participates in this study.

Data entered in the eCRF must be supported by source data in the subject records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (eg, sub-investigators, nurses) or an external third-party to enter study data into the eCRF. The delegation of this task will be documented on the Delegation of Authority Log or the Central Data Entry Agreement if delegated to an external 3rd party.

8.1.2 Electronic Case Report Forms

For each subject enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff (eg, research nurse) or delegated third-party personnel will be responsible for entering subject data into the validated EDC system. All site or delegated third-party personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry.

The site or delegated third-party personnel is also provided with the approved eCRF Completion Guidelines to assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log or delegated via the Central Data Entry Agreement.

8.1.3 Changes to Electronic Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel or designee. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff or designee, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed, and programs are run throughout the study, until the data is clean, and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An IB will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning the IMP becomes available.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing CRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Investigator. In accordance with this authority log, study site staff (eg, sub-investigators, nurses) is authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (eg, copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential subject identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the subject's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the subject's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An IDMC will be established by the Sponsor. The IDMC will be composed of recognized experts in the field who are not actively recruiting subjects.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

This section provides a summary of statistical methods along with the definition of analysis populations. More details will be included in a SAP maintained in a separate document, prepared and approved by the Sponsor prior to study unblinding or before the project manager or study statistician can access the data, whichever happens earlier.

9.1 Determination of Sample Size

A subject is determined to reach the primary endpoint “stabilization or improvement in clinical status defined as maintenance or improvement by one category on a 6-category clinical status scale on Day 7” if the clinical status category on Day 7 is not worse than the clinical status category at Baseline (Day 1 prior to IMP infusion).

The study is determined to be successful if the proportion of subjects randomized to the IVIG group who reach the primary endpoint is significantly greater than the proportion of subjects randomized to the placebo group who reach the primary endpoint.

High-dose IVIG is used as a therapeutic option for severe-type COVID-19 (37) and given the severity of the population in our study as compared to the reference study, we assume 80% of subjects in the IVIG group and 60% of subjects in the placebo group will meet the primary endpoint.

With overall two-sided significance level of 0.05 when testing the difference in proportions between two treatment groups using normality approximation, 176 subjects (n=88 for each treatment group) will provide statistical power of at least 80%. Assuming a drop-out rate of 15% from Baseline (Day 1) relative to the efficacy assessment date at Day 7 after first dose for both groups, a final sample size of 208 (n=104 for each treatment group) is sufficient to maintain the minimum statistical power as 80%.

9.2 Statistical Analysis

9.2.1 Timing of Analyses

The final primary analysis will take place after database lock.

The primary analysis may also be conducted prior to database lock but after the last subject enrolled completes their Day 33 visit (or discontinues). If conducted, this analysis would be distributed to a limited unblinded team to evaluate the need to submit an emergency use application. Full details on this process will be provided in an unblinding plan and the clinical study report.

Upon end of study follow up, an end of study analysis may be conducted.

9.2.2 Analysis Populations

The analysis population is a cohort of study subjects defined for analysis for different scientific purposes and interpretation. For this study, the populations for analysis are defined as:

I. Enrolled Population (EP)

All subjects who are enrolled in the study will be included in the enrolled population (EP).

II. Intent-To-Treat Analysis Population (ITT)

All subjects who are randomized will be included in the intent-to-treat (ITT) analysis population and analysis will be conducted according to the study arm in which subjects are randomized, regardless of randomization errors or protocol violations.

III. Safety Analysis Population (SAF)

All subjects who are randomized and received any amount of IVIG or placebo will be included in the safety analysis set (SAF) and analysis will be conducted according to the treatment which subjects actually received.

IV. Per-Protocol Population (PP)

The Per-Protocol (PP) Population includes subjects who receive at least 75% of the planned dose (3 completed infusions of IVIG or placebo) without major protocol deviations that would potentially interfere with the efficacy assessment.

9.2.3 Efficacy Analysis Plan

9.2.3.1 Baseline and Demographic Data

Descriptive statistics, including mean, standard deviation, median, maximum, and minimum will be provided for baseline age, weight, vital signs, physical exam, laboratory results, and oxygen saturation. Gender, race and ethnicity, and other demographic information will be tabulated. Medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 23.0 and tabulated with start date, ongoing status, and end date, if applicable.

9.2.3.2 Primary and Secondary Endpoints

The ITT set will be used as the primary analysis set to analyze the primary endpoint. The handling of missing data is described in later section. A subject is determined to be a success if the clinical status category on Day 7 is not worse than the clinical status category at Baseline (Day 1, prior to IMP infusion). Subjects who use prohibited

concomitant medication (medications being administered as part of other experimental studies or the use of experimental non-IVIG products, such as COVID-19 convalescent plasma, or interferons) prior to the Day 7 clinical status assessment will be counted as failure.

A sensitivity analysis using all available data, regardless of prohibited medication usage, will be conducted.

The null hypothesis of no difference in proportion of subjects who reach success (clinical status not worse than the clinical status category at Baseline at Day 7) in two treatment groups will be tested versus the alternative hypothesis that there is a difference between proportions of subjects who reach success in two groups. Hypothesis testing will be performed using Cochran-Mantel-Haenszel (CMH) stratified by age category (≤65 versus >65) at a two-sided 0.05 significance level. The difference in proportions between the two groups with standard deviation, and 95% Miettinen-Nurminen CI will also be provided.

The durability of the treatment effect will be reviewed based on the comparison between treatment arms of proportions who are stabilized or improved at Day 14, Day 21 and Day 33 in the final analysis. No formal hypothesis testing will be made for the Day 21 and Day 33 analyses and the comparison will be carried out by difference of proportions, standard error and 95% CI of the difference of proportions between two treatment groups.

The analysis for secondary endpoints will be based on the ITT population. The hypothesis testing with p-value assessments for key secondary endpoints will be implemented for confirmatory purpose after statistical significance is claimed from the primary endpoint. The following key secondary endpoints will be analyzed by hierarchical procedure in the order specified below with overall two-sided type I error of 0.05:

1. Length of hospital stay (time to discharge) through Day 33
2. Proportion of subjects with stabilized or improved clinical status of at least one category on the 6-point clinical status scale on Day 14.
3. Cumulative duration of IMV through Day 33
4. Proportion of subjects with severe progression defined as requiring ECMO, IMV and/or have died through Day 33
5. Length of time in ICU through Day 33
6. Mortality rate through Day 33

Length of hospitalization is defined as (date of discharge – randomization date + 1). Subjects who are still hospitalized as of Day 33, subjects with missing end dates due

to withdrawal, subjects with unusable end dates due to prohibited medication use, or those who died on/prior to Day 33 will be censored at Day 33. The median time to discharge and associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. Comparisons between treatment arms will be performed using a log-rank test, stratified by age category. A rate ratio and associated 95% CI, equivalent to a hazard ratio from a Cox proportional hazard model stratified by age, will also be presented.

Proportion of subjects that stabilized or improved at Day 14 is defined analogously to the primary endpoint and hypothesis testing for proportions will be conducted as described for the primary endpoint.

Cumulative duration on IMV through Day 33 is defined as (IMV end date – IMV start date + 1). Subjects who do not require IMV will have a duration set to 0. Subjects who die on or prior to Day 33 or are still on IMV at Day 33, will have a duration set to their actual/projected Day 33 date for the IMV end date, so long as prohibited medication was not administered. If IMV end date is missing but subject is discharged from ICU or hospital, then IMV end date will be set to the earlier of the ICU or hospital discharge date. Otherwise, subjects without usable IMV end date information due to withdrawal or prohibited medication use will use a projected Day 33 date for the IMV end date. Comparisons between treatment arms will be performed using a stratified Wilcoxon-Mann-Whitney (van Elteren) test with age category as a stratification factor.

Proportion of subjects with severe progression will be defined as the proportion that require ECMO, IMV, or died prior to Day 33. For this analysis, subjects who use prohibited medication prior to the earliest date of progression or Day 33 will not be included in analyses. Hypothesis testing for this endpoint will be conducted as described for the primary analysis.

Length of time in ICU includes number of days spent in the ICU from randomization through Day 33 and is defined as [ICU discharge date – (later of ICU admittance date, randomization date) + 1]. Subjects who are not admitted to the ICU will have a duration set to 0. Subjects who die on or prior to Day 33 or are still in the ICU at Day 33, will have a duration set to their actual/projected Day 33 date for the discharge date, so long as prohibited medication was not administered. If ICU discharge date is missing but subject is discharged from hospital, then ICU discharge date will be set to hospital discharge date. Otherwise, subjects without usable ICU end date information due to withdrawal or prohibited medication use will use a projected Day 33 date for the ICU end date. Comparisons between treatment arms will be performed using a stratified Wilcoxon-Mann-Whitney (van Elteren) test with age category and baseline ICU status (In ICU at baseline versus not in ICU at baseline) as stratification factors.

Mortality rate is defined as the proportion of subjects who have died on or prior to Day 33. For this analysis, subjects who use prohibited medication prior to the earliest of death or Day 33 will not be included in analyses. Hypothesis testing will be performed as described for the primary analysis.

Key secondary endpoints which demonstrate statistical significance will be analyzed by subgroups including sex (male/female), race, ethnicity, geographic region, and disease severity (according to the definitions in the eCRF). All key secondary endpoints will be analyzed by age using testing analogous (unstratified) testing methodology to the specified analyses. Sensitivity analyses, using all available data, regardless of prohibited medication usage, will be conducted where applicable.

Additional details for missing data handling for key secondary endpoints are described in Section 9.2.4.

A detailed SAP describing additional missing data handling, additional sensitivity and subgroup analyses, and further details with respect to testing for each endpoint will be compiled as a separate document.

9.2.4 Safety Analysis Plan

Safety data analysis will be based on the SAF. Descriptive statistics will be provided for imaging assessments, clinical laboratory parameters, AEs, SAEs, and vital signs, including physical examination, concomitant medicines, concomitant procedures, and safety laboratory test results.

AEs observed will be classified using the MedDRA classification system version 23.0. AEs will be summarized by MedDRA system organ plan and preferred terms. Separate tabulations will be produced for related AEs, SAEs, discontinuations due to AEs, and events of at least Grade 3 severity. A summary of the number and severity of treatment-emergent AEs and study drug related AEs will also be produced.

Laboratory results will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 whenever possible. Laboratory parameters will be summarized for changes across study using descriptive statistics including shifts relative to NCI-CTCAE criteria for laboratory abnormalities. Laboratory measures will also be compared with their corresponding normal ranges, and the incidence of abnormally high and abnormally low laboratory values will be summarized.

9.2.5 Handling of Missing Data

In support of the primary and key secondary endpoints of stabilization or improvement in clinical status the following imputation methods will be used. For subjects with clinical status assessment at Baseline (Day 1) and at least one non-missing post-baseline clinical status assessment, last observation carried forward (LOCF) will be used to

impute the missing data at Day 7. However, if there is available data that otherwise indicates events such as death, ECMO or IMV, ICU admittance, occurred after the last non-missing clinical status assessment but on or prior to Day 7, the clinical status will be imputed according to the worst-case of either the LOCF or the clinical information available. Subjects with missing data at Baseline (Day 1) will be imputed as failure. Subjects with no post-baseline clinical status assessment on or prior to Day 7 will be imputed as failure.

Sensitivity analyses will be implemented by assuming all failure (worst case scenario) if subject has missing data at Baseline (Day 1) or Day 7, and where subjects with missing data are excluded.

Missing data for the outcome of clinical status at Day 14 will be imputed in the same fashion as in primary endpoint.

For the key secondary endpoint involving severe progression (ECMO, IMV, death, ICU admittance), subjects who withdrew early from study prior to Day 33 without evidence of events will be treated as not having the event. Sensitivity analyses will be conducted (1) treating them as failures (having the event at their last study visit) and (2) excluding them from the analyses. An additional analysis of these endpoints will be provided, treating prohibited medication use prior to Day 33 as an event, as well as allowing for status (event or success) without regard to prohibited medication use.

9.3 Randomization, Stratification, and Code Release

Each eligible subject will be randomized to either the treatment (IVIG) or placebo groups by study site. The randomization will be conducted using permuted blocks with block size randomly selected in each site stratum. A randomization statistician, not otherwise involved in the study, will generate the randomization list using a validated randomization program and deliver the allocation schedule to the unblinded study pharmacist in a secure and confidential manner. For Russia and Ukraine, this will be delivered with the help of the interactive response technology system. The pharmacist at the dispensing site will be unblinded to treatment and is responsible for blinding the study drug so that the infusion nurse, subject, and other study staff remain blinded to treatment. Moreover, since the pharmacist is not involved in the recruitment or management of subject, allocation concealment will be preserved. The process of blinding the study drug will be described in detail in another study supporting document.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (eg, contract research organization [CRO]) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the subject information and informed consent form, any other materials provided to the subjects, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any subject is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (eg, CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

10.3 Subject Information and Informed Consent

The Investigator will obtain freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the subject's decision to participate. The informed consent form must be signed, with name and date and time noted by the subject, before the subject is exposed to any study-related procedure, including Screening tests for eligibility.

For subjects not capable of giving legal consent, written consent must be obtained from the LAR.

The Investigator will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each subject enrolled.

Each subject will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed upon between the Investigator (Coordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the subjects, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of subjects treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Subject Data

The Investigator will ensure that the subject's confidentiality is preserved. On CRFs submitted to the Sponsor, the subjects will not be identified by their names, but by a unique subject identifier.

Transmission of any confidential subject documents from the investigative site to the Sponsor's 3rd party designee (eg, consent forms, source records, etc.) will occur via a secure cloud-based portal with advanced security features such as audit trails and two-factor authentication upon each log-in. This usage is compliant with the FDA Guidance on Conducting Clinical Trials during the COVID-19 Public Health Emergency (dated 03Jun2020). Subjects have consented to the recording and inspection of their personal data via the informed consent form, by the Sponsor or designee, in addition to ethics committees, national and international competent authorities and the FDA.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

Due to the current COVID-19 pandemic travel and hospital visitation restrictions, most hospitals do not permit monitors to visit the sites or pharmacies to conduct in-person study monitoring and data review. In order for the Sponsor to maintain oversight of the study data investigators must make study source records available for remote review by the study monitor in compliance with local and federal guidelines. Data monitoring will be conducted on an ongoing basis.

If in-person monitoring visits become possible, the monitor will review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness, and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

The Clinical Monitoring Plan will describe the requirements for remote and in-person monitoring procedures.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study. The Coordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a subject in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

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