EBS-CVH-002 Clinical Study Protocol

A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) for Postexposure Prophylaxis in Susceptible Adults at Increased Risk of Moderate to Severe COVID-19 Disease Following Exposure to SARS-CoV-2

Funding Source: United States Department of Defense

Document History:

Version Number	Date	Document Change History
1.0	22 Feb 2021	New Document

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) for Postexposure Prophylaxis in Susceptible Adults at Increased Risk of Moderate to Severe COVID-19 Disease Following Exposure to SARS-CoV-2
Study Number:	EBS-CVH-002
Study Product:	Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human)
IND Number:	23023
Sponsor:	Emergent BioSolutions Canada Inc. 155 Innovation Drive Winnipeg, MB, R3T 5Y3, Canada
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SIGNATORY PAGE

EBS-CVH-002, Draft Version 0.1 07 Aug 2020:	A Phase 2, Double-Blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) for Postexposure Prophylaxis in Susceptible Adults at Increased Risk of Moderate to Severe COVID-19 Disease Following Exposure to SARS-CoV-2
Clinical Site(s):	[To be filled]

My signature below verifies that I have read and agree to this protocol. I am aware of my responsibilities as an investigator under the GCP guidelines of ICH, the Declaration of Helsinki, local regulations (as applicable) and the study protocol, and I agree to conduct the study according to these regulations.

Site Principal Investigator:

Principal Investigator Name (print)	Title (print)
Principal Investigator Signature	Date (YYYY/MMM/DD)

Sponsor Signatory:	*See signature page at end of document*	
Emergent BioSolutions Canada Inc. 155 Innovation Drive Winnipeg, MB, R3T 5Y3, Canada	Chris Cabell Sr VP, Clinical Development	Date (YYYY/MMM/DD)

EBS-CVH-002 STUDY SYNOPSIS

Study Title:

A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) for Postexposure Prophylaxis in Susceptible Adults at Increased Risk of Moderate to Severe COVID-19 Disease Following Exposure to SARS-CoV-2

Study Number: EBS-CVH-002

Study Product: Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) [COVID-HIGIV] is a purified liquid immunoglobulin G (IgG) preparation

Type of Study:	**Proposed Indication:**
Safety and Efficacy study	COVID-HIGIV is indicated for postexposure prophylaxis following exposure to SARS-CoV-2
Phase of Development: Phase 2	**Sites:** Up to 35 sites in North America

Sponsor:

Emergent BioSolutions Canada Inc. (Emergent)

155 Innovation Drive

Winnipeg, MB, R3T 5Y3, CANADA

Estimated Duration of Individual Participation: five weeks

Objectives and Outcome Measures:

Objectives		**Outcome Measure**
Primary Efficacy	To assess the efficacy of COVID-HIGIV (two dose levels) as postexposure prophylaxis for the prevention of symptomatic RT-PCR confirmed COVID-19	RT-PCR[1] confirmed symptomatic COVID-19[2] within 28 days (by Study Day 29) postdose
Primary Safety	To assess the safety of COVID-HIGIV (two dose levels)	Adverse events within 72 hours postdose Discontinuation or temporary suspension of infusion (for any reason) Adverse events within 28 days postdose Serious adverse events within 28 days postdose

Secondary Efficacy	To assess the efficacy of COVID-HIGIV (two dose levels) as postexposure prophylaxis for prevention of COVID-19 by symptom severity	Mild RT-PCR confirmed COVID-19 within 14 days (by Study Day 15) postdose Moderate to severe/critical RT-PCR[1] confirmed COVID-19[2] within 28 days (by Study Day 29) postdose
	To assess the effect of COVID-HIGIV (two dose levels) on SARS-CoV-2 virologic outcome measures	Change in nasopharyngeal viral load (as assessed by SARS-CoV-2 RT-qPCR[1]) from Day 1 (predose) to Days 4, 8, 15, and 29 postdose in participants with detectable virus (SARS-CoV-2 RT-PCR positive) at Day 1
		SARS-CoV-2 nasopharyngeal RT-PCR[1] status (positive/negative) from Day 1 (predose) to Days 4, 8, 15 and 29 in participants with no detectable virus (SARS-CoV-2 RT-PCR negative) at Day 1
Exploratory	To assess detection of SARS-CoV-2 viral RNA through RT-qPCR performed on saliva samples	SARS-CoV-2 saliva RT-PCR status (positive/negative) and viral load from Day 1 to Days 4, 8, 15, and 29 as assessed through RT-qPCR using saliva samples
	To assess the incidence of death	All-cause mortality and COVID-19 related mortality within 28 days (by Study Day 29) postdose
	To assess the efficacy of COVID-HIGIV (two dose levels) time (days) to onset and duration of COVID-19 symptoms	Time (days) to onset and duration of COVID-19 symptoms
	To assess the efficacy of COVID-HIGIV (two dose levels) by subgroups	Efficacy of COVID-HIGIV by age (<65 and ≥65 years of age), gender, race (white vs. non-white), ethnicity, Day 1 SARS-CoV-2 RT-PCR status, exposure risk (number of Level 2 criteria met), comorbidities (cardiac, pulmonary, renal, diabetes), BMI (< 30, ≥ 30-<40, ≥ 40 kg/m^2), and smoking status (current, prior, never)
	To describe anti-SARS-CoV-2 IgG levels postdose (two dose levels)	Anti-SARS-CoV-2 IgG titer postdose on Days 1, 4, 15 and Day 29 (calculation of PK endpoints to the extent that data allow (C_{max}, T_{max}, AUC_{0-7d}) using binding assay)

[1]RT-qPCR will be done to generate both qualitative (positive/negative status) and quantitative (viral load) data in positive RT-PCR samples.
[2]Cases of RT-PCR confirmed COVID-19 will be determined according to the case definition outlined in Section 7.1.

Overall design

This a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of COVID-HIGIV for postexposure prophylaxis in asymptomatic susceptible adults at risk for moderate to severe COVID-19 within five days of a high-risk exposure to SARS-CoV-2.

The study will evaluate the safety and efficacy of two dose levels of COVID-HIGIV (100 mL and 300 mL) compared to placebo for the prevention of symptomatic RT-PCR confirmed COVID-19 (N=360). Eligible participants will be randomized 1:1:1 to receive intravenously either COVID-HIGIV at one of two dose levels (n=120 each) or normal saline placebo (n=120) as shown in Table 1. Participants will be stratified by site and SARS-CoV-2 antigen status at screening. A minimum of 45 individuals with positive baseline SARS-COV-2 antigen test results (n=15 per study arm) will be targeted for enrollment.

Table 1 EBS-CVH-002 Study Design Schematic

Study Population	Treatment Group	Number of Participants Per Arm	Study Treatment[2]	Primary Outcome Measure
Asymptomatic susceptible adults with a high -risk exposure within 5 days N=360	Group 1	n=120	COVID-HIGIV[1] (300 mL)	RT-PCR symptomatic confirmed COVID-19 within 28 days (by Study Day 29)
	Group 2	n=120	COVID-HIGIV[1] (100 mL)[2]	
	Group 3	n=120	Placebo[3] (300 mL)	

[1]COVID-Hyperimmune Globulin – Intravenous.
[2]Volume will be administered to each participant in three separate 100 mL bags containing either undiluted product or 0.9% normal saline.
[3]0.9% normal saline placebo administered intravenous route.

Safety Monitoring Committee:

An independent blinded Safety Monitoring Committee (SMC) will be responsible for assessing safety and monitoring overall conduct and integrity of the study.

An unblinded team will support the SMC and review unblinded study data and make a recommendation on whether to pause study enrollment for SMC review according to prespecified rules outlined in the SMC charter in the event of a suspected risk of an excess of moderate to severe/critical COVID-19 outcomes in the treatment arm.

The blinded SMC will review blinded safety data. Study enrollment and IP administration may be temporarily paused at the discretion of the SMC chair for safety review by the SMC if any of the following adverse events occur after administration of COVID-HIGIV:

- ≥ one Grade 4 serious adverse event or death regardless of relatedness to IP
- ≥ one Grade 3 hypersensitivity event
- ≥ five of the same Grade 3 adverse events

The severity of AEs will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, DAIDS. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Total Number of Participants: N=360

Eligibility Criteria

Inclusion Criteria: All participants must meet all the following inclusion criteria to be enrolled into the study:
All participants must meet all the following inclusion criteria to be enrolled into the study:

1. Willing and able to provide written informed consent prior to performing study procedures
2. Males or females ≥18 years of age
3. Females must not be pregnant as demonstrated by either one of the following:
    a. Not of childbearing potential: surgically sterile (six weeks post-bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or postmenopausal defined as women ≥ 50 years of age with a history of ≥12 months without menses prior to randomization in the absence of other pathologic or physiologic causes, following cessation of exogenous sex-hormonal treatment

    or:

    b. Of childbearing potential (WOCBP): women who are not planning to be pregnant during the study period (up to 28 days after randomization) and meet all the following criteria:
        - Negative urine pregnancy test at Screening Visit
        - Use of an acceptable method of highly effective contraception (if female of CBP) for the duration of participation, such as:
            - Hormonal contraceptives (e.g., implants, pills, patches) initiated ≥30 days prior to dosing
            - Intrauterine device (IUD) inserted ≥30 days prior to dosing
            - Double barrier type of birth control (male condom with female diaphragm, male condom with cervical cap)

4. Rapid COVID-19 IgM and IgG antibody negative
5. No COVID-19 related symptoms defined as new or increased onset of ≥1 of the following symptoms: fever (temperature ≥100.4ºF), nasal congestion, sore throat, cough, muscle aches, headache, nausea or vomiting, shortness of breath, diarrhea, loss of smell or taste
6. Had a high-risk exposure to SARS-CoV-2 infection within five days of Screening as defined by at least one of the criteria below:
    a. Prolonged close contact[1] with one or more individuals with individual(s) with symptomatic, confirmed COVID-19[2] without wearing a mask/face shield while person's eyes, nose, mouth were potentially exposed to material infectious with SARS-CoV-2
    b. Present in the room for procedures that generate aerosols or during which respiratory secretions are likely to be poorly controlled (e.g., cardiopulmonary resuscitation, intubation, extubation, bronchoscopy, nebulizer therapy, sputum induction) on patients with confirmed COVID-19 when eyes, nose, or mouth were not protected. Exposure of any duration is considered a prolonged exposure if the exposure occurred during performance of an aerosol generating procedure

    [1]*Close contact is defined as follows: a) being within approximately six feet (two meters) of a person with confirmed, symptomatic COVID-19 for >15 minutes or b) having unprotected direct contact with infectious secretions or excretions (e.g., being coughed on, touching used tissues with a bare hand) of a confirmed, symptomatic COVID-19 patient. c) exposure during a confirmed outbreak in an institutional setting (e.g., long-term care facility) defined as follows: resident or health care provider with confirmed COVID-19, resident with severe respiratory infection due to confirmed COVID-19 resulting in hospitalization or death, or ≥3 residents or health care provider(s) with new onset respiratory symptoms within 72 hours of each other suspected to be due to COVID-19 (1),(2).*

    [2]*Confirmed COVID-19 patient defined as person with laboratory-confirmed symptomatic COVID-19 anytime during period from 48 hours before onset of symptoms until meeting criteria for discontinuing home isolation (3), (4). Documentation of confirmed COVID-19 contact is required.*
7. Having one or more risk factors for moderate to severe/critical COVID-19 disease (5) defined as the following:
    - BMI ≥30 kg/m^2
    - Age ≥65 years
    - Type 2 Diabetes Mellitus
    - Mild to moderate Chronic Kidney Disease defined as eGFR ≥30
    - Chronic Obstructive Pulmonary Disease

- Chronic cardiac condition (≥1 of the following): history of coronary artery disease, cardiomyopathy, congestive heart failure classified as New York Heart Association Class 1 or II

Exclusion Criteria: Participants who meet any of the following exclusion criteria will not be enrolled into the study:

1. Prior receipt of COVID-19 vaccines or COVID-19 antibody-based treatments (e.g., anti-SARS-CoV-2 monoclonal antibodies given individually or in combination regimens, convalescent plasma treatment from donors who have recovered from COVID-19; receipt of remdesivir within the last 24 hours)
2. Receipt of live attenuated virus vaccines within three months prior to screening or anticipated receipt of live attenuated virus vaccine within three months after receipt of COVID-HIGIV
3. Use of any investigational product within 30 days prior to screening
4. Planned use of any investigational product for the duration of the study with the following exception: participants who are hospitalized for management of moderate to severe/critical COVID-19 may be permitted to co-enroll in trials of COVID-19 investigational treatments for moderate to severe/critical disease.
5. History of allergy to latex or rubber
6. History of hypersensitivity to blood or plasma products or to COVID-HIGIV excipients (proline, PS80)
7. History of IgA deficiency and/or documented presence of anti-IgA antibodies
8. Current or prior history of hemolytic anemia
9. History of immunodeficiency defined as ≥1 of the following:
    - Steroids >10 mg/day for at least the last seven days
    - Treatment with biological medicine to treat autoimmune disease or cancer
    - Antirejection medicine after solid or stem cell transplantation
    - Cancer treatment in last six months
    - Primary or acquired severe and ongoing immune dysfunction affecting B- or T-lymphocyte function
10. A pre-existing condition or concomitant medication that may place the individual at a substantially increased risk of thrombosis[1]

[1]prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome, cryoglobulinemia, severe refractory hypertriglyceridemia, or clinically significant monoclonal gammopathy, or any of the following within one month prior: arterial or venous thrombosis, acute coronary syndrome, cerebrovascular syndrome

11. Acute illness within the last 14 days
12. Severe chronic illness that would preclude receipt of up to 300 mL volume of intravenous fluid (e.g., NYHA class III or IV heart failure, nephrotic syndrome, end stage renal disease on hemodialysis, end stage liver disease)
13. Abnormal lab results at screening with any of the following:
    - Absolute neutrophil count ≤800 cells/mm^3
    - Serum creatinine >2.5 times ULN
    - AST >2.5 X ULN
    - ALT >2.5 X ULN
    - Hemoglobin ≤9 g/dL
    - Rapid HIV ½ positive
14. Recent transsphenoidal surgery, cerebrospinal fluid leak, encephalocele (<three months)
15. Any condition that could prevent the ability of the participant to comply with the protocol-specified assessments, in the opinion of the investigator
16. Enrollment would not be in the best interest of the participant, in the opinion of the investigator
17. Life expectancy <3 months per the opinion of the investigator

Study Product, Dose, and Mode of Administration:

COVID-HIGIV (85–115 mg/mL protein), 300 mL single dose, intravenous

COVID-HIGIV (85–115 mg/mL protein), 100 mL, single dose, intravenous

Reference Product, Dose, and Mode of Administration:

Placebo: 0.9% normal saline, intravenous

Statistical Methods:

The primary endpoint is the odds ratios (OR) for participants to develop RT-PCR confirmed symptomatic COVID-19 by Day 29 where the two active dose groups will each be compared with the placebo group. Logistic regression will be used including baseline RT-PCR status as a covariate in addition to treatment indicator. Hypothesis testing of no treatment effect will be carried out at a 2.6% two-sided alpha with adjustment for multiplicity using Dunnett's method.

As a key secondary analysis of the primary endpoint, an average treatment effect between all COVID-HIGIV treated participants versus those who received placebo will be estimated using logistic regression with the same covariate adjustment, with one indicator for treated vs. placebo. OR and 95% CI will be reported for the average effect. Statistical

significance (at 5% level) will only be assessed when both dose levels show statistically significant benefits as described above.

Sample Size and Statistical Power:

It is assumed that the two dose levels are chosen such that both are expected to be efficacious with comparable effect sizes. As each dose level group will be compared with the placebo group, testing of no treatment effect will be carried out at the 2.6% level (two-sided) to control the overall 5% type I error rate using Dunnett's method.

The power of the study depends on the baseline risk of RT-PCR confirmed symptomatic COVID-19 in the placebo group and the treatment effect. A sample size of 120 participants per treatment group provides approximately 80% power to detect a relative risk of 50% (OR = 0.375) when the baseline risk is 40% using a one-sided 1.3% level chi-squared test for each comparison with allowance for ~20% of participants lost to follow-up.

Study Populations

The following analysis sets pertain to the study:

- Intent-to-Treat Set (ITT): participants who are randomized. This set will be used for the primary analysis for efficacy endpoints, and participants will be grouped by the study treatment to which they are randomized. For selected secondary endpoints, the following subsets will be used:
    - Baseline positive ITT subset: participants with positive Day 1 SARS-CoV-2 RT-PCR as determined by the central laboratory
    - Baseline negative ITT subset: participants with negative Day 1 SARS-CoV-2 RT-PCR as determined by the central laboratory
- Safety Set (SS): all ITT participants who receive any amount of study treatment (either COVID-HIGIV or normal saline placebo). This set will be used for safety analysis, and participants will be grouped by study treatment received.

Schedule of Events

An unplanned visit for suspected COVID-19 illness or adverse event (AE) can occur at any time between Day 1 and Day 29 if COVID-19 or an AE is suspected.

Table 2 Schedule of Events

Visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**Unscheduled**
Visit description	**Screening**	**Randomization/ Dosing (Day 1)**	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 29 Follow-Up Visit/End of Study Visit/Early Withdrawal visit**	**Potential COVID-19 illness visit/Potential AE visit**
Visit type	**In-clinic**	**In-clinic**	**Telephone**	**At home or in-clinic[13]**	**At home or in-clinic[13]**	**At home or in-clinic[13]**	**At home or in-clinic[13]**	**At home or in-clinic[13]**
Visit window	**0 to 1 day Before Day 1**	**+1 day**	**+1 day**	**±1 day**	**±1 day**	**±2 days**	**±2 days**	**Optimally Within 1-3 Days After Potential COVID-19 Illness Onset or Adverse Event**
Obtain Informed Consent	X							
Obtain demography[1] and medical history data, including exposure history	X							
Collect information on concomitant medications		X	X	X	X	X	X	X[14]
Perform physical examination [2]	X	X		X[14]	X[14]	X[14]	X[14]	X[14]
Measure vital signs[3]	X	X[4]		X	X	X	X	X[14]
Obtain height and weight and calculate BMI	X							
Collect blood samples for hematology and chemistry, viral marker laboratory tests (local lab)	X[5]			X[6]	X[14]	X[14]	X[14]	X[14]
Obtain nasal swab for rapid SARS-CoV-2 antigen test (local lab)[7]	X							
Obtain blood for rapid COVID-19 IgG/IgM (qualitative) (local lab)[7]	X							

Obtain nasopharyngeal swab and saliva sample (central lab)[8]		X		X	X	X	X	X[14]
Obtain blood for COVID-19 IgG/IgM (quantitative) (central lab)[9]	X	X[10] (1 hr postdose)		X	X	X	X	X[14]
Perform urine pregnancy test (if appropriate) (local lab)	X							X[14]
Review test results	X[11]	X[12]		X	X			X[14]
Confirm eligibility	X	X						
Confirm use of contraceptives (if appropriate)		X	X	X	X	X	X	X[14]
Randomization and Study Treatment Administration		X						
Monitor participants for at least six hours after the start of the infusion		X						
Provide symptom e-diary device or ensure participant has application on personal device & provide instructions		X						
Provide thermometer and pulse oximeter & provide participant instructions/guidance		X						
Review symptom e-diary card and/or assess for COVID-19 related symptoms and obtain start and stop dates for COVID-19 related symptoms			X	X	X	X	X[15]	X[14]
Collect AEs and SAEs		X	X	X	X	X	X	X[14]
Collect medical records from COVID-19 related hospitalizations and medical attended visits (if applicable)				X	X	X	X	X[14]
Counsel participants on precautions for reducing transmission of COVID-19	X	X	X	X	X	X	X	X[14]
Assess potential for re-exposure to SARS-CoV-2			X	X	X	X	X	X[14]

[1]Date of birth, gender, race/ethnicity.
[2] Physical examination will be performed on all participants at screening and day 1. At all other time points, physical exams will be performed if clinically indicated.
[3]Vital signs include temperature, sitting blood pressure, respiratory rate, pulse oximetry, and pulse for all visits.
[4]Vital sign assessments are performed 0–1 hour predose and at 1, 3 and 6 hours postinfusion (±15 minutes) for this visit only.

[5] Screening: serum BUN/creatinine, ALT, AST, CBC with differential, hepatitis B surface antigen, rapid HIV ½ test, anti-HCV. If anti-HCV is positive, obtain HCV-RNA.
[6]Days 4: serum BUN/creatinine, ALT, AST, hemoglobin.
[7]The nasal swab (taken at screening) will be tested using the rapid SARS-CoV-2 antigen test locally at the site and result used for stratification. The result from the rapid IgM/IgG antibody test will be used to determine eligibility (local).
[8]For Days 1, 4, 8, 15 and 29 one nasopharyngeal swab and one saliva sample will be taken and sent to the central laboratory. NP swab will first be tested for SARS-CoV-2 with qualitative RT-PCR (all participants). Quantitative RT-PCR will be run only on RT-PCR positive samples. Saliva sample will be tested with quantitative RT-PCR only if initially positive from NP qualitative RT-PCR test.
[9]Screening, Day 1, 4, 8, 15, 29 serum samples for SARS-CoV-2 IgM/IgG quantitative test (central lab).
[10]Draw Day 1 blood sample one-hour post infusion (±15 minutes) for SARS-CoV-2 antibody level assessment and send to central lab for all participants.
[11] Review results of local labs: serum BUN/creatinine, ALT, AST, CBC with differential, urine pregnancy test, rapid HIV ½ test, rapid COVID-19 IgM/IgG, rapid SARS-CoV-2 antigen test to determine eligibility.
[12]Review results of hepatitis B surface antigen, anti-HCV and determine whether additional tests are necessary (HCV-RNA) and enter results when available.
[13]Home visit or in-clinic visits permitted at these time points for collection of vital signs and samples (blood, nasopharyngeal swabs, saliva). All home visits will include an investigator follow-up (via telemedicine).
[14]If clinically indicated
[15]Review of e-diary card will only occur if early withdrawal visit occurs before Day 15 visit. Day 29 visit will not include e-diary card review. All visits will evaluate COVID-19 related symptoms.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Definition
ACE2	Angiotensin-converting enzyme 2
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
ALT	Alanine aminotransferase
anti-HCV	Antigen (HBsAg), Hepatitis C virus antibody
AST	Aspartate aminotransferase
CBC	Complete blood count
CCP	COVID-19 convalescent plasma
CFR	Code of Federal Regulations
CI	Confidence interval
CNJ-016®	Vaccinia immune globulin intravenous (Human)
COVID-19	Coronavirus disease 2019
COVID-HIGIV	Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human)
CRO	Contract research organization
CRF	Case Report Form
DAIDS	Division of Acquired Immunodeficiency Syndrome (AIDS)
DMP	Data management plan
EAP	Expanded access program
eCRF	Electronic case report form
EDC	Electronic data capture
Emergent	Emergent BioSolutions Canada Inc.
EUAs	Emergency use authorizations
FDA	U.S. Food and Drug Administration
GCP	Good clinical practices

Abbreviation or Specialist Term	Definition
HBsAg	Hepatitis B surface antigen
HepaGam B®	Hepatitis B immune globulin (human)
HIV	Human immunodeficiency virus
HRSV	Human respiratory syncytial virus
IB	Investigator's Brochure
ICH	International conference on harmonization
ICU	Intensive care unit
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G (gamma globulin)
IgM	Immunoglobulin M
IGIV	Immunoglobulin intravenous
IRB	Institutional review board
IP	Investigational Product
ITT	Intent-to-Treat Set
IUD	Intrauterine device
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MM	Medical monitor
NAAT	Nucleic acid amplification tests
NHP	Non-human primates
NIAID	National Institute of Allergy and Infectious Diseases
NP	Nasopharyngeal
NP-028	Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human)

Abbreviation or Specialist Term	Definition
OR	Odds ratio
PD	Protocol Deviations
PE	Physical exam
PEP	Postexposure prophylaxis
PI	Principal investigator
PK	Pharmacokinetics
PS80	Polysorbate 80
PSO	Postsymptom onset
PT	Prothrombin time
PV	Pharmacovigilance
REB	Research ethics board
RR	Relative risk
RTSM	Randomization and trial supply management
RT-PCR	Reverse transcriptase polymerase chain reaction
RT-qPCR	Reverse transcriptase quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TnBP	Tri-n-butyl phosphate
TNF-α	Tumor necrosis factor alpha
TRALI	Transfusion related acute lung injury

Abbreviation or Specialist Term	Definition
TX-100	Triton X-100 (octyl phenylpolyethylene glycol ether)
U.S.	United States of America
VARIZIG®	Varicella zoster immune globulin intravenous (human)
VIGIV	Vaccinia immune globulin intravenous (human)
WinRho® SDF	Rh_o (D) immune globulin intravenous (human)
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background Information

1.1.1 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19)

The COVID-19 pandemic caused by SARS-CoV-2 has resulted in significant worldwide increase in hospitalizations for pneumonia with multiorgan failure (6). In December 2019, a cluster of patients with pneumonia of unknown cause in Wuhan, China was reported and by January 2020 the causative agent of the illness was identified; initially termed novel coronavirus 2019 (2019-nCoV) and later renamed to SARS-CoV-2 (7). Due to the spread of SARS-CoV-2 resulting in sudden increase in COVID-19 cases throughout the world, a pandemic was declared by World Health Organization (WHO) in March 2020. By the end of December 2020, >83 million COVID-19 cases and >1.8 million COVID-19 attributed deaths have been reported to the WHO. In the U.S. and Canada, COVID-19 cases continue to rise prompting public health authorities to continue active monitoring and focus on containment of the outbreak to prevent further spread (8).

1.1.2 Natural History of COVID-19

The incubation period for SARS-CoV-2 is approximately four to five days (range: two to seven days) (9), (10), and most individuals who develop symptoms (~98%) will do so within 11.5 days post-infection (9). Acute manifestations of COVID-19 include the following signs and symptoms: fever, cough, shortness of breath, fatigue, myalgia, nausea/vomiting or diarrhea, headache, rhinorrhea, anosmia, ageusia, diarrhea (11).

Many COVID-19 patients present with mild disease (81%). Although mild, symptomatic COVID-19 often resolves five to seven days (and up to 14 days) after symptom onset, there is growing recognition of the occurrence of postinfectious sequelae lasting for months in individuals, including young, physically fit individuals who initially experienced mild acute illness (12). Fatigue, dyspnea, cough, arthralgia and chest pain are among the most commonly reported. Based on current available evidence, postinfectious sequelae may also include serious outcomes: cardiac (myocardial inflammation, ventricular dysfunction), respiratory (pulmonary function abnormalities); renal (acute kidney injury), dermatologic (rash, alopecia), neurologic (altered cognition, memory impairment, olfactory and gustatory dysfunction, sleep dysregulation) and psychiatric (depression and changes in mood).

Approximately 14% of patients develop severe COVID-19 characterized by worsening dyspnea and hypoxia, severe pneumonia with >50% lung involvement on imaging. The median time from symptom onset to hospitalization is seven days; range: three to nine days postsymptom onset (13). Five percent of patients progress to critical COVID-19 manifested as acute respiratory distress syndrome, septic shock and/or multiorgan system dysfunction (10), (14), (15), (16). Cardiac, neurologic, hepatic, renal and hematologic complications may occur (17). Mortality in hospitalized COVID-19 patients ranges from 15% to 40% (18).

Reports of reinfection have been infrequent despite millions of SARS-CoV-2 infections worldwide to date (19). Currently, the best characterized cases of reinfection occurred at least 90 days after first illness onset (19).

1.1.2.1 Risk Factors for Moderate to Severe COVID-19

Approximately 25% of infected patients have underlying health conditions; however, 60–90% of hospitalized COVID-19 patients have significant comorbidities. The strongest and most consistent evidence currently supports the increased risk of the following comorbidities with severe outcomes from COVID-19: chronic kidney disease, chronic obstructive pulmonary disease, chronic cardiac conditions, obesity (BMI ≥30 kg/m2) and type 2 diabetes mellitus (20). Older adults are at increased risk of requiring hospitalization or dying. Approximately eight out of 10 COVID-19 deaths reported in the U.S. have been in adults 65 years of age and older. The risk of hospitalization in adults 65–74 years of age is five times higher than younger adults 18–29 years of age; the risk of death is 90-fold higher (21), (13). The evidence to support the list of underlying risk factors for severe disease is rapidly evolving and may be updated as new information emerges (20).

1.1.2.2 High-Risk Exposure and SARS-CoV-2 Transmission

It is estimated that up to 62% of SARS-CoV-2 transmission may occur via presymptomatic carriers (22), (23), (24). Observational and epidemiological studies confirm the effectiveness of cloth masks (25), (26). For example, an investigation of a high-exposure event in a hair salon with 100% compliance with masks indicated that none of 67 clients who spent an average of 15 minutes with two symptomatically ill hair stylists were infected with SARS-CoV-2 (27). The epidemiology of SARS-CoV-2 currently indicates that most infections are spread through close contact via respiratory droplets generated when people cough, sneeze, sing, talk or breathe during close face-to-face contact (within six feet/two meters) without wearing a mask (22).

Aerosol spread (airborne transmission) may occur (28) in crowded, indoor, enclosed spaces, with prolonged exposure to respiratory particles (e.g., shouting, singing, exercising) and inadequate ventilation or air handling (27). Such conditions can lead to SARS-CoV-2 attack rates as high as 87%, as occurring in a 2.5-hour indoor choir practice attended by 61 persons including a symptomatic index patient (29).

In household settings, secondary attack rates range from 4% to 55% (30), (31). Higher secondary attack rates are associated with age >60 years, exposures to confirmed, symptomatic COVID-19 contacts, and spouse/intimate partner relationship to the confirmed contact (32).

Long-term care facilities, which account for 36% of virus-related deaths, are associated with high attack rates among residents, staff members and visitors that can be associated with hospitalization rates as high as 57% for elderly residents (33), (34). Despite the prioritization of long-term facilities in the Advisory Committee on Immunization Practices (ACIP) recommendations for COVID-19 vaccination, current reports indicate that outbreaks are expected to continue in the coming months even as the vaccination campaign accelerates

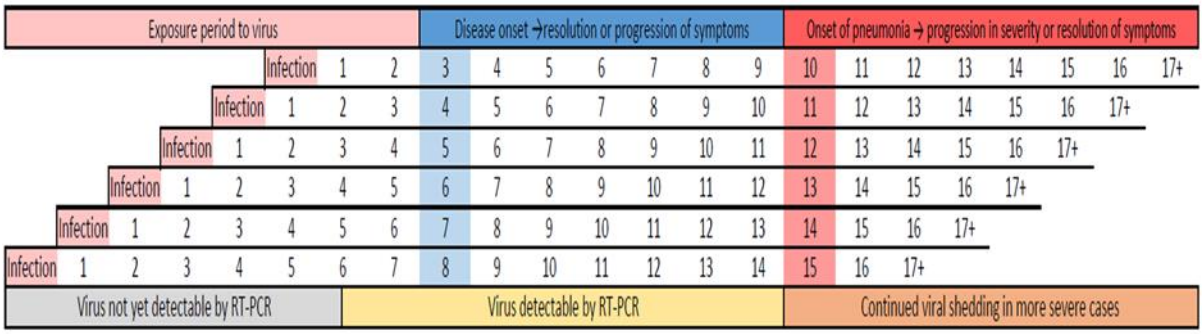
(35), (36) due to logistic challenges of the roll-out and vaccine hesitancy among staff members.

1.1.2.3 Viral Kinetics of SARS-CoV-2 Infection and Host Immune Response

Upon infection, SARS-CoV-2 viral replication starts in the upper respiratory tract followed by the lower respiratory tract and can progress to other ACE2-receptor containing cell types found in the GI tract, blood vessels, CNS and heart tissue (37). Viral shedding starts two to three days prior to symptom onset and peaks around the time of symptom onset (38), (39). Results from 43 studies in >3000 individuals show that mean viral ribonucleic acid shedding lasts for 17 days in the upper respiratory tract (reviewed in 40). Lower respiratory tract viral shedding lasts on average 14.6 days and typically peaks within the second week of illness (40). Although rare, maximum shedding duration has been reported as 83 days and 59 days in upper and lower respiratory tracts, respectively (41), (42). Viral shedding duration is correlated with disease severity, age, and sex (40). Although SARS-CoV-2 ribonucleic acid can often be detected in throat swabs for weeks after the onset of symptoms, viral cultures are generally negative eight days after symptom onset (38), (39), (43).

IgM and IgA antibodies to SARS-CoV-2 are detectable five days (range: three to six days) postsymptom onset (PSO). The IgM response peaks 18–20 days PSO and declines rapidly up to 60 days later, while IgA and IgG responses remain stable for 40 days and three up to four months PSO, respectively (44). IgG antibodies are detectable 14 days (range: five to 18 days) PSO (45). Neutralizing SARS-CoV-2 antibodies are detectable 10–15 days PSO (46) and although they decline over time, existing data shows they are still detectable in most individuals up to seven months later (47), (48), (49). Reinfections, while rare, primarily occur in mild cases that seem to have not mounted adequate immune responses (50). Most antibodies are targeted against the nucleocapsid (N) and viral spike (S) proteins, the latter being particularly important in sterilizing immunity (51). Although high variability in antibody kinetics has been described across individuals, IgG antibody titers correlate with disease severity (45), (52), (53). The level of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) produced is correlated with disease severity, and is a key driver in the cytokine storm that contributes to long-term tissue damage and mortality (54), (55).

Figure 1 Natural History of COVID-19 Following Exposure to SARS-CoV-2 (days)



1.1.3 Current Standard of Care for the Treatment and Prevention of COVID-19

General methods to prevent COVID-19 based on current guidance are to wear a mask in public settings, practice social distancing and avoid crowds and poorly ventilated indoor spaces (56). In December 2020, regulatory agencies in both the U.S. and Canada authorized emergency use of the Moderna® and Pfizer-BioNTech® vaccines for pre-exposure prophylaxis of COVID-19 (57), (58), (59), (60). The United States ACIP has recommended a phased roll-out of vaccine as follows: 1) vaccination of health care personnel and long-term care facility residents be offered COVID-19 vaccination first (Phase 1a); 2) vaccination of all persons aged ≥75 years and non-health care frontline essential workers (Phase 1b); 3) vaccination of persons 65–74 years, persons 16–64 years with high risk medical conditions and essential workers not included in Phase 1b (Phase 1c); 4) vaccination of individuals 16 years and older. Federal, state, and local jurisdictions are advised to use the ACIP guidance for COVID-19 vaccination program planning and implementation (61).

Individuals with mild to moderate COVID-19 disease not requiring supplemental oxygen are currently provided with symptomatic treatment if needed and instructed to follow public health protocols for self-isolation and return to the hospital if symptoms worsen. Current treatment guidelines in the U.S. and Canada do not recommend the use of specific therapies for acute illness except in a clinical trial (62), (63), (64). The current standard of care for hospitalized patients with severe disease requiring supplemental oxygen includes dexamethasone with or without remdesivir in addition to supportive care. Although monoclonal antibody (mAb) (bamlanivimab or casirivimab plus imdevimab) have been available through emergency use authorizations (EUAs) since November 2020 for outpatients who are at high risk of disease progression, current treatment guidelines (updated December 2, 2020) indicate that bamlanivimab or casirivimab plus imdevimab should not be considered for the standard of care for treatment of patients with COVID-19 (65), (66).

1.1.4 Postexposure Prophylaxis

Postexposure prophylaxis (PEP) refers to an intervention to prevent disease after suspected or documented exposure to a pathogen (67). Unlike pre-exposure prophylaxis which is intended for the prevention of disease in healthy individuals prior to a discrete (known) exposure, PEP is often administered within a short window period postexposure (e.g., 72 hours). The decision to administer PEP involves consideration of factors related to both the source (contact) and the exposed patient: 1) whether the source is determined to be infected with the disease 2) whether the source is infectious at the time of exposure 3) type and characteristics of the exposure 4) susceptibility of the exposed individual 5) anticipated risks and benefits of the PEP regimen.

There are numerous pathogens (e.g., influenza, varicella zoster virus, pertussis, tuberculosis) for which effective strategies for PEP have been developed (67). In some cases, PEP is effective not only in preventing development of disease in the exposed individual but also in reducing the risk of secondary transmission to other susceptible persons. In the case of highly transmissible respiratory pathogens (e.g., influenza), asymptomatic infection can occur early following exposure prior to the development of clinical symptoms. In addition, due to

practical considerations, the typically short window necessary to administer PEP following a documented exposure (e.g., <48 hours), rapid implementation of PEP in an outbreak setting often does not allow time to verify the infection status of the exposed individual.

Despite the availability of COVID-19 vaccines, it is expected that strategic use of primary, secondary and tertiary prevention methods, including PEP for COVID-19, will be crucial to controlling the pandemic and preventing severe outcomes. While the EUAs of both COVID-19 vaccines were based on compelling efficacy data from large adequate and well-controlled studies indicating >90% efficacy in preventing COVID-19 disease (68) (69), there are currently a number of data gaps pertaining to the benefits of vaccination (70). These include uncertainties regarding 1) the duration of protection >2 months postvaccination 2) vaccine effectiveness in certain populations at high risk of severe COVID-19 (e.g., immunocompromised) 3) vaccine effectiveness in individuals previously infected with SARS-CoV-2 4) vaccine safety and effectiveness in pediatric populations 5) future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus and/or potential effects of co-infections 6) vaccine effectiveness against asymptomatic infection and transmission 7) vaccine effectiveness in preventing death. The recent emergence of SARS-CoV-2 variants in the United Kingdom and South Africa (B.1.1.7 and B.1.351 lineages) raises additional questions pertaining to the ability of emerging variants of the SARS-CoV-2 virus to 1) transmit more easily 2) alter disease severity 3) evade detection by diagnostic tests 4) evade vaccine-induced immunity (71), (72). A phased roll-out of vaccination was initiated in December 2020 in the U.S. and Canada. Since it is expected that initial supplies will be scarce, certain groups have been targeted to receive vaccine with targets to vaccinate most of the population by the second half of 2021. To achieve this target, it is estimated that approximately 1.5–3 million people per day would need to be vaccinated to achieve at least 75% coverage by June 2021 (73). In the first month of the roll-out, an estimated 4.5 million doses were administered (74), highlighting barriers to uptake which include not only logistics of delivery but also vaccine hesitancy. Vaccine hesitancy among an estimated 43% of healthcare providers who typically play a crucial role in fostering vaccine acceptance among the vaccine hesitance has been a source of growing alarm (75). Modellers have forecasted a number of possible trajectories for the course of the COVID-19 pandemic in the U.S. (76), (77). These scenarios cite the potential for SARS-CoV-2 to either: 1) become endemic, resulting in seasonal transmission, or 2) be eliminated with the development of a late resurgence. For certain groups at high risk for COVID-19 transmission due to confined living spaces in congregate housing (e.g., nursing home population, military, college dorms), COVID-19 outbreaks are likely to continue to pose a challenge. For example, the COVID-19 outbreak on a nuclear-powered aircraft carrier USS Theodore Roosevelt with a crew of 4779 personnel highlights the ease with which SARS-CoV-2 spreads in military settings. After the first laboratory-confirmed infection, more than 1000 infections were identified within five weeks (78). Since the outbreak on the USS Theodore Roosevelt, it has become apparent that despite the institution of measures for preventing transmission such as strictly supervised quarantines, daily symptom monitoring and testing, transmission clusters within platoons among Marine Corps recruits still occur (79).

Thus, despite numerous recent advances, control of the COVID-19 pandemic continues to remain a challenge and safe and effective interventions continue to be urgently needed.

1.1.5 Unmet Medical Need for Postexposure Prophylaxis for COVID-19

Current guidance for individuals who have had close contact with a person with known or suspected COVID-19 is to 1) stay home until 10–14 days after last exposure and maintain social distance (at least six feet from others at all times 2) self-monitor for symptoms, and 3) avoid contact with people at higher risk for severe illness from COVID-19 (80) (81).

There are currently no products licensed or authorized in the U.S. or Canada for PEP of COVID-19 disease. Current treatment guidelines recommend against the use of any agents for SARS-CoV-2 postexposure prophylaxis except in a clinical trial (62). Therefore, there exists an unmet medical need for interventions to prevent disease in COVID-19 patients following exposure to SARS-CoV-2.

1.2 Study Drug

1.2.1 Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) – COVID-HIGIV

Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human), also referred to as COVID-HIGIV, is a hyperimmune product that consists of purified immunoglobulin (IgG) fraction of human plasma containing antibodies (including neutralizing antibodies) to SARS-CoV-2. COVID-HIGIV is prepared from pooled plasma collected at U.S. Food and Drug Administration (FDA) licensed and/or registered plasma and/or blood collection centers and Health Canada licensed/U.S. FDA licensed and/or registered plasma collection centers from healthy, adult donors who have elevated levels of SARS-CoV-2 antibodies.

COVID-HIGIV is provided as a sterile liquid for Intravenous (IV) administration only. The product is a clear to slightly opalescent and colorless or pale, yellow liquid essentially free of foreign particles. The final product is a liquid that contains 85–115 mg/mL protein (target 100 mg/mL) of which at least 90% is purified human IgG, stabilized with 250 mM proline and 0.03% polysorbate 80 (PS80), at target pH 5.8. The potency of the final product is determined by a validated immunoassay that measures concentration of binding SARS-CoV-2 antibodies (with SARS-CoV-2 trimeric S protein as the antigen) in relation to a reference standard.

Please refer to the most current version of the Investigator's Brochure (IB) for additional details.

1.2.2 Proposed Indication

COVID-HIGIV is indicated for postexposure prophylaxis (PEP) following SARS-CoV-2 exposure in adults ≥18 years of age.

1.2.3 COVID-HIGIV as an Intervention for SARS-CoV-2/COVID-19

Antibodies have been pursued as therapeutics for postexposure protection and treatment of COVID-19, both in early disease and in more severe patients with COVID pneumonia and hypoxia. Antibody therapeutics under development include the use of innate immune cells. The ability of antibody therapies to impact COVID disease course may depend on neutralizing titers and the timing of administration postinfection. As discussed below, it is becoming evident that earlier intervention may be more beneficial than later for convalescent plasma, mAbs and both human and equine-derived hyperimmune globulins. Antibody therapeutics can direct antiviral effects through neutralization of virus by blocking cellular entry and replication as well as immune mediated protection such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADCP) by administration after onset of severe respiratory symptoms in a proinflammatory state.

Preclinical data: Animal studies show that both polyclonal and monoclonal (mAb) antibodies administered intravenously are efficacious against SARS-CoV-2. Passive transfer of COVID-19 convalescent serum reduced lung virus load in both non-human primates (NHP) and hamsters when administered one day postinfection, with complete protection (sterile immunity) when treated one day before infection (82), (83). Several mAbs showed a protective effect by reducing tissue virus load and lung pathology when given within a window of one day before or one day postinfection in NHPs and hamsters (84), (85), (86), suggesting efficacy of antibodies in PEP. Evidence to date demonstrates that administration of antibodies in NHP and hamsters infected with a human SARS-CoV-2, significantly reduces the virus replication in the respiratory system and prevents the development of lung pathology.

In human clinical trials in recently tested SARS-CoV-2 positive patients, mAb treatments showed a reduction in viral load in upper respiratory samples, with the greatest effect seen in patients treated earlier in disease course (87), (88). These data suggest that antibody therapeutics have the potential to impact SARS-CoV-2 viral replication which may result in reduced disease severity.

Preclinical studies to demonstrate efficacy of COVID-HIGIV in animal models are ongoing and the report is pending. Preliminary data have shown that COVID-HIGIV reduces disease burden (lung virus load) in mice (transduced with adenovirus encoding hACE2) infected with SARS-CoV-2, and mortality of transgenic mice (expressing hACE2) infected with SARS-CoV-2 is also reduced by COVID-HIG treatment. Passive transfer of anti-SARS-CoV-2 antibodies with neutralizing activity [e.g., mAbs isolated from recovered COVID-19 patients] has been shown to be effective and disease burden in animals after exposure to SARS-CoV-2 at modulating SARS-CoV-2 infection and reducing viral load (including in the lung tissue) (89), (90), (91).

Clinical data: Two outbreaks, one on a fishery vessel and one at a high school overnight summer retreat, led to viral transmission to seronegative individuals but not to individuals who were seropositive after a previous SARS-CoV-2 infection (92), (93) supporting protective immunity postinfection. Clinical data on passive transfer of SARS-CoV-2

antibodies via transfusion of convalescent plasma collected from individuals who recovered from COVID-19 (i.e., COVID-19 convalescent plasma [CCP]; which contains binding and neutralizing IgA, IgM, and IgG antibodies against SARS-CoV-2) to COVID-19 patients suggest that there are no elevated safety risks due to CCP transfusion and that there may be a potential clinical benefit in patients with severe COVID-19 (94), (95), (96), (97), (98).

COVID-19 convalescent plasma rapidly became an intervention for hospitalized patients after initial reports from open label treatment studies (94), (95), (97) supported use under an expanded access program (EAP) in the U.S. Data emerging from the EAP and other published studies have demonstrated the safety and suggested the benefit of passive immunotherapy with CPP (96), (99), (100), (101), which supported EUA for CPP in hospitalized COVID-19 patients (102). Contrary to EAP experience, randomized controlled studies in India and Argentina have failed to demonstrate efficacy of CPP in patients hospitalized with COVID-19 (103), (104). Limitations to CPP include the 1:1 donor to recipient treatment and a lack of consistent neutralizing potency from unit to unit. Despite limitations, recent analyses of over 3000 patients treated with CPP in the U.S., has shown a mortality benefit for treatment with CPP with high neutralizing antibody titers in comparison to low titer CPP as well as benefit with intervention earlier in disease course (105) prior to the need for mechanical ventilation. These data speak both to a threshold of antibody levels and to the timing of intervention prior to a hyperinflammatory state. Selection of high titer CPP combined with early intervention has also been supported by a randomized placebo-controlled trial of high titer CPP in older adults treated within 72 hours of symptom onset mild COVID-19 (106). Despite stopping early due to a decrease in the regional COVID-19 incidence in Argentina, this study showed a 48% reducing in the incidence of severe COVID-19 in patients infused with high titer CPP. Neutralizing mAbs and antibody cocktails have also demonstrated the benefit of early treatment in the prevention of COVID disease progression. Bamlanivimab and the combination of casirivimab and imdevimab (REGN-CoV2) have received EUA for the treatment of mild to moderate COVID-19 in patients at high risk of disease progression (107), (108). In the BLAZE-1 trial, bamlanivimab treatment resulted in decrease in SARS-CoV-2 viral load a reduction in COVID-19-related hospitalizations and emergency room visits (87) compared to placebo treated patients. Similar results were observed for the REGN-COV2 mAb cocktail with a decrease in medically attended visits with antibody treatment in ambulatory patients (88). The study also demonstrated the benefit of early antibody seroconversion, as outpatients who were seropositive at baseline had lower viral load and a trend for faster alleviation of symptoms than seronegative patients (109). Additional studies are underway in hospitalized patients with COVID-19. Monoclonal antibody intervention may also be of benefit in moderate illness with evidence of COVID pneumonia, however mAbs may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Thus, mAb use support early treatment benefit and the benefit of early seroconversion.

Ongoing Clinical Studies with COVID-HIGIV: Currently two clinical trials with Emergent's COVID-HIGIV product are ongoing. Emergent has partnered with the U.S. Government (USG) to advance this program by working closely with Biomedical Advanced Research and

Development Authority (BARDA) and National Institute of Allergy and Infectious Diseases (NIAID) for participation in randomized controlled trials with COVID-HIGIV for treatment of COVID-19 [INSIGHT 013]. The INSIGHT 013 trial [NCT04546581] is an international, multi-center, adaptive, randomized, double-blind, placebo-controlled trial of the safety, tolerability and efficacy of a single dose infusion (400 mL) of COVID-HIGIV for the treatment of adult hospitalized patients at the onset of clinical progression of COVID-19 (N=500). Participants received one of four HIGIV products (from different manufacturers) or placebo. The primary efficacy endpoint is an ordinal outcome (ranging from death to asymptomatic COVID-19) based on the participant's clinical status on Day 7. As of February 1, 2021, INSIGHT 013 had randomized 521 participants, including 136 participants who received the Emergent COVID-HIGIV product (110) (111). There have been no other significant safety issues reported to date. Enrollment is currently targeted to be complete by mid-February 2021.

EBS-CVH-003 is a Phase 1 double-blind, randomized, placebo-controlled study in healthy adults to assess the safety and pharmacokinetics of three dose levels of COVID-HIGIV.

Seven participants enrolled as of January 25, 2021. No serious adverse events (SAE) have occurred to date. Enrollment is targeted to be complete by end-February 2021.

Risk assessment: The risk assessment for COVID-HIGIV and mitigation strategies for EBS-CVH-002 are summarized in Table 3.

Table 3 Risk Assessment for COVID-HIGIV

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: COVID-HIGIV		
Potential for infusion-related reactions (back or abdominal pain, nausea and vomiting, fever, headache, chills, rash or fatigue) within 30 minutes to six hours after starting the infusion.	These are common adverse reactions seen with other human hyperimmune IGIV products (VARIZIG®, HepaGam B®, ANTHRASIL®, WinRho® SDF, CNJ-016®-VIGIV) (112), (113), (114), (115), (116).	The study requires a safety monitoring period for at least six hours following the start of the infusion. Infusion stopping rules and study stopping rules are provided (Sections 8.6.5 and 8.6.6).
Potential for hypersensitivity reactions within six hours after starting the infusion.	Hypersensitivity reactions are rare. Severe immediate hypersensitivity reactions to plasma-derived products occur in individuals with IgA deficiency or hypersensitivity to human globulin.	Participants will be monitored for six hours from the start of infusion in a setting with appropriate equipment, medication and personnel trained in the management of hypersensitivity, anaphylaxis and shock. Participants at risk of hypersensitivity reactions are excluded from the study.
Potential for renal dysfunction/acute renal failure.	Renal dysfunction has been associated with HIGIV products containing sucrose as a stabilizer.	COVID-HIGIV does not contain sucrose. Serum blood urea nitrogen and creatinine will be monitored at

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Screening and at Day 4 postinfusion.
Potential for hematologic complications such as hemolytic anemia and thrombotic complications.	Rare thrombotic events have been associated with presence of activated factor XI resulting in elevated procoagulant activity in some immunoglobulin products. High doses (>1–2 g/kg) are associated with an increased risk of hemolysis.	COVID-HIGIV has been tested for procoagulant activity and has met the product release specification. The COVID-HIGIV doses being administered are well below 1 g/kg. Hemoglobin will be monitored at Screening and at Day 4 postinfusion. Participants with pre-existing thrombotic or procoagulant disorders are excluded from the study.
Potential for aseptic meningitis syndrome (AMS)	AMS rarely occurs in association with high doses (1–2 g/kg) of IGIV therapy. AMS begins within several hours to two days following IGIV treatment.	The COVID-HIGIV doses being administered are well below 1 g/day. Participants will be monitored for six hours from the start of infusion and at Days 2 and 4 postinfusion.
Potential for transfusion related acute lung injury (TRALI)	TRALI is associated with high doses (1–2 g/kg) of IGIV therapy. TRALI occurs one to six hours post transfusion.	The COVID-HIGIV doses being administered are well below 1 g/day. Participants will be monitored for six hours from the start of infusion.
Potential for transmission of infectious diseases	Human plasma is used in the manufacture of COVID-HIGIV. Plasma is collected in accordance with regulatory requirements and donors are screened to assess the risk of exposure. Plasma donations are tested for HIV ½, HCV, and Hepatitis B.	Viral markers for Hepatitis B, Hepatitis C, and HIV ½ will be obtained from participants at Screening to document baseline status. Additional follow-up tests will be performed only if clinically indicated.
Potential for immunologic interference with live attenuated virus vaccine or the COVID-19 vaccine	IGIV may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella. Concomitant administration of antibody therapies and the COVID-19 vaccine may result in immunologic interference.	The use of live virus vaccination before or after COVID-HIGIV should follow current recommendations. COVID-19 vaccination should be deferred for 90 days following SARS-CoV-2 infection or administration of antibody therapies per current ACIP recommendations (117).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential for COVID-19 enhancement	Disease enhancement has been identified with other viruses (e.g., MERS, respiratory syncytial virus, feline coronavirus). Available clinical data support the effectiveness of other immune-based therapies against severe disease and do not indicate a risk of enhanced disease (70), (106).	An unblinded team will review cumulative data during the study including rates of severe COVID-19 disease by treatment arm. All participants are followed for COVID-19 illness.
Study Procedures		
Participants may have in-clinic visits which could involve attendance at healthcare facilities during the global SARS-CoV-2 pandemic.	There is a potential for increased exposure/transmission of SARS-CoV-2.	Participants will have the opportunity to have a home visit for vital signs and collection of study specimens followed by a telemedicine appointment with the investigator so they may remain in quarantine. Participants will be counseled on precautions for reducing transmission of COVID-19.
Participants will undergo nasopharyngeal swab testing.	There is a potential for discomfort, risk of gagging during the test. Participants may have a minor nosebleed afterwards. Rarely cerebrospinal fluid leak has been reported following testing COVID-19 testing (118).	Only appropriately qualified personnel will obtain the nasopharyngeal swab. Individuals at risk for serious complications following nasopharyngeal swab testing (e.g., CSF leak) are excluded from participation in the study.
Blood draws will be performed during the study.	There is a risk of bleeding, bruising, hematoma formation and infection at the venipuncture site.	Only appropriately qualified personnel will obtain the blood draw.

The available clinical safety and efficacy data from immune based therapies such as convalescent plasma and mAbs that have achieved EUA support early intervention to prevent serious outcomes associated with COVID-19. Preclinical data with COVID-HIGIV and safety data from ongoing COVID-HIGIV studies (INSIGHT 013 and EBS-CVH-003) in >100 participants to date support the initiation of additional studies to evaluate the role of COVID-HIGIV as postexposure prophylaxis for COVID-19. The expected risks associated with IGIV therapy based on robust clinical experience with other IGIV therapies are mitigated as outlined in Table 3.

1.2.4 Scientific Rationale for Phase 2 Design

EBS-CVH-002 is designed to evaluate the safety and efficacy of COVID-HIGIV in asymptomatic susceptible adults following a high-risk exposure for the prevention of symptomatic laboratory-confirmed COVID-19. The study population for EBS-CVH-002

includes individuals with risk factors for developing severe disease. The safety and preliminary efficacy data are additionally intended to support evaluation of the product in a lower risk population (e.g., younger adults <45 years of age with and without risk factors for moderate to severe disease in an outbreak setting) in a separate study.

Dose selection: The goal of postexposure prophylaxis is to neutralize virus through binding and activation of antibody-dependent immunity to prevent disease progression. A rapid increase in SARS-CoV-2 viral replication can occur in the nasopharynx following a high-risk exposure (1–3 days prior to symptom onset), peaking prior to symptom onset (2–14 days postexposure) followed by peak viral replication in the lung in the weeks following symptom onset as discussed in Section 1.1.2. As a result, selection of an effective COVID-HIGIV dose for postexposure prophylaxis should be adequate to neutralize peak levels or viral titers. The neutralizing antibody level associated with protection from clinical manifestations of SARS-CoV-2 has not been established. The selected doses for evaluation are based on data available from convalescent plasma donors, including post-infection antibody levels and data from treatment studies with known titers of convalescent plasma, and data emerging from vaccine trials are suggestive of antibody levels that may be protective.

Emergent's manufacturing process for COVID-HIGIV includes the identification and screening of convalescent plasma donors. Plasma screening is primarily with an in-house binding assay to spike protein, however several assays including viral neutralization and external binding assays including Ortho Vitros (119) and Mount Sinai Laboratory COVID-19 ELISA (120) have been tested for correlation. This experience has identified a range of neutralizing titers in convalescent donors. Based on published reports demonstrating that seroconversion was associated with protection from SARS-CoV-2 infection (92), (93), the neutralizing antibody levels observed in convalescent plasma donors are expected to be above the protective threshold for SARS-CoV-2 infection and disease. Plasma testing data allow a high-level comparison of COVID-HIGIV neutralizing antibody potency to that of CCP used in therapeutic clinical trials. For example, comparison of COVID-HIGIV potency to the high titer CCP in an early treatment study in elderly patients Argentina (106), suggest that COVID-HIGIV contain four to six-fold higher neutralizing antibody levels than plasma. Thus, a dose of 250 mL high titer plasma associated with a reduction in incidence of severe disease, is expected to be equivalent to 40–60 mL COVID-HIGIV. When comparison to the recent analysis of CCP treatment in hospitalized patients from the U.S. National registry (105), higher titers of binding and neutralizing antibodies were associated with decreased 30-day mortality. In comparison to CCP in the high titer group, COVID-HIGIV is estimated to be approximately three times as potent as the high titer plasma. The medium titer plasma group in that analysis covers a large range of antibody potency, which represents the majority of convalescent plasma donors (unpublished data on file).

Vaccine studies also provide an early estimate of antibodies levels that correlate with protection, especially as vaccine studies include results comparing convalescent plasma control samples with samples from vaccinated subjects. Data from both the Moderna mRNA-1273 vaccine and Pfizer BNT162b2 mRNA vaccine suggest protection against symptomatic disease within a few weeks postvaccination (69), (121) (122), (123), (124). At that time,

antibody levels are similar to the low end of the CPP neutralizing antibody range. With second vaccination, antibody levels achieved postvaccination with both vaccines are toward the higher high end of the CPP neutralizing antibody range.

The potency of COVID-HIGIV plasma pools and final product is reported in Alliance Units (AU/mL) utilizing a standard that has been used across manufacturers in the NIAID sponsored treatment study INSIGHT 013. In AU/mL, the neutralizing antibody potency of COVID-HIGIV is approximately eight to 10-fold higher than the mean and median, respectfully, of convalescent donor plasma. Product lots planned for this trial have neutralizing potency > 800 AU/mL by a developmental neutralizing assay. The two dose levels selected for the clinical trial will be delivered as fixed dose volumes of 100 mL and 300 mL of COVID-HIGIV, corresponding to neutralizing potency doses of >80,000 AU and >240,000 AU, respectfully. These doses are expected to achieve neutralizing antibody levels within the range observed in CCP donors and is expected to provide higher antibody levels than high titer CCP used therapeutically in clinical trials. Considering that patients will be exposed to an unknown amount of virus, and viral levels can rapidly increase in asymptomatic individuals during the protocol allowed period between exposure and treatment, the range of 100 to 300 mL can assess whether there is a benefit across dose levels based on neutralizing potency.

Justification of Placebo Comparator: There is a critical need for placebo-controlled trials to establish the safety and effectiveness of products for the treatment and prevention of COVID-19 (125). There are no licensed or authorized products indicated specifically for postexposure prophylaxis in the U.S. and Canada. Current treatment guidelines recommend against the use of any agents for SARS-CoV-2 postexposure prophylaxis except in a clinical trial (last updated December 17, 2020) (62). In addition, COVID-19 vaccination is not indicated for postexposure prophylaxis and current recommendations indicate that vaccination for prevention of COVID-19 should be deferred for at least 90 days after infection or receipt of antibody therapies to avoid immunologic interference (117). All study participants will receive counseling per the current standard of care following a confirmed exposure to COVID-19 pertaining to quarantine, self-monitor for symptoms and avoid contact with people at higher risk for severe illness from COVID-19.

2 STUDY OBJECTIVES AND OUTCOME MEASURES

Objectives		**Outcome Measure**	**Endpoints & Analysis**
Primary Efficacy	To assess the efficacy of COVID-HIGIV (two dose levels) as postexposure prophylaxis for the prevention of symptomatic RT-PCR[1] confirmed COVID-19	RT-PCR[1] confirmed symptomatic COVID-19[2] within 28 days (by Study Day 29) postdose	Odds ratios from logistic regression analysis, adjusting for baseline SARS-CoV-2 RT-PCR status (central laboratory)

Objectives		Outcome Measure	Endpoints & Analysis
Primary Safety	To assess the safety of COVID-HIGIV (two dose levels)	Adverse events within 72 hours postdose Discontinuation or temporary suspension of infusion (for any reason) Adverse events within 28 days postdose Serious adverse events within 28 days postdose	Proportions, descriptive
Secondary Efficacy	To assess the efficacy of COVID-HIGIV (two dose levels) as postexposure prophylaxis for prevention of COVID-19 by symptom severity	Mild RT-PCR confirmed COVID-19 within 14 days (by Study Day 15) postdose Moderate to severe/critical RT-PCR[1] confirmed COVID-19[2] within 28 days (by Study Day 29) postdose	Odds ratios from logistic regression analysis, adjusting for baseline SARS-CoV-2 RT-PCR status (central laboratory)
	To assess the effect of COVID-HIGIV (two dose levels) on SARS-CoV-2 virologic outcome measures	Change in nasopharyngeal SARS-CoV-2 viral load (as assessed by SARS-CoV-2 RT-qPCR[1]) from Study Day 1 (predose) to Days 4, 8, 15, and 29 postdose in participants with detectable virus (RT-PCR positive) on Day 1	Difference between groups in time-weighted average change in nasopharyngeal viral load from Day 1 up to Day 29 in the baseline positive ITT subset
		SARS-CoV-2 nasopharyngeal RT-PCR[1] status (positive/negative) from Day 1 (predose) to Days 4, 8, 15 and 29 in participants with no detectable virus (RT-PCR negative) on Day 1	Relative risk of nasopharyngeal RT-PCR status conversion at any time through Day 29 between groups in the baseline negative ITT subset
Exploratory	To assess the detection of SARS-CoV-2 viral RNA through RT-qPCR[1] performed on saliva samples	SARS-CoV-2 RT-PCR status (positive/negative) and viral load from Day 1 to Days 1, 4, 8, 15 and 29 as assessed through RT-qPCR[1] using saliva samples	Difference between groups in time-weighted average change in saliva viral load from Day 1 up to Day 29 (baseline positive ITT subset) and relative risk of saliva RT-PCR status conversion at any time through Day 29 between groups (baseline negative ITT subset)
	To assess the incidence of death	All-cause mortality and COVID-19 related mortality within 28 days (by Study Day 29) postdose	Proportions, descriptive
	To assess the efficacy of COVID-HIGIV (two dose levels) time (days) to onset and duration of COVID-19 symptoms	Time (days) to onset and duration of COVID-19 symptoms	Descriptive using survival analysis (median). Participants with no symptoms have a duration of 0
	To assess the efficacy of COVID-HIGIV (two dose levels) by subgroups	Efficacy of COVID-HIGIV by age (<65 and ≥65 years of age), gender, race (white vs. non-white), ethnicity, Day 1 SARS-CoV-2 RT-PCR status, exposure risk (number of Level 2 criteria met), comorbidities (cardiac, pulmonary, renal, diabetes), BMI (<30, ≥30–<40, ≥40 kg/m^2), and smoking status (current, prior, never)	Descriptive

Objectives		Outcome Measure	Endpoints & Analysis
	To describe anti-SARS-CoV-2 IgG levels postdose (two dose levels)	Anti-SARS-CoV-2 IgG titer postdose on Days 1, 4, 15 and Day 29 (calculation of PK endpoints to the extent that data allow (C_{max}, T_{max}, AUC_{0-7d}) using binding assay)	Descriptive

[1]RT-qPCR will be done to generate both qualitative (positive/negative status) and quantitative (viral load) data.
[2]Cases of RT-PCR confirmed COVID-19 will be determined by the investigator according to the case definition outlined in Section 7.1.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of COVID-HIGIV for postexposure prophylaxis in asymptomatic susceptible adults at risk for moderate to severe COVID-19 within five days of a high-risk exposure to SARS-CoV-2.

The study will evaluate the safety and efficacy of two dose levels of COVID-HIGIV (100 mL and 300 mL) compared to placebo for the prevention of symptomatic reverse transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 (N=360). Eligible participants will be randomized 1:1:1 to receive intravenously either COVID-HIGIV at one of two dose levels (n=120 each) or normal saline placebo (n=120) as shown in Table 4. Randomization of participants will be stratified by site and SARS-CoV-2 antigen status at screening. A minimum of 45 individuals with positive baseline SARS-COV-2 antigen test results (n=15 per study arm) will be targeted for enrollment.

Table 4 EBS-CVH-002 Phase 2 Study Design Schematic

Study Population	Treatment Group	Number (n) of Participants Per Arm	Study Treatment	Primary Outcome Measure
Asymptomatic susceptible adults with a high risk exposure within 5 days N=360	Group 1	n=120	COVID-HIGIV[1,2] (300 mL)	RT-PCR symptomatic confirmed COVID-19 (regardless of severity) within 28 days (by Study Day 29)
	Group 2	n=120	COVID-HIGIV[1,2] (100 mL)	
	Group 3	n=120	Placebo[2,3] (300 mL)	

[1]COVID-Hyperimmune Globulin – Intravenous.
[2]Volume will be administered in three separate 100 mL bags containing either undiluted product or 0.9% normal saline as described in Section 3.1.3 Total volume administered= 300 mL.
[3]0.9% normal saline placebo administered intravenous route.

An independent blinded Safety Monitoring Committee (SMC) will be responsible for assessing safety and monitoring overall conduct and integrity of the study.

An unblinded team (consisting of an unblinded medical monitor and statistician) will support the SMC and review unblinded study data and make a recommendation on whether to pause study enrollment for SMC review according to prespecified rules outlined in the SMC charter in the event of a suspected risk of an excess of moderate to severe/critical COVID-19 outcomes in the treatment arm.

The blinded SMC will review blinded safety data. Study enrollment and IP administration may be temporarily paused at the discretion of the SMC chair for safety review by the SMC if any of the following adverse events occur after administration of COVID-HIGIV:

- ≥ one Grade 4 serious adverse event or death regardless of relatedness to IP
- ≥ one Grade 3 hypersensitivity event
- ≥ five of the same Grade 3 AEs

The severity of AEs will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, DAIDS. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

3.1.1 Study Centers

The study will be conducted in up to 35 sites in North America. Additional study centers within or outside of these geographic areas may be added if enrollment cannot be completed in a timely manner. Sites also may be closed if they fail to enroll.

3.1.2 Randomization

Eligible participants will be randomized by blocks into three treatment arms at 1:1:1 ratio (COVID-HIGIV 100 mL; COVID-HIGIV 300 mL; placebo), stratified by site and SARS-CoV-2 antigen status based on a rapid test at screening visit (positive vs negative).

3.1.3 Blinding

Except for designated unblinded individuals, the study personnel (sponsor, site, CROs, etc.) will remain blinded to participants' treatment assignment. The details will be covered in the applicable study specific plans, manuals and instructions.

Each participant enrolled will receive three separate 100 mL IV bags (total of 300 mL) containing either undiluted product or 0.9% normal saline as follows:

Group 1 (300 mL): three separate 100 mL IV bags with undiluted product

Group 2 (100 mL): three separate 100 mL IV bags – 1 bag with undiluted product and 2 bags with 0.9% normal saline

Group 3 (placebo): three separate 100 mL IV bags with 0.9% normal saline

Infusion bag covers will be used to mask the bags to maintain the blind during infusion.

While this is a double-blind study, the blind may be broken if a participant's health or safety is at risk as outlined in Section 8.6.4.

4 SELECTION OF STUDY PARTICIPANTS

4.1 Participant Inclusion Criteria

All participants must meet all the following inclusion criteria to be enrolled into the study:

1. Willing and able to provide written informed consent prior to performing study procedures
2. Males or females ≥18 years of age
3. Females must not be pregnant as demonstrated by either one of the following:
    a. Not of childbearing potential: surgically sterile (six weeks post-bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or postmenopausal defined as women ≥ 50 years of age with a history of ≥12 months without menses prior to randomization in the absence of other pathologic or physiologic causes, following cessation of exogenous sex-hormonal treatment

    or:

    b. Of childbearing potential (WOCBP): women who are not planning to be pregnant during the study period (up to 28 days after randomization) and meet all the following criteria:
        - Negative urine pregnancy test at Screening Visit
        - Use of an acceptable method of highly effective contraception (if female of CBP) for the duration of participation, such as:
            - Hormonal contraceptives (e.g., implants, pills, patches) initiated ≥30 days prior to dosing
            - Intrauterine device (IUD) inserted ≥30 days prior to dosing
            - Double barrier type of birth control (male condom with female diaphragm, male condom with cervical cap)
4. Rapid COVID-19 IgM and IgG antibody negative
5. No COVID-19 related symptoms defined as new or increased onset of ≥1 of the following symptoms: fever (temperature ≥100.4ºF), nasal congestion, sore throat, cough, muscle aches, headache, nausea or vomiting, shortness of breath, diarrhea, loss of smell or taste
6. Had a high-risk exposure to SARS-CoV-2 infection within five days of Screening as defined by at least one of the criteria below:
    a. Prolonged close contact[1] with one or more individuals with individual(s) with symptomatic, confirmed COVID-19[2] without wearing a mask/face shield while person's eyes, nose, mouth were potentially exposed to material infectious with SARS-CoV-2

b. Present in the room for procedures that generate aerosols or during which respiratory secretions are likely to be poorly controlled (e.g., cardiopulmonary resuscitation, intubation, extubation, bronchoscopy, nebulizer therapy, sputum induction) on patients with confirmed COVID-19 when eyes, nose, or mouth were not protected. Exposure of any duration is considered a prolonged exposure if the exposure occurred during performance of an aerosol generating procedure

[1]*Close contact is defined as follows: a) being within approximately six feet (two meters) of a person with confirmed, symptomatic COVID-19 for >15 minutes or b) having unprotected direct contact with infectious secretions or excretions (e.g., being coughed on, touching used tissues with a bare hand) of a confirmed, symptomatic COVID-19 patient c) exposure during a confirmed outbreak in an institutional setting (e.g., long-term care facility) defined as follows: resident or health care provider with confirmed COVID-19, resident with severe respiratory infection resulting in hospitalization or death, or ≥3 residents or health care provider(s) with new onset respiratory symptoms within 72 hours of each other suspected to be due to COVID-19 (1), (2).*

[2]*Confirmed COVID-19 patient defined as person with laboratory-confirmed symptomatic COVID-19 anytime during period from 48 hours before onset of symptoms until meeting criteria for discontinuing home isolation (3), (4). Documentation of confirmed COVID-19 contact is required.*

7. Having one or more risk factors for moderate to severe/critical COVID-19 disease (5) defined as the following:
    - BMI ≥ 30 kg/m^2
    - Age ≥ 65 years
    - Type 2 Diabetes Mellitus
    - Mild to moderate Chronic Kidney Disease defined as eGFR ≥ 30
    - Chronic Obstructive Pulmonary Disease
    - Chronic cardiac condition (≥1 of the following): history of coronary artery disease, cardiomyopathy, congestive heart failure classified as New York Heart Association Class 1 or II

4.2 Participant Exclusion Criteria

Participants who meet any of the following exclusion criteria will not be enrolled into the study:

1. Prior receipt of COVID-19 vaccines or COVID-19 antibody-based treatments (e.g., anti-SARS-CoV-2 monoclonal antibodies given individually or in combination regimens, convalescent plasma treatment from donors who have recovered from COVID-19; receipt of remdesivir within the last 24 hours)

2. Receipt of live attenuated virus vaccines within three months prior to screening or anticipated receipt of live attenuated virus vaccine within three months after receipt of COVID-HIGIV
3. Use of any investigational product within 30 days prior to screening
4. Planned use of any IP for the duration of the study with the following exception: participants who are hospitalized for management of moderate to severe/critical COVID-19 may be permitted to co-enroll in trials of COVID-19 investigational treatments for moderate to severe/critical disease.
5. History of allergy to latex or rubber
6. History of hypersensitivity to blood or plasma products or to COVID-HIGIV excipients (proline, PS80)
7. History of IgA deficiency and/or documented presence of anti-IgA antibodies
8. Current or prior history of hemolytic anemia
9. History of immunodeficiency defined as ≥1 of the following:
    - Steroids >10 mg/day for at least the last seven days
    - Treatment with biological medicine to treat autoimmune disease or cancer
    - Antirejection medicine after solid or stem cell transplantation
    - Cancer treatment in last six months
    - Primary or acquired severe and ongoing immune dysfunction affecting B- or T-lymphocyte function
10. A pre-existing condition or concomitant medication that may place the individual at a substantially increased risk of thrombosis[1]
11. Acute illness within the last 14 days
12. Severe chronic illness that would preclude receipt of up to 300 mL volume of IV fluid (e.g., NYHA class III or IV heart failure, nephrotic syndrome, end stage renal disease on hemodialysis, end stage liver disease)
13. Abnormal lab results at screening with any of the following:
    - Absolute neutrophil count ≤800 cells/mm^3
    - Serum creatinine >2.5 times ULN
    - AST >2.5 X ULN
    - ALT >2.5 X ULN
    - Hemoglobin ≤9 g/dL
    - Rapid HIV ½ positive
14. Recent transsphenoidal surgery, cerebrospinal fluid leak, encephalocele (<three months)

15. Any condition that could prevent the ability of the participant to comply with the protocol-specified assessments, in the opinion of the investigator
16. Enrollment would not be in the best interest of the participant, in the opinion of the investigator
17. Life expectancy <3 months per the opinion of the investigator

[1]prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome, cryoglobulinemia, severe refractory hypertriglyceridemia, or clinically significant monoclonal gammopathy, or any of the following within one month prior: arterial or venous thrombosis, acute coronary syndrome, cerebrovascular syndrome

4.3 Participant Withdrawal

The participant must be available, without coercion, for all parts of the study. If continued participation jeopardizes the participant's health, the participant should be withdrawn from the study. The investigator is encouraged to consult Emergent prior to the withdrawal of any participant, except in the event of a medical emergency. The reason for withdrawal of any participant must be clearly documented on the study source documents and the appropriate Case Report Form (CRF).

4.3.1 Participant Withdrawal Criteria

All participants are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the participant is otherwise entitled. The PI will request (but cannot require) such subjects to provide the reason(s) for withdrawal of consent. Reasons for withdrawal from the study may include the following:

- Participant refused further follow-up
- Lost to follow-up: Loss to follow-up, which requires documentation of at least three unsuccessful attempts to contact participants.
- Death
- Participant request
- Investigator request
- Protocol Deviations (PD): The participant is not compliant with the requirements of the study to the satisfaction of the investigator and/or sponsor (e.g., noncooperative, misses appointments).
- Study terminated by sponsor
- AEs: It is the opinion of the Principal investigator (PI) that it is unwise for the participant to continue in the study

A participant who is withdrawn from the study will not be re-entered into the study for any reason.

4.3.2 Replacement of Participants

Participants withdrawn from the study or who withdraw consent after randomization will not be replaced. The study sample size determination has included consideration for some participants to be lost to follow-up or withdrawal of consent.

4.3.3 Follow-up of Withdrawn Participants

Every attempt will be made to ensure that participants who are withdrawn, or who withdraw from the study during the active treatment or follow-up period, will complete all safety and available efficacy assessments for the early withdrawal visit as outlined in this protocol. The investigator should inform the participants that these assessments are for their safety.

5 INVESTIGATIONAL PRODUCT INFORMATION

COVID-HIGIV (85–115 mg/mL protein), 300 mL single dose, intravenous

COVID-HIGIV (85–115 mg/mL protein), 100 mL, single dose, intravenous

The placebo is 0.9% normal saline

5.1 COVID-HIGIV

5.1.1 Packaging and Formulation

Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) [COVID-HIGIV] is a sterile liquid preparation of purified human immunoglobulin (IgG) fraction containing SARS-CoV-2 antibodies. The final product contains 85–115 mg/mL of human plasma proteins, of which at least 90% is human IgG. Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) is formulated with 250 mM proline and 0.03% (w/w) PS80 and has a pH between 5.5 and 6.0 (target pH 5.8). The final product contains no preservatives.

The final COVID-HIGIV product will be supplied in 50 mL Type 1 glass vials sealed with 20 mm siliconized bromobutyl rubber stoppers, aluminum seals, and plastic flip-off caps. The extractable volume per vial is 25 mL. Each vial is intended for single use. The vials will be provided in shelf cartons (four vials per shelf carton).

For more information, please refer to the IB for COVID-HIGIV.

5.1.2 Labeling

Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) [COVID-HIGIV] vial and shelf carton labels will include information to comply with local regulations for the country in which the study is conducted, in the appropriate language(s).

For dispensing labels for secondary receptacles, see Section 5.1.5 Preparation.

5.1.3 Shipment

Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) [COVID-HIGIV] will be shipped to the sites at a temperature of 2–8°C (35–46°F). During shipment, the temperature will be monitored to ensure the required temperature conditions are maintained. The site pharmacist or designate will be responsible for checking the number of vials and the condition of the vials received and entering this information into the drug accountability records, reporting the condition to Emergent or designate. The site pharmacist or designate will be responsible for confirming the requisite storage temperature was maintained during the shipment and completing the relevant documentation, if applicable. (See Pharmacy Manual for details). COVID-HIGIV will be released for use by the site only after the temperature monitor results are reviewed and written authorization has been issued to the investigator/designate by Emergent/designate. Temperature excursions during shipment must be reported to Emergent/designate as per instructions provided in the Pharmacy Manual.

At the end of the study or upon request of Emergent, all unused, partially used, or empty vials will be returned to Emergent or destroyed at the site as directed by Emergent.

5.1.4 Storage Conditions

Once at the site, COVID-HIGIV vials must be stored at 2–8°C (35–46°F) in a secured area until used for dose preparation by the assigned pharmacy staff. The temperature in the storage area should be monitored with properly calibrated instruments and recorded on a temperature log. Temperature excursions must be reported to Emergent or designate as per instructions provided in the Pharmacy Manual.

For further information, refer to the COVID-HIGIV IB and the Pharmacy Manual.

To preserve the double blinded design of the study, the blinded team must not have access to the IP.

5.1.5 Preparation

The site must maintain documentation of a clear written formalized procedure for study drug preparation activities (including any sample labels and documentation to be completed), and documented training and delegation of the activity to appropriate study staff.

Participant identifier (participant ID number) must be recorded on the labels of the vial(s) used to prepare the dose. The qualified unblinded pharmacy staff assigned to this study will prepare COVID-HIGIV as follows:

Visually inspect the vials to ensure the product is free from particulate matter and discoloration prior to dose preparation and administration. The solution should be clear or slightly opalescent and colorless or pale yellow. **Do not use solutions that are cloudy or have particulates. DO NOT SHAKE VIALS; AVOID FOAMING.**

Prepare COVID-HIGIV at the required dosage into an IV infusion bag. In general, perform the following:

- Remove the protective caps from the product vials.
- Wipe the exposed central portion of the rubber stopper with an isopropyl alcohol swab.
- Withdraw the vial content (note: extractable volume is up to 25 mL per vial) into a sterile syringe (that can accommodate up to 25 mL) using standard aseptic techniques and transfer the content into an appropriately sized and labeled IV infusion bag.

Once punctured, use the vial contents to prepare the infusion bag promptly. Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) contains no preservatives. Vials are for single use only. **Do not reuse or save vial(s) for future use.**

Retain used and empty vials for drug accountability as per instructions in the Pharmacy Manual.

The IV infusion bag for COVID-HIGIV (and placebo) requires that the dispensing label is affixed to the bag. The label on the IV infusion bag will capture at a minimum: participant ID, expiry date and time of the prepared dose, the investigator's name, protocol code (EBS-CVH-002) and caution statement "For investigational use only". The IV infusion bag will require a cover to maintain the blind. Protective coverings for the IV infusion bags will be provided by Emergent as part of the study materials. For further details, refer to the Pharmacy Manual.

5.1.6 Administration

The study treatment is to be administered for the first 30 minutes under the direct supervision of the investigator or a qualified sub-investigator or designate. Under no circumstances will the investigator allow the study treatment to be used other than as specified in the protocol. For full details on COVID-HIGIV administration please see the IB.

Ensure the recipient is adequately hydrated prior to initiation of IV infusion.

Administer COVID-HIGIV by IV infusion through a dedicated IV line using a constant infusion pump (e.g., IVAC® pump or equivalent).

Administer COVID-HIGIV within 24 hours of preparation into an IV infusion bag.

Set the starting infusion rate at 1 mL/min for the first 30 minutes. If the infusion is well tolerated, double the infusion rate every 30 minutes, until a maximum infusion rate of 4 mL/min (maximum rate), which should be used for the remainder of the infusion. [See Section 8.6.6 for Infusion Stopping Rules.]

Participants will be monitored in-clinic closely during infusion and for at least six hours from the start of the COVID-HIGIV infusion, longer if clinically indicated. A follow up for participants will occur by telephone one day post-infusion.

Participants will be instructed to avoid prolonged immobilization in the week following the infusion.

For additional details regarding administration of COVID-HIGIV please see the IB and Pharmacy Manual.

5.1.7 Drug Accountability

An unblinded pharmacist or a designated individual is responsible for maintaining accurate inventory records of IP supplies, inventory of IP shipments upon receipt, acknowledge possession by signing all required documentation, returning these to the sponsor, and ensuring that all drug supplies are kept in a secure location in the site pharmacy in accordance with recommended storage conditions.

The inventory record for the COVID-HIGIV will be kept in a secure place with documented access and control and will include:

- Protocol name, number, and sponsor
- Product name and description
- Study site and investigator name
- Product lot number and date of manufacture and/or use-by/expiry/retest date
- Number of vials dispensed, date and time of dispensing, and study participant for whom product was dispensed
- Product balance
- Name and title of qualified individual dispensing product

These records will be reviewed by an unblinded monitor and QA staff (as applicable) prior to unblinding and may be reviewed by regulatory agencies.

5.2 Description of Placebo

The placebo is a normal saline (0.9% sodium chloride) liquid solution suitable for IV administration.

Placebo will be prepared at the same volume as COVID-HIGIV doses and administered in the same manner as COVID-HIGIV (e.g., IV infusion, starting infusion rates/incremental increases in infusion rates). Refer to the Pharmacy Manual for additional details.

6 STUDY PROCEDURES

6.1 Screening (Screening Visit, Day -1, ≤1 day prior to randomization) (In-clinic Visit)

Participants will first undergo informed consent counselling and provide voluntary and written study specific informed consent. See section 11.2 for details.

Once informed consent has been obtained, participants will undergo a screening visit to ascertain their eligibility in this study.

The screening visit assessments will include:

- Obtain written informed consent.
- Obtain demographic information (date of birth, gender, race and ethnicity).
- Collect information on estimated date and history of exposure to SARS-CoV-2 (per Appendix II), risk factors for moderate to severe COVID-19, comorbidities and history of allergies, list of medications currently taken.
- Perform physical examination (including skin, head, eyes, ears, nose, throat, lymph nodes, cardiac, lungs, abdomen, and lower and upper extremity assessments, neurologic). Additional organ systems can be examined with baseline abnormalities documented if determined by the investigator to be clinically significant.
- Obtain vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry, height, and weight [for body mass index calculation]).
- Collect blood samples for laboratory assessments [local labs]: serum blood urea nitrogen/creatinine, ALT, AST, complete blood count with differential, hepatitis B surface antigen, rapid HIV 1/2 test, anti-HCV. If anti-HCV test is positive, obtain HCV-RNA.
- Collect blood sample for rapid COVID-19 IgM/IgG antibody test [local lab] (qualitative).
- Collect a blood sample for COVID-19 IgM/IgG antibody test (quantitative) [central lab].
- Collect nasal swab for rapid SARS-CoV-2 antigen test [local lab].
- Collect urine sample [local lab] for pregnancy test [for WOCBP only].
- Review results of local labs required to determine eligibility.
- Confirm eligibility.
- Obtain consent from participants for release of medical records if participant becomes hospitalized with COVID-19.
- Complete the source documents.
- Complete the CRF.

- Counsel participants on precautions for reducing transmission of COVID-19.

6.1.1 Rescreening

Rescreening is not permitted.

6.2 Day 1 (+1 day) Visit 1 (In-clinic Visit)

The following will take place prior to IP administration (predose):

- Review screening lab test results.
- Confirm eligibility, including assessment of COVID-19 symptoms.
- Perform physical examination (including skin, head, eyes, ears, nose, throat, lymph nodes, cardiac, lungs, abdomen, and lower and upper extremity assessments, neurologic). Additional organ systems can be examined with baseline abnormalities documented if determined by the investigator to be clinically significant.
- Obtain vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry) zero toone hour prior to IP administration.
- Collect information on concomitant medications.
- Confirm use of contraceptives (for WOCBP).
- Collect a Nasopharyngeal (NP) swab [central lab] for SARS-CoV-2 RT-PCR/RT-qPCR.
- Collect a saliva sample for SARS-CoV-2 RT-qPCR [central lab].
- Randomization occurs on Day 1 after eligibility criteria are verified and pregnancy test is confirmed to be negative for WOCBP. Randomization should be performed as close as possible to the time of infusion. Stratification will be based on SARS-CoV-2 RT-PCR antigen test result from screening visit only.

Investigational Product administration:

The IP to which the participant is randomized is to be administered as described in Section 5.1.6.

The following will take place after IP administration (postdose):

- Monitor/assess AEs and SAEs in-clinic for six hours from the start of infusion, longer if clinically indicated. Please see Section 8.6.6 for instructions on how to adjust the infusion rate if necessary.
- Obtain blood sample for COVID-19 IgG/IgM (quantitative) one hour postdose (±15 minutes) to be sent to central lab.
- Vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry) one, three and six hours (±15 minutes) following the start of infusion.

- Counseling on precautions for reducing transmission of COVID-19.
- Provide symptom electronic diary (e-diary) device for daily reporting (Days 2 to 15) to participants who do not have their own device or ensure participant has the e-diary application on personal device and provide instructions.
- Review instructions with participants on how to fill out the symptom e-diary.
- Provide thermometer and pulse oximeter for home use by the participant. Provide instructions on pulse oximetry and thermometer use. Instruct participants as to how to record results and when to seek further advice or emergency care related to health status or oxygen saturation levels.

6.3 Day 2 (+1 day) Visit 2 (Telephone Call)

- Scripted telephone call one day post infusion to monitor for AEs and SAEs post infusion.
- Review of symptom e-diary and assess COVID-19 symptoms.
- Collect information on concomitant medications.
- Confirm use of contraceptives (for WOCBP).
- Counsel participants on precautions for reducing transmission of COVID-19.
- Assess for potential for re-exposure to SARS-CoV-2.

6.4 Days 2-15 Symptom E-Diary Card

- Participants will fill out the symptom e-diary daily.
- Participants will record their temperature twice daily and pulse oximetry reading once daily.
- Participants will be provided with instructions on when to seek medical help and a contact number will be provided to call for emergencies.
- The investigator will receive an alert for participants with symptoms that require follow-up.

For all follow-up visits for Days 4, 8, 15 and 29, an in-clinic visit is optional. A home-attended visit for collection of vital signs and samples (e.g., blood, NP swab, saliva) followed by telemedicine appointment with investigator is permitted. The investigator will perform an assessment by telemedicine on the same day. Participants who per the investigator's assessment require a physical examination will be referred to the study site if an in-person evaluation by an investigator is necessary.

6.5 Day 4 (±1 day) Visit 3 (In-clinic or Home-Attended Visit)

- Collect information on concomitant medications.

- Confirm use of contraceptives (for WOCBP).
- Review of symptom e-diary and any test results.
- Assess for COVID-19 related symptoms.
- Collect AEs and SAEs.
- Obtain vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry).
- Collect blood samples for laboratory assessments [local labs]: BUN/creatinine, ALT, AST, hemoglobin.
- Collect NP swab [central lab]: SARS-CoV-2 RT-PCR/RT-qPCR.
    - Only for participants with respiratory symptoms [cough or shortness of breath]: a respiratory pathogen panel will additionally be run using the same NP specimen [central lab].
- Additionally, collect saliva sample for SARS-CoV-2 RT-qPCR [central lab].
- Collect blood sample [central lab]: SARS-CoV-2 IgM and IgG antibody (quantitative).
- Collect information from medical records from intercurrent hospitalizations and medical attended visits (if applicable).
- Counsel participants on precautions for reducing transmission of COVID-19.
- Assess potential for re-exposure to SARS-CoV-2.
- Determine if unscheduled clinic visit is necessary for physical exam, if clinically indicated.

6.6 Day 8 (±1 day) Visit 4 (In-clinic or Home-Attended Visit)

- Collect information on concomitant medications.
- Confirm use of contraceptives (for WOCBP).
- Review of symptom e-diary and test results.
- Assess for COVID-19 related symptoms.
- Collect AEs and SAEs.
- Obtain vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry).
- Collect NP swab [central lab]: SARS-CoV-2 RT-PCR/RT-qPCR.
    - Only for participants with respiratory symptoms [cough or shortness of breath]: a respiratory pathogen panel will additionally be run using the same NP specimen [central lab].

- Additionally, collect saliva sample for SARS-CoV-2 RT-qPCR [central lab].
- Collect blood sample [central lab]: SARS-CoV-2 IgM and IgG antibody (quantitative).
- Collect blood samples for laboratory assessments [local labs]: BUN/creatinine, ALT, AST, hemoglobin, if clinically indicated.
- Collect information from medical records from intercurrent hospitalizations and medical attended visits (if applicable).
- Counsel participants on precautions for reducing transmission of COVID-19.
- Assess potential for re-exposure to SARS-CoV-2.
- **For home visits:** Investigator to determine if unscheduled clinic visit is necessary for physical exam, if clinically indicated.

6.7 Day 15 (±2 days) Visit 5 (In-clinic or Home-Attended Visit)

- Collect information on concomitant medications.
- Confirm use of contraceptives (for WOCBP).
- Review of symptom e-diary.
- Assess for COVID-19 related symptoms.
- Collect AEs and SAEs.
- Obtain vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry).
- Collect NP swab [central lab]: SARS-CoV-2 RT-PCR/RT-qPCR.
    - Only for participants with respiratory symptoms [cough or shortness of breath]: a respiratory pathogen panel will additionally be run using the same NP specimen [central lab].
- Collect saliva sample for SARS-CoV-2 RT-qPCR [central lab].
- Collect blood sample [central lab]: SARS-CoV-2 IgM and IgG antibody (quantitative).
- Collect blood samples for laboratory assessments [local labs]: BUN/creatinine, ALT, AST, hemoglobin, if clinically indicated.
- Collect information from medical records from intercurrent hospitalizations and medical attended visits (if applicable).
- Counsel participants on precautions for reducing transmission of COVID-19.
- Assess potential for re-exposure to SARS-CoV-2.

For home visits: Investigator to determine if unscheduled clinic visit is necessary for physical exam, if clinically indicated.

6.8 Day 29 End of Study/Early Withdrawal Visit (±2 days) Visit 6 (In-clinic or Home-Attended Visit)

- Collect information on concomitant medications.
- Confirm use of contraceptives (for WOCBP).
- Assess for COVID-19 related symptoms.
- Collect AEs and SAEs.
- Obtain vital signs (temperature, pulse, respiratory rate, sitting blood pressure, pulse oximetry).
- Collect NP swab [central lab]: SARS-CoV-2 RT-PCR/RT-qPCR.
    - Only for participants with respiratory symptoms [cough or shortness of breath]: a respiratory pathogen panel will additionally be run using the same NP specimen by the central lab.
- Collect saliva sample for SARS-CoV-2 RT-qPCR [central lab].
- Collect blood sample [central lab]: SARS-CoV-2 IgM and IgG antibody (quantitative).
- Collect blood samples for laboratory assessments [local labs]: BUN/creatinine, ALT, AST, hemoglobin, if clinically indicated
- Collect information from medical records from hospitalizations and medical attended visits (if applicable).
- Counsel participants on precautions for reducing transmission of COVID-19.
- Assess potential for re-exposure to SARS-CoV-2.
- COVID-19 symptoms will be followed for the duration of the study. Any symptoms that continue at Day 29 will be marked as “unresolved.”

For home visits: Investigator to determine if unscheduled clinic visit is necessary for physical exam, if clinically indicated.

6.9 Unscheduled Visits

- Participants with suspected AEs or potential COVID-19 illness onset can be evaluated during an unscheduled visit.
- Review of symptom e-diary (if unscheduled visit occurs prior to Day 15 visit) and assessment of COVID-19 related symptoms.

- Patients with potential COVID-19 illness should have the following measurements taken: vital signs, NP swab for SARS-CoV-2 RT-PCR/RT-qPCR, saliva sample for SARS-CoV-2 RT-qPCR and blood sample for COVID-19 IgM/IgG. Symptom details will be documented.
- Additional assessments listed in Schedule of Events as clinically indicated.
- Participants with severe or rapidly progressive COVID-19 symptoms will be referred for emergency medical care (i.e., to emergency room or hospital) if clinically indicated.

6.10 Concomitant Medications

The administration of concomitant medication is permitted during the trial period in keeping with the standard of care for participants.

Study participants will be queried about all concomitant medications during in-clinic follow-up visits including blood or plasma-derived products/plasma exchange procedures required for medical emergency reasons, vaccines and herbal preparations that they are receiving. Use of concomitant medications and the reason for such use will be recorded on the appropriate electronic case report form (eCRF). Concomitant medications taken in relation to AEs and SAEs and/or COVID-19 will be noted.

6.10.1 Pre-Infusion Medications

Pre-infusion medications are not recommended to ensure consistency across enrollment and procedures at study sites. Medications for symptomatic relief to treat minor ailments (e.g., headache, nausea) will be allowed at the discretion of the investigator. Use of pre-medications or medications to treat any infusion-related reactions will be recorded on the eCRF.

6.11 Prohibited Medications for the Treatment or Prevention of COVID-19

For the study target population there is currently no treatment that has proven efficacy and safety for the treatment of COVID-19. There are also no specific treatments recommended by the NIH COVID-19 Treatment Guidelines following exposure to a confirmed case of COVID-19, for asymptomatic infection or for mild to moderate COVID-19 not requiring oxygen supplementation.

Per current recommendations, COVID-19 vaccination should be deferred for 90 days following infection or administration of antibody therapies (117). Subjects may be notified of their assigned study treatment after he/she has completed the Day 29 visit and data have been cleaned for that subject so that they can follow current COVID-19 vaccine recommendations.

Passive immune therapies for treatment of COVID-19 are prohibited for participants who are not hospitalized. Examples of passive immunotherapies include the following: 1) plasma treatment from donors who have recovered from COVID-19 (i.e., convalescent plasma) 2)

concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 3) anti-SARS-CoV-2 mAbs given individually or in combination regimens.

7 ASSESSMENT OF EFFICACY

7.1 Efficacy Outcome Measures

7.1.1 Laboratory-Confirmed Symptomatic COVID-19

7.1.1.1 Assessment of Laboratory-Confirmed Symptomatic COVID-19 [Primary Outcome]

Efficacy will be assessed throughout the duration of the follow-up period for surveillance of potential cases of COVID-19. If, at any time, a participant develops acute COVID-19 symptoms, the participant should contact the site and an at home or in-clinic visit will occur, and assessments should be conducted as specified in the Schedule of Events. Participants will additionally complete symptom e-diary cards daily from Days 2–15 (Appendix I). Symptom e-diary cards will be reviewed by the investigator as described in Section 7.1.2 and the investigator will additionally contact the participant if any symptoms are reported that require further evaluation. Temperature and SpO_2 measures by the participant will not be used to support criteria for meeting the case definition or severity of COVID-19 cases but will inform the need for evaluation or escalation of care.

At each study visit or unscheduled visit (home/in-clinic), investigators will assess whether participants' reported symptoms are COVID-19 related and verify vital sign measurements.

Investigators will enter the clinical and laboratory data into the EDC for symptomatic, laboratory-confirmed COVID-19 (see Table 5). The classification of severity of symptomatic, laboratory-confirmed COVID-19 cases (e.g., mild, moderate, severe/critical) will be performed centrally based on investigator's assessments as per Table 6. The presence of ≥1 of the following symptoms will be considered COVID-19 related per the investigator's assessment that there is no alternative medical explanation for the cause of the symptoms: fever (≥100.4ºF), sore throat, new or increased cough, new or increased muscle aches, vomiting, new or increased shortness of breath, diarrhea, new loss of smell or taste. The presence of the following additional symptoms will be assessed and included in an exploratory case definition: congestion or runny nose, headache, nausea, or fatigue.

If symptoms are considered by the investigator to be COVID-19 related, investigators will obtain a NP swab for SARS-CoV-2 RT-PCR to be sent to the central lab and obtain a blood sample for COVID-19 IgG/IgM.

Case definitions for laboratory-confirmed COVID-19 illness by clinical severity are described in Table 6. The onset date of the case will be recorded by the investigator and will be the date that COVID-19 related symptoms were first reported by the participant; the date of resolution of symptoms will be recorded by the investigator and will be the date that

COVID-19 related symptoms resolved completely (for ≥2 consecutive days) per the report of the participant.

Clinical information and results from local standard of care tests will be assessed. All hospital admissions and medically attended events (MAEs) outside of study visits for medical care during the 28 day follow-up period will be reported, including information on reasons for admission and events occurring during admission classified and grouped according to the definitions described in Table 6. The CRFs used to capture hospital admission or MAEs will also be used to collect relevant information that defines the AE. Local nucleic acid amplification tests (NAAT) to detect SARS-CoV-2 infection obtained during hospital admission or MAEs will be considered acceptable if it was obtained using any one of the following:

- An FDA-cleared (including EUA) assay
- An assay that is not FDA-cleared but was conducted in a laboratory that is currently CLIA-certified
- An assay performed by a laboratory accredited according to the ISO 15189 standard by a national or a regional accreditation body

Participants who are admitted to the hospital for laboratory-confirmed COVID-19 related illness that has met the case definition for moderate to severe/critical COVID-19 may enroll in other trials examining other interventions for treatment of severe COVID-19.

Table 5 Clinical and Laboratory Criteria for SARS-CoV-2 Infection and Symptomatic COVID-19 Disease

Description	Clinical Criteria	Laboratory Criteria
Uninfected	Asymptomatic defined as having no COVID-19 related symptoms[1] **AND** Health status at the same level as prior to SARS-CoV-2 exposure	All nasopharyngeal swabs[1] negative for SARS-CoV-2 by RT-PCR (central lab)
Asymptomatic SARS-CoV-2 Infection		At least one nasopharyngeal swab[1] positive for SARS-CoV-2 by RT-PCR (central lab)
Symptomatic COVID-19 disease	Clinical manifestations of COVID-19 as described in Table 6	At least one nasopharyngeal swab positive for SARS-CoV-2 by RT-PCR during, or within four days before or after the symptomatic period **OR** Other equivalent nucleic acid- amplification-based test (i.e., NAAT) to detect SARS-CoV-2 infection if obtained locally at an outside hospital[2]

[1]Saliva specimens will be collected for exploratory analyses only.
[2]See Section 7.1.1.1 for additional details.

7.1.1.2 Moderate to Severe/Critical COVID-19 [Secondary Outcome]

The severity of all symptomatic, laboratory-confirmed COVID-19 cases will be classified according to the clinical and laboratory criteria described in Table 6 to support analyses of the secondary endpoints. The worst outcome through 28 days of follow-up will be used. Final classification will be confirmed by the sponsor.

Cases will additionally be classified centrally according to the Ordinal Scale described in Appendix III to facilitate comparison to the results of other studies. This grading scale will not be used to support analyses of primary and secondary endpoints.

Table 6 Symptomatic, Laboratory-Confirmed COVID-19 Disease: Clinical Criteria for Mild, Moderate, Severe, Critical Disease Severity

Clinical Severity	Clinical Criteria	Laboratory Criteria
Mild, Symptomatic COVID-19	≥1 COVID-19 related symptom[1] **AND** No change in capacity for activity or ability to work **AND** No clinical signs indicative of moderate, severe/ critical COVID-19 (resting SpO_2 ≥95% on room air in individuals with normal baseline SpO_2,; RR 17–20 breaths per minute)	At least one nasopharyngeal swab positive for SARS-CoV-2 by RT-PCR (central lab) during, or within 4 days before or after the symptomatic period **OR** other equivalent nucleic acid-amplification-based test (i.e., NAAT) to detect SARS-CoV-2 infection if obtained locally at an outside hospital
Moderate COVID-19	New or increased shortness of breath on exertion causing greater than minimal interference with usual social & functional activities (e.g., reduced capacity for activity that you used to be able to do, inability to work if previously working, including virtual/remote work options, requiring increased assistance to perform activities of daily living) **OR** Resting SpO_2 < 95% on room air in individuals with normal baseline SpO_2 (or ≥2L increase in O_2 requirement for individuals on home O_2 and/or those with lower baseline SpO_2) for at least 24 hours; RR 21–29 breaths per minute	
Severe COVID-19	New or increased shortness of breath at rest causing inability to perform usual social and functional activities **OR** Clinical signs at rest indicative of severe systemic illness: RR ≥30 breaths per minute, HR ≥125 beats per minute, resting SpO_2 ≤93% on room air (in individuals with normal baseline SpO_2) or PaO_2/FiO_2 <300 mm Hg **OR** Deep venous or arterial thrombotic event **OR** Hypoxia requiring new or increasing supplemental oxygen (increase of ≥5 L of conventional low-flow O_2) for at least 24 hours in any individual, including individuals on home O_2 and/or those with low baseline SpO_2	
Critical COVID-19	Respiratory failure defined as ≥1 of the following: endotracheal intubation and invasive mechanical ventilation, oxygen delivered by high flow nasal	

	cannula at flow rates <20 L/min with fraction of delivered oxygen >0.5); non-invasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure **OR** Shock (systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg or requiring vasopressors) **OR** End-organ dysfunction/failure (e.g., renal, hepatic, or neurologic dysfunction) **OR** Death NOTE: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection	

[1]COVID-19 related symptoms (as assessed by the Investigator) include the presence of ≥1 of the following (new or increased): fever (≥100.4ºF) sore throat, cough, muscle aches, vomiting, shortness of breath, diarrhea, loss of smell or taste.

7.1.2 Symptom E-Diary [Participant-Reported, Days 2-15]

Participants will be instructed to complete an e-diary to report symptoms from Study Days 2 to 15. Participants will receive training and a printed user guide for e-diary data entry following receipt of IP. Participants will be instructed to complete the e-diary at the same time from Days 2 to 15 and to capture observations in the previous 24 hour period. Data on symptoms reported by participants will be available for review by investigators at all times. Investigators (or designee) will be required to review the e-diary data online daily as part of the ongoing safety review. An alert will be generated to the PI or designee when participants develop symptoms that require further evaluation. (Please see Appendix I for additional detail.) The investigator will determine whether an unscheduled visit for evaluation of symptoms or referral for urgent medical treatment (e.g., emergency room or hospital) is warranted. The investigator must verify start dates with the participant and obtain stop dates from the participant for any ongoing symptoms at Day 15 and document the information entered in the CRF. Use of antipyretic medications or anti-inflammatory medications reported in the symptom e-diary should be captured during the investigator's assessment of concomitant medications. Temperature and pulse oximetry readings reported by the participant are being collected to inform the need for evaluation or escalation of care. Vital signs must be assessed by the investigator or designee during a study visit (home or in-clinic, as appropriate) except in cases where the patient is hospitalized in which case the assessments recorded in the medical records should be entered in the CRF.

Participants can contact the AXIOM Helpdesk if the participant is unable to perform data entry using vendor-provided devices or if the participant experiences any issues with "Fusion ePRO app." Failure of a participant to comply with e-diary entry requirements will prompt automated compliance alerts being issued to the participant and clinical site staff will follow-

up if participant is noncompliant with the e-diary data entry. Additional details on the ePRO system can be found in the ePRO Manual.

7.1.3 Rapid SARS-CoV-2 Tests

A rapid SARS-CoV-2 antigen test will be performed on a nasal swab specimen at screening for the purposes of stratification only. A rapid COVID-19 IgM/IgG test will be performed on a blood sample drawn at screening to determine eligibility.

7.1.4 Saliva Specimens for SARS-CoV-2 RT-PCR

Saliva samples will be used only for scientific research. Saliva specimens for SARS-CoV-2 RT-PCR will only be collected on Days 1, 4, 8, 15, and 29 from participants enrolled by investigators or designees according to the procedures outlined the Laboratory Manual.

7.1.5 Nasopharyngeal (NP) Swabs

Collection, handling and shipment of NP swab specimens to the central lab for SARS-CoV-2 RT-PCR will be performed by investigators or designees according to procedures outlined the Laboratory Manual. Nasopharyngeal swabs will be taken on Days 1, 4, 8, 15, and 29. The Day 1 central laboratory result will be used for analysis purposes.

Nasopharyngeal specimens will be tested with a respiratory pathogen panel to assess participants with respiratory symptoms (e.g., new onset fever/cough, new onset/worsening shortness of breath). The respiratory pathogen panel NxTag Luminex technology will assess for the following pathogens: adenovirus, chlamydophila pneumonia, coronavirus 229E, coronavirus OC43, coronavirus NL63, coronavirus HKU1, influenza A, influenza A subtype H1, influenza A subtype H3, influenza B, human bocavirus, human metapneumovirus (HMPV), human parainfluenza Virus (HPIV), human parainfluenza Virus (HPIV) 2, human parainfluenza virus (HPIV) 3, human parainfluenza virus (HPIV) 4, human respiratory syncytial virus (HRSV) A, HRSV B, mycoplasma pneumonia, rhinovirus/enterovirus.

7.1.6 Samples for Storage

Samples for storage (aliquots of cDNA samples) will be prepared by the central lab from NP swabs for research purposes (for viral sequencing, subgenomic RNA RT-qPCR) to be conducted in the future as detailed in the Laboratory Manual. Samples will be stored in a secure storage place with adequate measures to protect confidentiality. The results from these potential analyses will not be reported in the Clinical Study Report (CSR).

7.1.7 SARS-CoV-2 Antibody Test (serum IgM and IgG)

Blood samples for SARS-CoV-2 antibody (IgG binding assay and IgM) assessment will be collected by the site at Screening, Days 1 (1 hour postdose), 4, 8, 15, 29. Participants may have a sample for IgG/IgM drawn during unscheduled visits for suspected COVID-19 illness. Samples will be shipped to the central laboratory as detailed in the Laboratory Manual.

8 ASSESSMENT OF SAFETY

Adverse events reported spontaneously by the participant and/or in response to an open question from the investigator (or designee), revealed by observation (e.g., during study visit or from a laboratory test result) or reported on the symptom e-diary card will be recorded by the investigator (or designee) on the AE eCRF if they occurred during the study period, regardless of causal association with the IP.

Participants who demonstrate a drop in hemoglobin 2 g/dL or greater from baseline should undergo additional testing to aid the detection/evaluation of intravascular hemolysis (lactate dehydrogenase, serum haptoglobin, urine hemosiderin and serum direct anti-globulin [DAT, Coombs] testing).

The occurrence of AEs will be monitored throughout the study and will cover all participating participants. All AEs reported from the signing of the ICF until immediately before the first dose of IP will be recorded as medical history. Capture of AEs starts during IV infusion of study treatment until the end of study period.

All AEs, including those that are not of a serious nature and those that are expected and unexpected, will be documented by the investigators (or designates) in the source documents and appropriately transcribed.

All participants will be provided a thermometer and will be instructed to take an oral temperature twice daily and record the results in the e-diary. All participants will be provided a pulse oximeter and will be instructed on how to take an SpO_2 reading once daily and record the result in the e-diary. Participants will be asked about new or worsening symptoms listed in the e-diary. An alert for new onset symptoms will be sent to the investigator for further evaluation to assess for any potential AEs. Participants will be instructed to seek further advice or emergency care related to threshold oxygen saturation levels and symptoms of concern that require further evaluation.

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that 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 a medicinal (investigational) product, whether related to the medicinal (investigational) product or not.

NOTE: A diagnosis should be preferentially captured as an AE term and signs and symptoms should be captured only in the absence of a unifying diagnosis. If there are multiple diagnoses, then all diagnoses should be captured. A chronic baseline abnormal laboratory finding that is stable and deemed by the PI as not clinically significant will not be captured as an AE, but the severity of an abnormal laboratory finding that worsens after dosing with

the study drug will be graded and is considered an AE. Surgical procedures are not AEs. They are the action taken to treat a medical condition. Interventions that were planned prior to study entry for medical conditions that started prior to study entry but did not worsen during the clinical study are not reported as AEs.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Important medical events which may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Death is an outcome and not an event. The condition leading to death is the event. Death will be considered an event only when no other information regarding the cause of death is available.

Hospitalization that is planned before inclusion into the study or outpatient treatment without overnight hospitalization is not considered a SAE. Hospitalization that occurs during a study for social reasons (e.g., transportation difficulties, respite care) is not considered to be a SAE.

8.1.3 Adverse Drug Reaction

A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]1. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline).

8.1.3.1 Expected Adverse Drug Reaction/Event

An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g., IB for an unapproved IP or package insert/summary of product characteristics for an approved product).

8.1.3.2 Unexpected Adverse Drug Reaction/Event

An adverse reaction, the nature or severity of which is not consistent with the applicable product information contained in the IB.

8.1.3.3 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Reaction (SUSAR) is the term used to refer to an adverse event that occurs in a clinical trial subject, which is assessed by the Sponsor and or PI as

being unexpected, serios and as having a reasonable possibility of a causal relationship with the investigational product.

8.2 Assessment of Severity

The severity of AEs will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, DAIDS. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

8.3 Assessment of Causality

The investigator is responsible for the assessment of the causality of an AE. Emergent's Medical Monitor (MM) will also assess SAE causality independent of the investigator.

The following guidelines are provided for this assessment.

- **Unrelated:** No relationship between the IP and the reported event.
- **Possibly related:** The event follows a reasonable temporal sequence from the time of administration of IP and/or follows a known response pattern to the IP but could also have been produced by other factors.
- **Probably related**: A reasonable temporal sequence of the event with administration of IP exists and, based on the known response to the IP, known or previously reported adverse reactions to the IP or similar products, or in the investigator's (or designates) clinical judgment the association of the event with the IP seems likely.
- **Definitely related**: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to IP administration, and which cannot be explained by concurrent disease or other drugs or chemicals (e.g., injection site pain, anaphylaxis, TRALI). The response to withdrawal of the IP (DECHALLENGE) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory RECHALLENGE procedure if necessary.

If the relationship between the AE and the IP is determined to be "possible" or "probable" or "definite" the event will be "related" to the IP.

8.4 Description of Known Adverse Event Profile for COVID-HIGIV

For general description of safety profile for COVID-HIGIV, see Section 1.2.3. For more details, refer to the most current version of the COVID-HIGIV IB.

8.5 Requirements for Immediately Reportable Events

8.5.1 Principal Investigator's Reporting Requirements

The investigator will report all SAEs and confirmed pregnancies to Emergent by e-mail within 24 hours of the investigator's knowledge of occurrence. The SAE report should include a medical summary of the SAE.

An email notification will be sent to EBCI pharmacovigilance team through Fusion to: productsafety@ebsi.com and pharmaocivigilance@ebsi.com.

For SAEs, the Pharmacovigilance (PV) Serious Adverse Event Report Form will be completed (abbreviated hereafter SAE Report Form) in the EDC. The SAE Report Form is NOT the same as the AE form. Participant identifiers (e.g., name, address, telephone number, social security number, medical record number, or hospital/laboratory number) must be redacted from the source documentation attached to the SAE forms as supporting documentation. The redaction must be done prior to submitting to PV.

All SAEs that are unexpected and related (e.g., adverse drug reactions) must be reported to the IRB/IEC/REB by the investigator (or designate) as required by ICH GCP E6 (126).

If a participant becomes pregnant during a study, Emergent will be notified. All pregnancies where conception occurred after first exposure to the IP through the End of Study visit are to be followed to outcome (e.g., delivery, spontaneous/elective/therapeutic abortion), including after the study is completed and even if the participant is withdrawn from the study. If a pregnancy results in an abnormal outcome that the reporting health care professional considers might be due to the IP, then the guidelines for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) should be followed.

Any pregnancy that occurs during study participation must be reported on a clinical study pregnancy form ("Pregnancy Notification Form" and "Pregnancy Follow-up Form") in the EDC. To ensure participant safety, each pregnancy must be reported to Emergent within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as a SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention during or after the participant has completed the study and considered by the investigator as possibly, probably, or related to the study treatment, must be promptly reported to Emergent.

The investigator is responsible for notifying their IRB/IEC/REB according to their policy.

8.5.2 Emergent's Reporting Requirements

Serious and unexpected suspected adverse reactions (SUSARs) will be reported by Emergent to the applicable regulatory authorities and to all participating investigators in an individual case safety report as soon as possible, no later than 15 calendar days after Emergent becomes

aware of the suspected adverse reaction (21 CFR 312.32). An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed (127).

Unexpected fatal or life threatening suspected adverse reaction will be reported to the national regulatory authority as soon as possible but in no case later than seven calendar days after Emergent's initial receipt of the information (21CFR 312.32).

8.5.3 Reporting of Other Information - Unanticipated Problems

For investigational sites in the U.S., as outlined by the Office for Human Research Protection (OHRP), unanticipated problems must be reported to the IRB/IEC/REB according to the requirements of 45 CFR Part 46. Unanticipated problems are considered to include any incident, experience, or outcome that meets **ALL** the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  a. Procedures that are described in the study related documents, such as the IRB/IEC/REB approved research protocol and informed consent document.
  b. The characteristics of the participant population being entered into the study.
- Related or possibly /probably related to participation in the study which means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the sample collection.
- Suggests that the study places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incidence, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the study or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others. Only a small subset of AEs occurring in human participants in a clinical study will meet these three criteria for an unanticipated problem. There are other types of incidents, experiences, and outcomes that occur during the conduct of clinical study that represent unanticipated problems but are not considered AEs. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with AEs. In other cases, unanticipated problems place participants or others at increased risk of harm, but no harm occurs.

The investigator should promptly notify the IRB when an unanticipated problem involving risks to participants or others is identified. Also, the investigator should notify Emergent of unanticipated problem(s), as well as U.S. Army Medical Research and Development Command (USAMRDC) Office of Research Protections (ORP) – Human Research Protection Office.

8.6 Follow-up of Adverse Events

All AEs/SAEs will be followed until resolution, stabilization, or up to 30 days after the last study visit.

8.6.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified on the last scheduled visit must be recorded on the AE eCRF with the current status noted. All nonserious events that are ongoing at this time will be recorded as "Not Recovered/Not Resolved" on the AE eCRF. The status of ongoing, previously reported AEs will be subject to active follow-up. Participants will be interviewed at the study visits to determine if any previously ongoing AEs are resolved.

8.6.2 Follow-up of Serious Adverse Events

Confirmed SAEs will be recorded on the AE eCRF.

The investigator will provide or arrange appropriate care for participants for whom SAEs are experienced.

All SAEs will be followed by the investigator until at least one of the following conditions is met:

- The SAE is resolved or stable if expected to remain chronic.
- The participant is referred to a specialist or other physician for treatment and follow-up. The investigator (or designate) will follow the participant's condition even if the participant is seen by another physician, to obtain information about the diagnosis and outcome and any treatments and medications administered for the event.

The following will be considered acceptable reasons for discontinuation of follow-up of ongoing SAEs:

- Participant withdraws consent
- Participant is referred to appropriate long-term medical care
- Participant is considered lost to follow-up

It is expected that the investigational site will obtain supporting medical records from appropriate physicians and record this information on the SAE Report Form and AE eCRF. The site must report SAEs to Emergent (study MM and Global PV Department) within 24 hours of knowledge of the SAE and the SAE Report Form must be completed and provided to Emergent's study MM and to Global PV Department within 72 hours (productsafety@ebsi.com and pharmacovigilance@ebsi.com). Additional information received related to any SAE must be forwarded within 24 hours of awareness to the Emergent Global PV Department (productsafety@ebsi.com and pharmacovigilance@ebsi.com).

8.6.3 Safety Monitoring Committees (SMC)

An independent, blinded SMC will be convened.

The blinded SMC consisting of at least one statistician and two clinicians with expertise in relevant clinical specialties will be responsible for assessing safety and monitoring overall conduct and integrity of the study. In fulfilling these responsibilities, the SMC may make recommendations concerning continuation and/or pausing of the study as it relates to safety and risk to the participant population as outlined in the Charter.

Monitoring for Enhanced Disease: To monitor for enhanced disease, an unblinded team supporting the blinded SMC, including a statistician and an unblinded MM, will review cases of moderate to severe/critical COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe/critical COVID-19. At any point, the unblinded team may discuss with the Chair whether the SMC should review cases for an adverse imbalance of cases of moderate to severe/critical COVID-19 between the treatment and placebo groups. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population. The SMC will evaluate the incidence of moderate to severe/critical COVID-19 by treatment arm to determine if excess harm (negative treatment effects on the primary efficacy endpoint) is observed in the treatment group. The details of this analysis will be provided in the Statistical analysis plan (SAP) and Charter.

For additional details please see the SMC Charter.

8.6.4 Breaking the Blind for Individual Participants

If the investigator determines that knowledge of a participant's treatment assignment is urgently needed in order to guide treatment or ensure the participant's safety, the investigator may gain information to the unblinding treatment information in the RTSM system. The investigator may not delegate this responsibility. The investigator must attempt to notify the MM prior to unblinding and must notify the MM within 24 hours after unblinding at the latest.

Documentation of breaking the blind must be entered in the study participants' source documents with the following information recorded: (1) date and time the blind was broken; (2) the rationale behind the unblinding decision/occurrence; (3) the names of the personnel involved; and (4) date of contact with the MM(s).

8.6.5 Study Pause Rules

Study enrollment and IP administration may be temporarily paused at the discretion of the SMC chair for safety review by the SMC if any of the following AEs occur after administration of COVID-HIGIV:

- ≥ one Grade 4 SAE or death regardless of relatedness to IP

- ≥ one Grade 3 hypersensitivity event
- ≥ five of the same Grade 3 AEs

These events will be reviewed by the SMC. The procedures for SMC notification and review of safety data will be outlined in the SMC Charter.

8.6.6 Infusion Stopping Rules

If AE(s) occur during the IV infusion, such as grade 1 (mild) events of flushing, headache, chills, fatigue, nausea, changes in pulse rate or blood pressure, slow the rate of infusion or temporarily stop the infusion until symptoms subside (as per the discretion of the investigator).

Once the AE(s) resolve, resume the infusion at a rate at a rate that is comfortable to the participant (e.g., start the infusion at half of the last tolerated infusion rate and increase gradually).

If the recipient reports grade 2 (moderate) or higher AEs such as chest pain, difficulty breathing, vomiting, arthralgia, or severe headache, unresponsive to slowing the infusion rate or stopping of the infusion, do not resume the infusion.

Stop the infusion for signs or symptoms of anaphylaxis/severe hypersensitivity reactions and administer appropriate medical management.

All sites will be expected to have bedside access to emergency crash cart (e.g., use of epinephrine) in the event of suspected anaphylaxis and referral to higher level of care (e.g., hospital, Intensive care unit [ICU]) in the event of a serious adverse reaction (e.g., thrombosis or fluid overload) if clinically appropriate.

8.6.7 Termination of the Clinical Study

Emergent reserves the right to stop or terminate the study at any time for clinical or administrative reasons.

Emergent and the investigator may elect to terminate the study early as defined by the clinical study agreement.

Any decision to voluntarily suspend or terminate a clinical study will be carefully reviewed and fully justified. Emergent will notify the applicable national regulatory authority(ies) of any suspension or termination, along with justification for terminating the study.

The investigator must notify the IRB/IEC/REB in writing of the study's completion or early termination. Emergent must receive a copy of the notification letter from the IRB/IEC/REB indicating receipt of the completion or early termination letter.

8.6.8 Terminating the Study at an Individual Investigational Site

An investigational site may be terminated from the study at the discretion of the investigator, Emergent, or IRB/IEC/REB. Emergent may decide to replace a terminated investigational

site. The study monitor will promptly notify Emergent if the study is terminated by the investigator or the IRB/IEC/REB at the investigational site.

9 STATISTICAL CONSIDERATIONS

This section is a summary of the key planned statistical analyses. The details are described in the Statistical Analysis Plan (SAP).

9.1 Sample Size Calculation

9.1.1 Sample Size

The two dose levels of COVID-HIGIV are expected to show similar efficacy during the primary observation period (28 days postdose [Day 29]) of the study and will be compared with the placebo arm individually using odds ratio (OR). To control the overall type I error rate at 5% (two-sided), each comparison of COVID-HIGIV arm with placebo will be made at the 2.6% level based on Dunnett's method for multiplicity adjustment.

The study assumptions for the baseline risk of 40% are based on evidence on secondary attack rates in untreated household contacts and health care workers who have had high risk exposures (128), (129). Several studies report the secondary attack rate in household contacts can be as high as 50% (130), (81), (131), (132). Among household contacts, age and spousal relationship are the strongest predictors of risk; the family secondary attack rate of the spouses of the family index cases is 63.87%, significantly higher than that of their children (30.53%), parents (28.37%), and other family members (20.93%) and the difference was statistically significant (31). Within households, the nonprimary attack rate was much lower in contacts <20 years of age, 5.26% (95% CI, 2.43–9.76%), as compared to 13.72% (95% CI, 10.68–17.24%) and 17.69% (95% CI, 11.89–24.83%) in contacts 20–59 years of age and ≥60 years of age, respectively (p-values <0.005).

The power of the study for the primary endpoint depends on the baseline risk of RT-PCR confirmed symptomatic COVID-19 in the placebo group and the treatment effect. A sample size of 120 participants per treatment group provides approximately 80% power to detect a relative risk (RR) of 50% (OR=0.375) when the baseline risk is 40% using a chi-squared test at 2.6% level for each comparison with allowance for ~20% of participants lost to follow-up. For the secondary endpoint of RT-PCR confirmed moderate to severe/critical COVID-19, assuming a 20% baseline risk in the placebo group, a sample size of 100 in the placebo versus 200 in the pooled treatment group (accounting for loss to follow-up) provides 66% power to detect a RR of 50% (OR=0.44) for prevention against moderate to severe/critical disease.

9.2 Analysis Sets

The following analysis sets will be evaluated in the study:

- Intent-to-Treat Set (ITT): participants who are randomized. This set will be used for the primary analysis for efficacy endpoints, and participants will be grouped by the arm to which they are randomized. For selected secondary endpoints, the following subsets will be used:
    - Baseline positive ITT subset: participants with positive Day 1 SARS-CoV-2 RT-PCR as determined by the central laboratory
    - Baseline negative ITT subset: participants with negative Day 1 SARS-CoV-2 RT-PCR as determined by the central laboratory
- Safety Set (SS): all ITT participants who receive any amount of study treatment (either COVID-HIGIV or normal saline placebo). This set will be used for safety analysis, and participants will be grouped by study treatment received.

9.3 Statistical Endpoints

9.3.1 Efficacy Endpoints

9.3.1.1 Primary Efficacy Endpoint

- Odds ratios of RT-PCR confirmed symptomatic COVID-19, including moderate to severe/critical COVID-19, for each active treatment group relative to the placebo group and the associated 95% confidence intervals (95% CIs) within 28 days postdose (Day 29) in the ITT set, adjusted for baseline (Day 1) SARS-CoV-2 RT-PCR status as determined by the central laboratory.

9.3.1.2 Secondary Efficacy Endpoints

- Odds ratios of RT-PCR confirmed mild COVID-19 for each active treatment group relative to the placebo group and the associated 95% CIs within 14 days postdose (Day 15) in the ITT set, adjusted for baseline (Day 1) SARS-CoV-2 RT-PCR status as determined by the central laboratory.
- Odds ratios of RT-PCR confirmed moderate to severe/critical COVID-19 for each active treatment group relative to the placebo group and the associated 95% CIs within 28 days postdose (Day 29) in the ITT set, adjusted for baseline (Day 1) SARS-CoV-2 RT-PCR status as determined by the central laboratory.
- Differences between each active treatment group and the placebo group in time-weighted average change from baseline (Day 1) in NP SARS-CoV-2 viral load through Day 29 postdose in the baseline positive ITT subset.
- Relative risks of NP RT-PCR status conversion between each active treatment group and the placebo group at any time through Day 29 postdose in the baseline negative ITT subset.

9.3.2 Safety Endpoints

- Incidence of participants in the SS with any AEs and SAEs within 72 hours postdose by treatment group, overall and by severity.
- Incidence of discontinuation or temporary suspension of infusion (for any reason) in the SS by treatment group.
- Incidence of AEs within 28 days postdose in the SS by treatment group.
- Incidence of SAEs within 28 days postdose in the SS by treatment group.

9.3.3 Exploratory Endpoints

- Differences between each active treatment group and the placebo group in time-weighted average change from baseline (Day 1) in saliva SARS-CoV-2 viral load through Day 29 postdose in the baseline positive ITT subset and RRs of saliva RT-PCR status conversion between each active treatment group and the placebo group at any time through Day 29 postdose in the baseline negative ITT subset.
- Proportions of ITT set participants by treatment group with death from any cause and with COVID-19 related death within 28 days postdose (by Study Day 29).
- Median time (days) to RT-PCR confirmed symptomatic COVID-19 by treatment group in the ITT set and the associated 95% CI. Log-rank tests compared to placebo will be performed stratified by baseline RT-PCR status (central laboratory).
- Median duration (days) of RT-PCR-confirmed COVID-19 symptoms (any symptom) by treatment group in the ITT set and the associated 95% CI. Log-rank tests compared to placebo will be performed stratified by baseline RT-PCR status (central laboratory).
- For the primary and first two secondary efficacy endpoints (RT-PCR confirmed mild COVID-19 and RT-PCR confirmed moderate to severe/critical COVID-19), a logistic regression model will be fit for each endpoint using the ITT set including both active dose levels and adjusting for age (<65 and ≥65 years of age), gender, race (white vs. non-white), ethnicity, Day 1 SARS-CoV-2 RT-PCR status (central laboratory), exposure risk (number of Level 2 criteria met), comorbidities (cardiac, pulmonary, renal, diabetes), BMI (<30, ≥30-<40, ≥40 kg/m^2), and smoking status (current, prior, never); interaction between baseline SARS-CoV-2 PCR status and treatment indicator will be examined.
- PK parameters by treatment group in the SS based on anti-SARS-CoV-2 binding assay IgG titers postdose on Days 1, 4, 15 and Day 29 to the extent that data allow (e.g., C_{max}, T_{max}, $AUC_{0\text{-}7d}$).

9.4 Handling of Missing Data

In general, missing data will not be imputed. More details about handling of missing data are included in the SAP.

Determination of the primary endpoint will be centrally confirmed based on investigator assessment of COVID-19 symptoms, in addition to samples for RT-PCR that are collected by the participants themselves, by home visit personnel or by the clinic as well as qualified local NAAT test results (see Section 7.1.1.1). For participants with missing investigator assessment of COVID-19 symptoms, the endpoints will be determined based on self-reported symptoms. The precise definitions will be provided in the SAP, including how to handle partially missing data.

9.5 Planned Method of Analyses

In general, continuous endpoints will be summarized by descriptive statistics including number of participants, mean, standard deviation (SD), median, minimum, and maximum. Categorical endpoints will be summarized by the total number of participants, frequencies, and percentages. Time-to-event endpoints will be summarized using Kaplan-Meier (KM) estimates by the median event time with 95% CI. Unless otherwise specified, CIs are two-sided with 95% confidence.

9.5.1 Participant Disposition, Demographics, and Medical History

Participant disposition, including early termination reasons, will be summarized by study treatment for all screened participants with signed ICF.

- A participant is considered as having completed study treatment if the subject was randomized and received any study treatment (COVID-HIGIV or placebo).
- A participant is considered as having completed the study if the subject was randomized, treated, and completed the Day 29 visit; was a screen failure; or died.

Important PDs will be summarized by treatment group for the ITT set. Participant demographics, medical history, exposure to SARS-CoV-2 infection, and risk factors for moderate to severe/critical COVID-19 disease will be tabulated by treatment group for the ITT set.

9.5.2 Treatment Exposure and Concomitant Medications

Study treatment dosing data will be tabulated by treatment group for the SS.

Concomitant medications will be coded using the WHO Drug Dictionary and displayed by treatment group for the SS.

9.5.3 Efficacy Analyses

9.5.3.1 Primary Efficacy Analysis

The primary efficacy endpoint is the ORs for participants in the ITT set to develop RT-PCR confirmed symptomatic COVID-19 by Day 29, where the two active dose groups will each be compared with the placebo group. Logistic regression will be used including baseline (Day 1) SARS-CoV-2 RT-PCR status as determined by the central laboratory as a covariate in addition to treatment indicator. Hypothesis testing of no treatment effect will be carried out at a 2.6% one-sided alpha with adjustment for multiplicity using Dunnett's method. 95% CIs will be reported. Frequencies and percentages of participants who have RT-PCR confirmed symptomatic COVID-19 by Day 29 (28 days postdose) will be summarized by treatment group. As an exploratory analysis, the possible interaction between baseline RT-PCR status (central laboratory) and treatment effect will be analyzed and reported.

As a key secondary analysis of the primary endpoint, an average treatment effect between all COVID-HIGIV treated participants in the ITT set versus those who received placebo will be estimated using logistic regression with the same covariate adjustment, with one indicator for treated vs. placebo. The OR and 95% CI will be reported for the average effect. Statistical significance (at 5% level) will only be assessed when both dose levels show statistically significant benefit as described above. 95% CIs will be reported.

9.5.3.2 Secondary Efficacy Analyses

For both RT-PCR confirmed mild symptomatic COVID-19 by Day 15 and RT-PCR confirmed moderate to severe/critical COVID-19 by Day 29, separate ORs for each active treatment group relative to the placebo group and the associated 95% CIs will be reported for the ITT set. Logistic regression will be used including baseline (Day 1) SARS-CoV-2 RT-PCR status as determined by the central laboratory as a covariate in addition to treatment indicator. Hypothesis testing of no treatment effect will be carried out at a 2.6% one-sided alpha with adjustment for multiplicity using Dunnett's method. 95% CIs will be reported. Frequencies and percentages of participants who have RT-PCR confirmed mild symptomatic COVID-19 by Day 15 will be summarized by treatment group for the ITT set, as will those with moderate to severe/critical COVID-19 by Day 29.

Differences between each active treatment group and the placebo group in time-weighted average change from baseline (Day 1) in NP SARS-CoV-2 viral load through Day 29 postdose will be estimated in the baseline positive ITT subset.

Relative risks of NP RT-PCR status conversion (negative to positive) between each active treatment group and the placebo group at any time through Day 29 postdose will be analyzed in the baseline negative ITT subset.

9.5.3.3 Exploratory Efficacy Analyses

Proportions of ITT set participants by treatment group with death from any cause and with COVID-19 related death within 28 days postdose by Study Day 29 will be tabulated by treatment group.

Differences between each active treatment group and the placebo group in time-weighted average change from baseline (Day 1) in saliva SARS-CoV-2 viral load through Day 29 postdose will be estimated in the baseline positive ITT subset. Relative risks of saliva RT-PCR status conversion between each active treatment group and the placebo group at any time through Day 29 postdose will be analyzed in the baseline negative ITT subset.

Time-to-event and duration outcomes will be summarized by KM methods. The median event time (if available) with 95% CIs will be reported by treatment group. To compare the treatment arms, log-rank tests stratified by baseline RT-PCR status as determined by the central laboratory will be used.

Time to RT-PCR confirmed symptomatic COVID-19 will be defined as days from dosing to the earlier choice between the earliest COVID-19 symptom onset date and earliest sampling date of positive RT-PCR result (or qualified local NAAT test result). Participants who do not have RT-PCR confirmed symptomatic COVID-19 will be censored at the earlier of Day 29 or last contact date.

Duration of COVID-19 symptoms will be defined as the earliest date when the COVID-19 symptoms occur until they are completely resolved as determined by the investigator. A duration of zero days will be used for participants who do not have RT-PCR confirmed COVID-19 symptoms. Median duration of COVID-19 symptoms (if available) will be summarized by treatment group for RT-PCR confirmed cases and the 95% CI will be calculated.

The primary efficacy endpoint (symptomatic COVID-19 disease) and first two secondary efficacy endpoints (RT-PCR confirmed mild COVID-19 and RT-PCR confirmed moderate to severe/critical COVID-19) will be analyzed by logistic regression for the ITT set including both active dose levels to adjust for baseline factors including: age (<65 and ≥65 years of age), gender, race (white vs. non-white), ethnicity, Day 1 SARS-CoV-2 RT-PCR status (central laboratory), exposure risk (number of Level 2 criteria met), comorbidities (cardiac, pulmonary, renal, diabetes), BMI (<30, ≥30-<40, ≥40 kg/m^2), and smoking status (current, prior, never); interaction between baseline SARS-CoV-2 PCR status and treatment indicator will be examined.

Descriptive statistics will be presented by treatment group for the ITT set for SARS-CoV-2 binding assay IgG titers postdose on Days 1, 4, 15 and Day 29. PK parameters will be calculated to the extent that data allow (C_{max}, T_{max}, AUC_{0-7d}) using standard noncompartmental analysis methods and will be summarized descriptively for the ITT set by treatment group.

9.5.4 Safety Analyses

All safety endpoints will use the SS and will be descriptive.

9.5.4.1 Analysis of Solicited COVID-19 Symptoms

The following summaries of solicited COVID-19 symptoms will be performed:

- COVID-19 symptoms by time point of onset
- Time (days) to first onset of COVID-19 symptoms
- COVID-19 symptoms by maximum severity
- Duration (days) of COVID-19 symptoms

For additional details please see the SAP.

9.5.4.2 Adverse Events and Serious Adverse Events

Adverse events will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be defined as events beginning after study treatment administration that were not present prior to study treatment administration or those that were present prior to study treatment administration and subsequently worsened in severity.

Adverse events and SAEs within 72 hours postdosing will be summarized by SOC and PT, and by treatment group, severity, relatedness to IP, and by racial and age groups.

Adverse events and SAEs within 28 days postdosing will be summarized in the same manner.

Incidence of discontinuation or temporary suspension of infusion will be summarized by treatment group.

9.5.4.3 Clinical Laboratory Tests

Laboratory test results and changes from baseline will be summarized at Days 4, 8, 15 and 29 by treatment group for the SS.

The toxicity grade of any laboratory abnormality will be assessed by the investigator. Abnormal laboratory results will be graded according to the DAIDS *Table for Grading the Severity of Adult and Pediatric Adverse Events*, Corrected Version 2.1 (133). Values within normal range or not meeting criteria for at least Grade 1 will be considered Grade 0.

Shift tables of laboratory ranges (Low, Normal, High) will be provided for selected laboratory parameters by treatment group and time point for the SS. Shift tables by grade (0, 1-2, ≥3) will be provided for selective laboratory parameters by treatment group and time point for the SS.

9.5.4.4 Vital Signs

Vital signs include oral temperature, sitting blood pressure, resting heart rate, pulse oximetry, and respiratory rate. Vital sign results and changes from baseline will be summarized at Days 1 (for each time point), 4, 8, 15 and 29 by treatment group for the SS.

A chronic baseline abnormal vital sign that is stable and deemed by the PI to not be clinically significant will not be captured as an AE. The severity of an abnormal vital sign that worsens after dosing with the study drug will be graded (Grade 1=mild through Grade 4=potentially life threatening) according to the Division of AIDS (DAIDS) *Table for Grading the Severity of Adult and Pediatric Adverse Events*, (also known as the DAIDS AE Grading Table) (133). Grade 0 includes all values not meeting criteria for Grade 1 or higher.

Shift tables by toxicity grade will be summarized by treatment group and time point for the SS in the same manner as for laboratory data.

10 DATA HANDLING PROCEDURES

10.1 Recording of Data

The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data queries received from Emergent or designee. Such documentation is subject to inspection by Emergent or its designee(s) and relevant regulatory agencies. If the investigator withdraws from the study (e.g., due to relocation or retirement), all study related records will be transferred to a mutually agreed upon designee within Emergent's specified timeframe. Notice of such transfer will be given to Emergent in writing.

10.2 Data Quality Assurance

Emergent's Quality Assurance Department (or designee) may conduct investigational site audits, either on-site or remote, before study initiation, during the study, or after study completion. Audits will include, but are not limited to, review of source documents, verification of eCRFs against source documents and review of essential documents to ensure compliance with protocol and applicable local and federal regulations. The investigator agrees to participate in site audits and assist in the prompt resolution of any issues found during audits.

In the event the investigator is contacted by a regulatory agency in relation to this study, the investigator and investigational site staff must be available to respond to reasonable requests and inspection queries made during the inspection process. The investigator must provide Emergent with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, inspectional observations, warning letters). Emergent will provide any needed assistance in responding to regulatory inspections.

10.3 Record Retention

A study document binder will be provided by Emergent for the investigator for all requisite study documents (constituting the "Investigator Study File").

Following completion of the study, the investigator will retain copies of the approved study protocol, ICF, relevant source documents, and all other supporting documentation related to the study according to applicable regulatory requirements.

The investigator must not dispose of any records relevant to this study without either (1) written permission from Emergent or (2) provision of an opportunity for Emergent to collect such records.

The investigator must arrange for the retention of the participant identification codes for at least 25 years after the completion or discontinuation of the study (Revised Canadian CTA Regulations, September 2001). Participant files and other source data must be securely stored and kept for the maximum time permitted by the hospital, institution or private practice but not less than 25 years after completion or termination of the study. Archival data may be held on microfiche or electronic record, provided that a backup exists, and that hard copy can be obtained from it if required. If source documents are to be destroyed as per hospital or local regulatory policy, the investigator is requested to contact Emergent.

Records from the study that identify the participant will be confidential except that they may be inspected by Emergent representatives for the study, the IRB/IEC/REB, the FDA, other government agencies as appropriate, and will not otherwise be released except as required by law. All information provided to the investigator by Emergent is to be considered confidential unless otherwise stated.

10.3.1 Data Management

A validated, electronic data capture (EDC) system will be used during the study. Data management activities to be performed for the study will be described in detail in the Data Management Plan (DMP).

10.3.2 Data Collection and Discrepancy Management

The study will employ eCRFs provided by Emergent. Certain clinical information requested in this protocol will be recorded on these eCRFs. The investigator is responsible for the adequacy and accuracy of all data entered on the eCRFs. The investigator is also responsible for signing all eCRFs, after which they will be locked by Emergent to prevent further data entry or modification.

For further information on eCRFs please refer to the CRF Completion Guidelines. Details on data handling will be described in the DMP.

10.3.3 Laboratory Data

This study will employ electronic transfers of external laboratory data generated from clinical specimens collected by the investigator. The investigator is responsible for the adequacy and accuracy of data associated with collection of these specimens. Emergent is responsible for ensuring the adequacy and accuracy of the data generated by external laboratories.

See Section 6 for description of types of specimens and assays.

10.3.4 File Management at the Investigational Site

The investigator will ensure that the essential study documents are maintained in accordance with the ICH GCP Guidelines and as required by applicable local and federal regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.3.5 Protocol Deviations

The investigator agrees to conduct the clinical study in compliance with the protocol agreed to by Emergent and approved by the investigational site's IRB/IEC/REB. The investigator or designee should capture the reason for PD in the CRF for all participants.

A PD is any minor or major change, divergence, or departure from the study design or procedures defined in the protocol that was made without prior sponsor and IRB approval.

The occurrence of PDs will be routinely monitored for evaluation of investigator compliance with the protocol, GCP, and regulatory requirements. Emergent will review all PDs on an ongoing basis and will be responsible for determining if the deviation should be categorized as a major PD. Important PDs are deviations that have an impact on participant safety, rights or welfare and/or the integrity of the study data. Important PDs may require additional documentation as requested by Emergent.

The investigator or investigational site staff may not deviate from the protocol, except, in rare circumstances, as necessary to eliminate immediate hazards to study participants. In such event, both Emergent and IRB/IEC/REB will be immediately notified.

Continued PDs despite re-education of investigational site personnel, or persistent PDs that are reportable to regulatory agencies may result in discontinued shipment of IP and termination of further enrollment at the investigational site, or termination of the investigational site from the study.

11 ETHICAL & REGULATORY CONSIDERATIONS

11.1 Ethical Considerations

This study must be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, current ICH GCP Guidelines, and applicable local and federal regulations, and all other applicable local laws.

Each investigational site will seek approval by an IRB/IEC/REB according to regional requirements. The IRB/IEC/REB will evaluate the ethical, scientific and medical appropriateness of the study. Further, in collecting and handling participant data and completing eCRFs, the investigator and investigational site staff will take measures to ensure adequate care in protecting participant privacy. To this end, a participant identification number will be used to identify each participant.

11.2 Informed Consent

Informed consent is a process that is initiated prior to the participant's agreeing to participate in the study and continues throughout their study participation.

Emergent or designee will generate and provide a master ICF template to each investigational site for development of a site-specific ICF.

All site-specific ICFs must comply with ICH GCP Guidelines, local regulatory requirements, and legal requirements and must be approved by Emergent or designee and the IRB/IEC/REB. Emergent or designee will advise the investigational site of required changes to the master ICF template during the study.

The participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or think about it prior to agreeing to participate. The participant will sign the informed consent/assent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent/assent document will be given to the participants for their records. The informed consent/assent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.3 Institutional Review Board

Before the start of the study, the IB, the protocol, proposed ICFs, participant compensation (if any), Emergent approved study materials and advertisements, and any other written information to be provided to the participant, will be submitted to a properly constituted IRB/IEC/REB for review. Emergent must receive a copy of the written approval from the IRB/IEC/REB for all the above applicable documents prior to recruitment of participants into the study and shipment of COVID-HIGIV.

The IRB/IEC/REB must provide written approval for all amendments to any of the above documents prior to implementation of these amendments at the investigational site. The investigator is obliged to report SAEs, as well as any unanticipated problems, to the IRB/IEC/REB in addition to other information as required by the IRB/IEC/REB.

The names (or title, if IRB/IEC/REB procedures prohibit publishing of names) and associated backgrounds of the members of IRB/IEC/REB (to assist in assuring that the board membership is properly constituted and operates according to 21 CFR part 56) will be given to Emergent prior to the start of the study along with a signed and dated statement stating that the protocol and ICF and, where applicable, any other document listed above, have been approved by them.

All correspondence between the investigator and the IRB/IEC/REB will be available for review by Emergent (or designate), contract research organization (CRO) personnel, and the applicable regulatory authority(ies).

11.4 Study Files and Materials

Source data are all information, original records of clinical findings, and observations in a clinical study necessary for the reconstruction and evaluation of the study. The source documentation requirements described below apply to all source documentation and study records in any form, including those maintained in the institution's Electronic Health Record system, if applicable.

The investigator/institution will maintain adequate and accurate source documents and study records that include all pertinent information related to participants' participation in the study, including details but not limited to signed and dated notes on consenting, eligibility, medical history, study assessments, IP administration, AEs, concomitant medications, participant follow-up information and other relevant observations.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g., via an audit trail).

The investigator/institution shall permit study related monitoring, audits, IRB/IEC/REB review, and regulatory inspection(s), providing direct access to source data/documents.

Records from the study that identify the participant will be confidential except that they may be given to and inspected by Emergent (or designee), the IRB/IEC/REB, the applicable regulatory authorities, other government agencies as appropriate, and will not otherwise be released except as required by law. All information provided to the investigator by Emergent is to be considered confidential unless otherwise stated.

12 ADMINISTRATIVE ASPECTS

12.1 Clinical Study Agreement

This study will be conducted under a Clinical Study Agreement between Emergent (or delegate) and the respective institutions representing the study sites. Any financial support given to the study sites will be detailed in the Clinical Study Agreement. The Clinical Study Agreement, which must be signed before the start of any study related procedures, will clearly delineate the responsibilities and obligations of the investigator and Emergent, and will form the contractual basis upon which the study will be conducted.

12.2 Documentation Required Prior to Study Initiation

The investigator (or designate) is responsible for forwarding the following documents to Emergent for review prior to study initiation:

- Signed protocol signature page, form FDA 1572 (or equivalent, depending on local regulatory requirements), financial disclosure form, debarment certification statement, Clinical Study Agreement, and any other required regulatory documents.
- Copy of IRB/IEC/REB approved ICF(s).
- Copy of the written IRB/IEC/REB approval for the protocol, IB, ICF(s), participant compensation (if any), any study materials and advertising, and any other written information to be provided to the participant.
- Current Curriculum Vitae (signed and dated) and a photocopy of medical license (if applicable) of the investigator, co/sub-investigators and other site personnel as required by Emergent/CRO.
- Written statement that the IRB/IEC/REB is properly constituted and operates according to ICH GCP Guidelines and applicable local and federal regulations. Investigators participating in this study, if IRB/IEC/REB members, should state in writing that they have abstained from voting regarding this protocol.
- Laboratory normal ranges and documentation of laboratory certification.

12.3 Clinical Study Registration

Emergent is responsible for clinical study registration and reporting to Clinicaltrials.gov in accordance with applicable regulations.

12.4 Participant Reimbursement

Where relevant, participants will be reimbursed for reasonable travel costs associated with participation in this study. Participants will be paid for participating in the study at a rate to be approved by the IRB/IEC/REB.

12.5 Liability and Insurance

Emergent will adhere to local regulations and guidelines regarding clinical study compensation to participants whose health is adversely affected by taking part in the study. Compensation for injury will be described in the ICF.

12.6 Participant Identification and Confidentiality

The investigator must ensure the anonymity of each participant is always maintained. Participants should only be identified by participant ID number on the CRF, or on any other study documents provided to Emergent or their designate(s). Any documents that identify the participant should be kept in strict confidence by the investigator.

Based on ICH GCP guidelines and regulatory requirements, the investigator is required to allow authorized personnel of Emergent (or its designate), the IRB/IEC/REB, and members of the appropriate regulatory authority(ies) to review participant's files that are related to EBS-CVH-002. Participants must be informed that his/her records may be reviewed by Emergent, its designate(s), the IRB/IEC/REB and the appropriate regulatory authority(ies) through direct access to the participant's original medical records.

12.7 Monitoring

The assigned clinical study monitor will verify eCRF entries against source documentation at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP Guidelines and local and federal regulations applicable to the conduct of the clinical study. The investigator must make source documentation accessible to the study monitor as needed to verify the information in eCRFs. The investigator agrees to meet with the study monitor at regular intervals to discuss study progress and ensure that any problems detected during data monitoring are resolved appropriately.

12.8 Protocol Amendments

Protocol amendments will only be made by Emergent. In general, any change to the protocol must be made in the form of a formal amendment to the protocol and must be approved in writing by the investigator, Emergent, and the IRB/IEC/REB prior to implementation. The investigator must receive written IRB/IEC/REB approval for all protocol amendments prior to implementing protocol amendments at the investigational site; copies of IRB/IEC/REB correspondence including approval/disapproval letters from the IRB/IEC/REB must be provided to Emergent.

A protocol change intended to eliminate an apparent immediate hazard to participants will be implemented immediately, followed by IRB/IEC/REB notification within five working days. Emergent will submit protocol amendments to the applicable regulatory authority(ies).

Administrative amendments are defined as having no effect on the safety or physical or mental integrity of participants, the conduct or management of the study, the scientific value of the study or the quality or safety of IP(s) used in the study.

12.9 Use of Data and Publications

Data arising from this study are the sole property of Emergent. Emergent must provide written, prior agreement to any publication based, in whole or in part, on data from this study. All proposed abstracts, manuscripts or presentations from the study must be provided to Emergent for review at least 60 days prior to submission for publication/presentation. Any information identified by Emergent as confidential must be deleted prior to submission.

The Publication Policy applicable to this protocol is the one agreed upon and described in the Clinical Study Agreement between Emergent and the investigator.

12.10 Future Use of Stored Samples

Participants will be asked to consent to the future use of stored samples as part of the informed consent process.

Stored specimens from participants who provide consent will be identified by sample numbers/codes. Samples may be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two years have elapsed since the formal discontinuation of clinical development.

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14 APPENDICES

APPENDIX I SYMPTOM E-DIARY CARD

Instructions to participants: Please fill out this symptom e-diary card once daily preferably at the same time each day. Fill out all the questions to the best of your ability. Please do not allow others to fill out the card for you.

For participants who are determined by the Investigator to be unable to fill out the e-diary card by themselves, an adult caregiver or household member may be permitted to fill out the diary card.

Symptom	**Participant Response Options (Scoring)**	**Investigator Alert Generated (Scoring)**
For items 1-7 what was the severity of your symptom at its worst over the last 24 hours?		
1. Stuffy or runny nose	None (0) Mild = I was able to continue daily activities as usual. (1) Moderate = I had difficulty performing daily activities. (2) Severe= I could not perform my daily activities. (3) I had to be treated in a hospital or emergency room because of my symptoms. (4)	(2) (3) (4)
2. Sore throat		
3. Cough		
4. Low energy or tiredness		
5. Muscle or body aches		
6. Headache		
7. Nausea (feeling like you wanted to throw up)		
8. Fever[1] Please enter your temperature (°F) reading. First reading: Time of day _____ (AM/PM) Temp____(°F) Second reading: Time of day _____ (AM/PM) Temp____(°F)	No fever < 100.4 (0) Mild 100.4-102°F (1) Moderate 102.1-104°F (2) Severe >104°F (3)	(1) (2) (3)
9. How many times did you vomit (throw up) in the last 24 hours	I did not vomit at all (0) 1-2 times (1) 3-4 times (2) 5 or more times (3)	(1) (2) (3) (4)

	I had to be treated in a hospital or emergency room because of my symptoms. (4)	
10. How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	I did not have diarrhea at all (0) 1-2 times (1) 3-4 times (2) 5 or more times (3) I had to be treated in a hospital or emergency room because of my symptoms. (4)	(1) (2) (3) (4)
11. Did you take any medications to treat any of the symptoms listed in Questions 1-10?	No (0) Yes (1)	(1)
12. If you answered Yes to Q11, please indicate which medication you took.		
13. Pulse oximeter[2] Please enter your pulse oximeter reading. Time of day_____(AM/PM) Result_____%	95-100% (0) <95% (1)	(1)
14. Shortness of breath	I do not feel short of breath (0) I have mild shortness of breath with my daily activities or wheezing (1) I had difficulty performing daily activities. (2) I could not perform my daily activities. (3) I had to be treated in a hospital or emergency room because of my symptoms. (4)	(1) (2) (3) (4)
15. Rate your sense of smell in the last 24 hours	My sense of smell is the SAME as usual (0) My sense of smell is LESS than usual (1) I have NO sense of smell (2)	(1) (2)
16. Rate your sense of taste in the last 24 hours	My sense of taste is the SAME as usual (0) My sense of taste is LESS than usual (1) I have NO sense of taste (2)	(1) (2)
Note: Score values will not be provided within the response options presented to trial participants. Detailed instructions to participants on how to perform temperature and pulse oximetry readings will be provided.		

APPENDIX II COVID-19 EXPOSURE HISTORY FORM

The following information will be obtained to ascertain history of exposure. Contact refers to the person with confirmed COVID-19.

1. Estimated date of exposure: [Month/Date/Year]
2. Did you have direct contact with secretions (vomit, sputum, stool) of a person with confirmed COVID-19? (Yes/No)
3. Were you wearing a mask and/or face shield at the time of contact? (Yes/No)
4. What was the estimated time you were exposed to the contact (within 6 feet) without a facial covering? A) 15 minutes to <1 hour B) 1 to <12 hours C) ≥12 hours
5. Was the contact symptomatic? (Yes/No/Don't know) If yes, did the contact require hospitalization? (Yes/No/Don't know)
6. In what setting did the suspected exposure occur? Please check one.
    - Community gathering of > 10 people without universal mask wearing and/or physical distancing (e.g., church gathering, political rally, social event)
    - Hospital or health care setting
    - Household
    - Nursing home
    - Assisted living facility
    - College Dorm
    - Rehabilitation facility
    - Correctional facility
    - Funeral Home
    - Airplane
    - Other (please specify)
7. Did the exposure occur outdoors or indoors? (indoor/outdoor)

Follow-Up Questions (based on response to Question 5)

For health care workers:

1. Were you present in the room during an aerosol generating procedure? Yes/No

For household contacts:

1. What is the number of persons living in the household? A) <four people B) four-eight people C) >eight people

2. Are you the caregiver of the contact? (Yes/No)
3. Is the contact with COVID-19 an intimate partner? (Y/N) If not, what is your relationship to the contact?
    - Parent
    - Adult child
    - Roommate
    - Other (please specify)
4. Was the contact with COVID-19 sharing a room or bathroom at the time of exposure? (Yes/No)

Risk categories will be centrally classified by the number of Level 2 criteria met as defined in the table below.

COVID-19 High Risk Exposure Level 1	**COVID-19 High Risk Exposure Level 2**
Duration of exposure <12 hours	Duration of exposure ≥12 hours
Outdoor exposure	Indoor exposure
< 4 people living in household	≥4 people living in household
Not a caregiver of the COVID-19 contact	Caregiver of COVID-19 contact
COVID-19 contact was not hospitalized	COVID-19 contact was hospitalized
COVID-19 contact is not an intimate partner	COVID-19 contact is an intimate partner
Age <65	Age ≥65

APPENDIX III ORDINAL OUTCOME CATEGORIES AND CRITERIA

The following ordinal outcome categories will be used to classify the severity of illness in participants with laboratory-confirmed COVID-19.

Category	Clinical Severity	Criteria
1	**Asymptomatic and no limitations in usual activity due to COVID-19**	Both of the following criteria for symptoms and limitations: • No symptoms related to COVID-19, either asymptomatic infection or resolution of prior symptoms, **AND** • Health status is at the same level as prior to SARS-CoV-2 infection and is without limitations due to COVID-19
2	**Mild COVID-19 illness or minor limitations to usual activity**	One of the following criteria indicating mild illness: • Experiencing ≥1 symptoms of COVID-19 (see PIM) that were not present or are worse than pre-illness status; criteria for a higher category must not be met if involving a major symptom, such as difficulty breathing or confusion or any symptom of a 'severe' quality. • Minimal or mild interference in usual social or functional activity due to acute or resolving COVID-19 illness
3	**Moderate COVID-19 illness and major limitations to usual activity**	**ALL** of the following criteria for symptoms and limitations: • One or more major symptoms including difficulty breathing, confusion, or any symptom of COVID-19 that is 'severe' in quality and also worse than pre-illness health status, **AND** • Without need for new oxygen supplementation (i.e., higher oxygen needs from pre-COVID levels for >24 hours), **AND** • Moderate or major limitations in usual social or functional activity due to acute or resolving COVID-19 illness ***NOTE:*** *limitations must be the result of symptoms and not due solely to isolation precautions or quarantine*
4	**Severe COVID-19 or other serious disease manifestation**	One of the following criteria indicating severe illness: • Hospitalization requiring medical care for COVID-19 or an associated manifestation and resulting in stay >18hrs, but not observation or quarantine status • Transfer or escalation of care for medical management of COVID-19 or an associated manifestation, if previously hospitalized for observation or quarantine status • Hypoxia defined by new oxygen supplementation (i.e., >24 hours at levels > pre-COVID), but not managed in a hospital • Serious vascular thrombosis (e.g., arterial or DVT) that is requiring current treatment but not managed in a hospital

Document Approvals

Approved Date: 23 Feb 2021

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