EBS-CVH-003 Clinical Study Protocol

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A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) Administered as a Single Dose Regimen to Healthy Adults

Version 4.0

21 Apr 2021

Funding Source:

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Study Sponsor:

Emergent BioSolutions Canada Inc.

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1.0	14.Sep.2020
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CONFIDENTIAL

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Study Sponsor:

Emergent BioSolutions Canada Inc.
(Emergent BioSolutions)

R3T 5Y3, Canada

Sponsor's Clinical Study Scientist:

Sponsor's Study Medical Monitor:

Immediately Reportable Adverse Events:

Signatory Page

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Clinical Site:	Icahn School of Medicine at Mount Sinai New York, NY 10029, United States

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 (DD/MMM/YYYY)

Sponsor Signatory:

Emergent BioSolutions

	Date (DD/MMM/YYYY)

EBS-CVH-003 Protocol Synopsis

Title	A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) Administered as a Single Dose Regimen to Healthy Adults
Sponsor	Emergent BioSolutions Canada Inc. (Emergent BioSolutions) R3T 5Y3, Canada
Funding Source	The United States Department of Defense
Study Start	Q4 2020
Objectives	The objectives of the study are to assess safety and pharmacokinetics (PK) of several dose levels of COVID-HIGIV in healthy adults. Primary Objectives: • To evaluate safety of three dose levels of COVID-HIGIV administered IV as a single dose to healthy adults. • To evaluate PK of three dose levels of COVID-HIGIV administered IV as a single dose to healthy adults.
Endpoints	**Primary Endpoints** The following primary safety endpoints will be evaluated: • Adverse events (AEs) within 72 hours post-dosing. • AEs leading to discontinuation or temporary suspension of infusion. • AEs and serious adverse events (SAEs) in healthy adults up to 84 days post-administration of a single dose. The following primary COVID-HIGIV PK endpoints (based on PK sample test results by an immunobinding IgG assay and a pseudovirus neutralization assay) will be evaluated in healthy adults: • $AUC_{0\text{-last}}$: area under the concentration-time curve from time 0 to the last quantifiable concentration after dosing. • $AUC_{0\text{-inf}}$: $AUC_{0\text{-last}}$ plus the additional area extrapolated to infinity after dosing • $AUC_{0\text{-14d}}$ after dosing. • $AUC_{0\text{-28d}}$ after dosing. • C_{max}: maximum observed concentration after dosing.

	• T_{max}: time at which C_{max} occurs after dosing. • C_{min28d}: observed or estimated concentration at 28 days after dosing • λ_z: terminal elimination rate constant after dosing. • $T_{1/2}$: apparent terminal elimination half-life after dosing. • CL: systemic clearance after dosing. • V_Z: volume of distribution after dosing. **Secondary PK Endpoints:** following body weight normalized PK parameters will be estimated as PK parameter divided by subject body weight (kg) at baseline. • CmaxBWN: Body weight normalized Cmax • Cmin28dBWN: Body weight normalized Cmin28d • AUC_{0-14d}BWN: Body weight normalized AUC_{0-14d} • AUC_{0-28d}BWN: Body weight normalized AUC_{0-28d} • AUC_{0-last}BWN: Body weight normalized AUC_{0-last} • AUC_{0-inf}BWN: Body weight normalized AUC_{0-inf}
Subject Population	Healthy adult (18-60 years of age) non-pregnant females and males, with no evidence of prior exposure to SARS-CoV-2 (negative RT-PCR result for SARS-CoV-2 RNA and negative SARS-CoV-2 antibody test result) at Screening.
Sample Size	28 subjects
Number of Study Sites	One site in US: Icahn School of Medicine at Mount Sinai New York, NY 10029, United States
Test Product	COVID-HIGIV is a purified liquid immunoglobulin G (IgG) preparation containing antibodies (including neutralizing antibodies) to SARS-CoV-2. COVID-HIGIV is intended for IV administration only. COVID-HIGIV product contains a target of 100 mg/mL protein and is formulated with 250 mM proline and polysorbate 80 (0.03% w/w).
Reference Product	The reference product will be a placebo control consisting of normal saline (0.9% w/v sodium chloride) liquid solution suitable for IV administration. Placebo dose will be prepared to match the volume of COVID-HIGIV dose.

<table>
<tr><td>Dosage</td><td>Three dose levels of COVID-HIGIV are planned for the study:
Dosage 1: 100 mg/kg (≈1 mL/kg), with a maximum of 100 mL for ≥100 kg body weight
Dosage 2: 200 mg/kg (≈2 mL/kg), with a maximum of 200 mL for ≥100 kg body weight
Dosage 3: 400 mg/kg (≈4 mL/kg), with a maximum of 400 mL for ≥100 kg body weight</td></tr>
<tr><td>Protocol Design</td><td>This study will be a Phase 1, single-center, double-blind, randomized, placebo-controlled design to evaluate three dose levels of COVID-HIGIV for safety and PK in healthy adults. Healthy adult subjects will be enrolled into the study to receive a single dose.
<table>
<tr><th>Study Arm</th><th>No. of Subjects</th><th>Dosing Schedule – Day 1</th></tr>
<tr><td>1</td><td>8</td><td>COVID-HIGIV dosage 1*</td></tr>
<tr><td>2</td><td>8</td><td>COVID-HIGIV dosage 2**</td></tr>
<tr><td>3</td><td>8</td><td>COVID-HIGIV dosage 3***</td></tr>
<tr><td>4</td><td>4</td><td>Placebo (saline)</td></tr>
<tr><td colspan="3">* 100 mg/kg (≈1 mL/kg), with a maximum of 100 mL COVID-HIGIV for ≥100 kg body weight.
** 200 mg/kg (≈2 mL/kg), with a maximum of 200 mL COVID-HIGIV for ≥100 kg body weight.
*** 400 mg/kg (≈4 mL/kg), with a maximum of 400 mL COVID-HIGIV for ≥100 kg body weight.</td></tr>
</table>
Twenty-eight subjects will be enrolled and randomized 2:2:2:1 into four study arms to receive a single intravenous (IV) dose of one of three COVID-HIGIV dose levels (1-3) or saline placebo (4), respectively (see the table above).

The enrollment/dosing of the first seven subjects (randomized 2:2:2:1) in the study) will be staggered wherein no more than three subjects will be dosed on the same day (to be dosed at least one hour apart). Principal Investigator (PI) and the Sponsor’s Medical Monitor (MM) will review blinded data (up to 24 hours after end of IV infusion) before proceeding with dosing subsequent set of remaining subjects for the stagger. Available safety (blinded) data will be reviewed by Study Monitoring Committee (SMC) (consisting of at least three independent external members) after seven subjects have completed at least 72 hours of safety follow-up. If unblinding of the safety data is required, closed session by the SMC will be held. An overall decision by the SMC will be made whether or not to proceed with full randomization (2:2:2:1) and dosing of the remaining study subjects (n=21).

Following dosing, each subject will stay overnight in the inpatient unit for close observation; each dosed subject will be discharged from the inpatient</td></tr>
</table>

	unit once all assessments at 24 hours post-dosing timepoint (i.e., Day 2) are completed. The SMC will perform overall ongoing review of safety data during the study. Study enrollment and administration of study treatments may be temporarily paused by the SMC for safety review if any of the following occur after study product administration and during the study's follow-up period: • One or more serious adverse event(s) [SAE(s)]. • Three or more of the same adverse events (AEs) classified as grade 3 severity. • Five or more of the same AEs classified as grade 2 severity. Note: refer to Section 8.2 for AE severity grading. Placebo recipients may be unblinded upon request after all subjects have completed Day 29 to allow them to follow current COVID-19 vaccination guidelines. Subjects will be followed up for safety and PK up to 84 days post-administration of a single dose. If any subjects become positive for SARS-CoV-2 during the study follow-up period, they will be assessed using modified WHO ordinal score (see Appendix I – Modified WHO Ordinal Scale) until they compete their last follow-up visit (via telemedicine).
Inclusion Criteria	The following criteria will be used for inclusion into the study: 1. Able and willing to provide written informed consent (voluntarily signed by the subject) prior to performing study procedures. 2. Females and males 18-60 years of age, inclusive. 3. Have a body mass index (BMI) less than or equal to 35.0 kg/m^2. 4. Women who are either: A) Not of childbearing potential: either surgically sterile (at least six weeks post bilateral tubal ligation, bilateral oophorectomy or hysterectomy); or post-menopausal (defined as ≥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) Women of childbearing potential (WOCBP) who are not planning to be pregnant during the study period and meet all of the following criteria: Negative PT prior to randomization/dosing at Day 1; **and** Use of a highly effective contraception during the study period: • Hormonal contraceptives (e.g., implants, pills, patches) initiated ≥30 days prior to Day 1; or • Intrauterine device (IUD) inserted ≥30 days prior to Day 1; or • Double barrier type of birth control (e.g., male condom with female diaphragm, male condom with cervical cap). 5. Subject understands and agrees to comply with planned study procedures. 6. Healthy as determined by the Principal Investigator based on medical history, physical exam, vital signs, urinalysis, blood chemistry and hematology test results at Screening and evidence of no prior exposure to SARS-CoV-2 (i.e., RT-PCR negative for SARS-CoV-2 and negative for SARS-CoV-2 antibodies) at Screening.
Exclusion Criteria	The following criteria will be used for study exclusion: 1. Use of any investigational product, within 30 days prior to Screening, or use of any SARS-CoV-2 vaccines or monoclonal antibodies, or COVID-19 convalescent plasma at any time prior to Screening or during the study follow-up period, or subject plans to participate in another clinical study during the study period. 2. Screening clinical laboratory test result greater than the laboratory's upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), random glucose, total and/or bilirubin, blood urea nitrogen (BUN), or creatinine. Other serum chemistry parameters that are not within the reference range will not be considered exclusionary unless deemed clinically significant by the Principal Investigator. 3. History of allergy or hypersensitivity to blood or plasma products or to COVID-HIGIV excipients (proline, PS80).

	4. History of allergy to latex or rubber. 5. History of hemolytic anemia. 6. History of IgA deficiency. 7. Receipt of any blood product within the past 12 months. 8. Plasma donation within 7 days or significant blood loss or blood donation within 56 days of randomization/dosing. 9. History of known congenital or acquired immunodeficiency or receipt of immunosuppressive therapy (e.g., prednisone or equivalent for more than two consecutive weeks within the past three months). 10. History of thrombosis or hypercoagulable state with increased risk of thrombosis. 11. History of clinically significant chronic illness (e.g., requiring hospitalization in the past three months) such as cardiac, pulmonary, renal, hepatic or other chronic conditions. 12. Receipt of a live vaccine within 28 days prior to screening or anticipated receipt of a live vaccine during the study period. 13. Currently pregnant, breastfeeding, or planning to become pregnant during the study. 14. History of, or suspected substance abuse problem (including alcohol). 15. Other medical condition which may place subject at increased risk due to participation in the study as determined by the investigator. 16. Any planned elective surgery or procedure during the follow-up period that impacts study compliance. 17. An opinion of the investigator that it would be unwise to allow the individual to be randomized into the study.
Visits and Assessments	For a tabular summary of visits/assessments refer to Table 1 at the end of the synopsis. **Screening:** in-clinic visit; within seven days prior to randomization. • Informed consent. • Eligibility assessment. • Demography (age, gender, race/ethnicity, height, body weight, BMI). • NP swab sample for SARS-CoV-2 point-of-care RT-PCR test.

	• Medical history and ongoing medications.
	• Complete physical exam (to include assessment of general appearance, and the following body systems: head/eyes/ears/nose/throat, respiratory, cardiovascular, gastrointestinal, dermatological, lymphatic/hematological, musculoskeletal, neurological, metabolic/endocrine).
	• For WOCBP: instruct on use of contraception from the time of Screening through end of study (up to Day 85.
	• Vital signs including body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate.
	• Safety laboratory assessments:
	  • Chem 7 panel [sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), blood urea nitrogen (BUN), creatinine, glucose], total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH),
	  • Complete blood count (CBC); i.e., red blood cells, white blood cells, platelets, hemoglobin, and hematocrit, with differential (neutrophils, eosinophils, basophils, monocytes and lymphocytes).
	  • Urinalysis.
	• Viral marker testing [Human immunodeficiency virus 1/2 (HIV 1/2) antibody, Hepatitis B virus (HBV) surface antigen, Hepatitis C virus (HCV) antibody].
	• Serum PT, if WOCBP.
	• Serum sample for SARS-CoV-2 antibody (IgM, IgG) point-of-care rapid test.
	• Provide counselling to subjects on precautions/measures to prevent contracting SARS-CoV-2 infection.
	Randomization/Dosing – Day 1: in-clinic visit.
	• If WOCBP, perform urine pregnancy test (UPT).
	• If required, update medical history and ongoing medications.
	• Inquire if the subject has had a suspected or confirmed exposure to SARS-CoV-2 in the period of Screening visit to Day 1.
	• Confirm eligibility.
	• Collect NP swab sample for SARS-CoV-2 point-of-care RT-PCR test.
	• Collect pre-dose serum sample (within 4 hours prior to dosing) for SARS-CoV-2 antibody level assessment.

	• Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]; within 2 hours prior to dosing. • Randomize. • Administer randomized study treatment via a single IV infusion. • Monitor/assess AEs during the infusion and after the end of infusion for the time period the subject is in the clinic (i.e., for at least 24 hours after end of the infusion). • Concomitant medications. • Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate] at 30 minutes (±5 mins) and 1 hour (±10 mins) after end of IV infusion. • Serum samples for post-dosing assessment of SARS-CoV-2 antibodies at 1 hour (±15 mins), 2 hours (±15 mins), 4 hours (±30 mins), 8 hours (±1 hour) and 12 hours (±1 hour) after end of IV infusion. • Keep the subject in the inpatient unit overnight (*i.e., for 24 hours after end of IV infusion*). **Post-Dosing Assessments (Days 2-85):** **Day 2 – Discharge Day** [i.e., 24 hours (±2 hours) after end of IV infusion]; in-clinic visit. • Assessment of AEs and concomitant medications. • Serum sample for SARS-CoV-2 antibody PK assessment. • Safety laboratory assessments (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential). • Urinalysis. • Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]. • Targeted physical exam (if clinically indicated). • Assessment of clinical status based on modified WHO ordinal scale. Note: perform this assessment ONLY if the subject's prior RT-PCR test (i.e., Day 1) returned as positive. • Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection. • Discharge the subject.

	Day 4 (3±0.5 days)*, Day 8 (7±1 day)*, Day 15 (14±2 days)*, Day 22 (21±2 days)*, Day 29 (28±2 days)*, Day 43 (42±3 days)* and Day 57 (56±3 days)*: visits conducted as in-clinic or telemedicine/home healthcare follow-ups. * Visits are indicated as calendar days, while the time post-dosing (after end of IV infusion) and the visit windows are indicated in the brackets. Perform the following in-clinic or via telemedicine follow-up: • Assessment of AEs and concomitant medications. • Targeted physical exam, if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medication during telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if more immediate medical attention is required. • Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessment (via telemedicine) ONLY if the subject became positive at any time during the study period (i.e., Day 2 - Day 85). • Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection. In-clinic staff or home healthcare attendant to perform the following: • NP swab sample for SARS-CoV-2 point-of-care RT-PCR test. • Serum sample for SARS-CoV-2 antibody PK assessment. • Blood sample for safety laboratory assessments (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential) at Day 4 only; at other follow-ups, collect sample only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up). • Sample for urinalysis at Day 4 only; at other follow-ups, collect sample only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up). • Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate] at Day 4 only; perform only if clinically indicated (as per investigator/sub-investigator's assessment of the subject in-clinic or during the telemedicine follow-up). **Day 85 (±3 days)*:** visit conduced in-clinic or as telemedicine/home healthcare follow-up. * Visit window is based in relation to Day 1 visit.

	Perform the following in-clinic or via telemedicine follow-up: • Assessment of AEs and concomitant medications. • Targeted physical exam, if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medications during the telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if more immediate medical attention is required. • Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessment ONLY if the subject became positive at any time post-dosing during the study period. • Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection. In-clinic staff or home healthcare attendant to perform the following: • NP swab samples for SARS-CoV-2 point-of-care RT-PCR test. • Serum sample for SARS-CoV-2 antibody PK assessment. • Safety laboratory assessments: o Blood sample for Chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential). Note: collect sample only if clinically indicated (as per the investigator's discretion during in-clinic or telemedicine follow-up). o Sample for urinalysis. Note: collect sample only if clinically indicated (as per the investigator's discretion during in-clinic or telemedicine follow-up). • Blood sample for viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody). • Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up). • If WOCBP, perform UPT. **Withdrawal Visit (WV):** in-clinic or telemedicine/home healthcare follow-up. Perform if withdrawal occurs at any time during the follow-up period, but outside of scheduled visits / visit windows. Perform the following in-clinic or via telemedicine follow-up:

	• Assessment of AEs and concomitant medications. • Targeted physical exam, if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medications during telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if immediate medical attention is required. • Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessments (via telemedicine) ONLY if the subject became positive at any time post-dosing during the study period. • Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection. In-clinic staff or home healthcare attendant to perform the following: • NP swab samples for SARS-CoV-2 point-of-care RT-PCR test. • Serum sample for SARS-CoV-2 antibody PK assessment. • Safety laboratory assessments: o Chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential) if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up). o Urinalysis if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up). • Blood sample for viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody). • Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]. Note: perform vital signs assessment only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up). • If WOCBP, perform UPT. **Unscheduled Visit(s):** in-clinic or telemedicine/home healthcare follow-up. Subjects can be evaluated during an unscheduled visit if the investigator deems it necessary to further follow-up on subject's safety. The following may be performed at an unscheduled visit at investigator's discretion: Perform the following in-clinic or via telemedicine follow-up: • Assessment of AEs and concomitant medications.

	• Targeted physical exam, if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medications during telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if immediate medical attention is required. • Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform this assessment (via a telemedicine) ONLY if the subject became positive at any time post-dosing during the study period. • Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection. In-clinic staff or home healthcare attendant to perform the following: • NP swab samples for SARS-CoV-2 point-of-care RT-PCR test. • Safety laboratory assessments o Blood sample for Chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential). o Sample for urinalysis. • Vital signs [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate].

Table 1 Schedule of Events

Assessments	In-Clinic Visits			In-clinic Visits or Telemedicine/Home Healthcare Follow-ups									
	Screening (≤7 days prior to Day 1)	Day 1	Day 2	Day 4	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 85	Withdrawal Visit (WV)	Unscheduled
Informed consent	X												
Eligibility	X	X[1]											
Demography (age, gender, race/ethnicity, height, body weight, BMI)	X												
Medical history & ongoing medications	X	X[2]											
Complete physical exam	X												
Targeted physical exam[3]			X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Counselling on measures to prevent SARS-CoV-2 infection	X		X	X	X	X	X	X	X	X	X	X	X
Randomization and dosing (IV infusion)		X											
Discharge (24±2 hrs after end of IV infusion)			X										
Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry), respiratory rate]	X	X[4]	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Safety laboratory tests	X		X	X	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X
Urinalysis	X		X	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X
Urine pregnancy test, if WOCBP		X[8]									X	X	
Viral markers (HBV surface antigen, HCV antibody, HIV 1/2 antibody)	X										X	X	
NP sample for SARS-CoV-2 point-of-care RT-PCR	X	X		X	X	X	X	X	X	X	X	X	X
Serum sample for SARS-CoV-2 antibody (IgM, IgG) point-of-care rapid test	X												
Serum sample for SARS-CoV-2 antibody PK		X[9]	X	X	X	X	X	X	X	X	X	X	
Adverse events & concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
COVID-19 symptoms/modified WHO ordinal scale[9]			X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]

[1] Review and confirm eligibility.
[2] If required, update medical history and ongoing medications.
[3] Perform only if clinically indicated. Based on the investigator's assessments of adverse events/concomitant medications at telemedicine follow-ups, an unscheduled in-clinic visit can be arranged to perform targeted PE.
[4] Collect vital signs within 2 hours prior to dosing and at 30±5 mins and 1 hour±10 mins after end of IV infusion.
[5] Perform vital signs assessment at Day 4 only; at other follow-ups perform if clinically indicated.
[6] Perform safety laboratory tests (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential) only if clinically indicated (as per the investigator's discretion during in-clinic or telemedicine follow-up).
[7] Perform urinalysis only if clinically indicated (as per the investigator's discretion during in-clinic or telemedicine follow-up).
[8] Perform UPT prior to randomization on Day 1.
[9] Collect serum PK samples at pre-dose (within 2 hrs prior to dosing) and post-dose (after end of IV infusion) at 1 hr±15 min, 2 hrs±15 min, 4 hrs±30 min, 8 hrs±1 hr and 12 hrs±1 hour.
[10] Perform (via telemedicine) only if the subject became SARS-CoV-2 positive at any time post-dosing during the study period.

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List of Abbreviations

Abbreviation	Definition
ACE2	Angiotensin-converting enzyme 2
ADE	Antibody-dependent enhancement
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AMS	Aseptic meningitis syndrome
ANTHRASIL®	Anthrax immune globulin intravenous (human)
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CCP	COVID-19 convalescent plasma
CFR	Code of Federal Regulations
C_{max}	Maximum serum concentration
CNJ-016®	Vaccinia immune globulin intravenous (human)
COVID-19	Coronavirus disease 2019
COVID-HIGIV	Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human)
CRF	Case report form
CV	Coefficient of variation
DMP	Data management plan
EC	Ethics committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration in US
GCP	Good clinical practices

Abbreviation	Definition
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HepaGam B®	Hepatitis B immune globulin (human)
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G (gamma globulin)
IgM	Immunoglobulin M
IGIV	Immunoglobulin intravenous
IL-1	Interleukin-1
IL-6	Interleukin-6
IP	Investigational product
IPD	Important protocol deviation
IRB	Institutional review board
IV	Intravenous route of administration
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOD	Limit of detection
LOQ	Limit of quantitation
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical monitor
NP-028	Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human)
OHRP	Office for Human Research Protection
PE	Physical exam
PEP	Post-exposure prophylaxis
PI	Principal investigator
PK	Pharmacokinetics

Abbreviation	Definition
ppm	Parts per million
PS80	Polysorbate 80
PSO	Post symptom onset
PT	Pregnancy test
PT/PTT	Prothrombin time/partial thromboplastin time
REB	Research ethics board
RNA	Ribonucleic acid
RTSM	Randomization and trial supply management
RT-qPCR	Reverse transcriptase quantitative polymerase chain reaction
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse drug reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SMC	Study monitoring committee
SOC	System organ class
SUSAR	Suspected unexpected serious adverse drug reactions
$T_{½}$	Apparent first order terminal elimination half-life
T_{max}	Time at which C_{max} occurs
TnBP	Tri-n-butyl phosphate
TNF-α	Tumor necrosis factor alpha
TRALI	Transfusion-related acute lung injury
TX-100	Triton X-100 (octyl phenylpolyethylene glycol ether)
UPT	Urine pregnancy test
US	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

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 (1). 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 (2). 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 early September 2020, >26 million COVID-19 cases and >864,000 COVID-19 attributed deaths have been reported to the WHO.

SARS-CoV-2 transmission typically occurs via respiratory droplets from close face-to-face contact (within six feet/two meters) and, to a lesser degree, via contaminated surfaces (3). Aerosol spread (airborne transmission) may occur (4), but the role of airborne transmission in humans remains unclear (5). It is estimated that up to 62% of SARS-CoV-2 transmission may occur via pre-symptomatic carriers (3).

SARS-CoV-2 utilizes its envelope homotrimeric Spike (S) glycoprotein to interact with a cellular receptor on human cells termed angiotensin-converting enzyme 2 (ACE2). Binding with ACE2 triggers a cell membrane fusion cascade leading to viral cellular entry (6), (7). Cell types within tissues of nasopharynx, lung, heart, esophagus, kidney, bladder and ileum (i.e., type II alveolar cells, myocardial cells, proximal tubule cells of the kidney, ileum and esophagus epithelial cells, and bladder urothelial cells) express ACE2, which suggests tissue targets for SARS-CoV-2 infection (8), (9).

SARS-CoV-2 viremia starts in the upper respiratory tract, and typically peaks around time of symptom onset (4-5 days post-infection); however, viral shedding starts 2-3 days prior to symptom onset (10). Pharyngeal viral shedding is high within the first week post-infection at a time when symptoms are typically mild (11). Although SARS-CoV-2 RNA can be detected in throat swabs for up to six weeks after the onset of symptoms, viral cultures are generally SARS-CoV-2 negative 8 days after symptom onset (10), (11), (12).

Humoral immune response is induced during SARS-CoV-2 infection; IgM and IgA antibodies are typically detectable 5 days (range: 3-6 days) post symptom onset (PSO), while IgG antibodies are detectable 14 days (range: 5-18 days) PSO (13), (14). The IgM response starts to decline 25-30 days PSO, while IgA and IgG responses remain stable 40 days (15) and 3 months PSO (16), respectively. Neutralizing SARS-CoV-2 antibodies are detectable 10-15 days post symptom onset (13) and can persist up to 3 months (16). T-cell responses against SARS-CoV-2 Spike protein have been characterised and correlated well with IgG and IgA antibody titres in COVID-19 patients (17).

As previously mentioned, the incubation period for SARS-CoV-2 is approximately 4-5 days (range: 2-7 days) (18), (19), and most individuals who develop symptoms (~98%) will do so within 11.5 days post-infection (18). COVID-19 has various clinical manifestations, including the most commonly reported symptoms of fever, dry cough and dyspnea (shortness of breath); other reported symptoms include fatigue, myalgia, nausea/vomiting or diarrhea, headache, weakness, rhinorrhea, anosmia, ageusia, hypoxia, pneumonia (20), (21), (22). However, current clinical experience with COVID-19 patients indicates hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, ophthalmologic, and dermatologic symptoms, which may reflect extrapulmonary dissemination and replication of SARS-CoV-2 (23).

Most COVID-19 patients present with mild disease (81%); however, 14% of patients develop severe COVID-19 [characterized by hospitalization (median time from symptom onset to hospitalization is 7 days; range: 3-9 days), (24), worsening of dyspnea and hypoxia, severe pneumonia with >50% lung involvement on imaging], while 5% of patients progress to critical COVID-19 [manifested as respiratory failure/acute respiratory distress syndrome (ARDS), septic shock and/or multiorgan system dysfunction, which can result in death] (19), (22), (25), (26).

Mild COVID-19 resolves 5–7 days (and up to 14 days) after symptom onset without requirement for special medical interventions. Some infected individuals are asymptomatic after SARS-CoV-2 infection but are capable of transmitting the virus (27), (28). Approximately 25% of infected patients have underlying health conditions; however, 60-90% of hospitalized COVID-19 patients have significant comorbidities, including hypertension, obesity, diabetes, cardiovascular disease, chronic pulmonary disease, chronic kidney disease, malignancy and chronic liver disease (24), (29), (30). Abnormal laboratory values observed in hospitalized patients include lymphopenia (83%), elevated inflammatory markers (e.g., C-reactive protein, ferritin, tumor necrosis factor-α (TNF-α), interleukins (IL-1, IL-6)] indicative of cytokine storm, and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer (46% of patients), low fibrinogen) (31), (32), (33). Complications due to COVID-19 other than lung/pulmonary abnormalities include impaired function of the heart, brain, liver, kidney and coagulation system (23).

Mortality in hospitalized COVID-19 patients ranges from 15% to 20%; however, up to 40% mortality has been observed among patients requiring intensive care unit (ICU) admission (29). In addition, hospital mortality ranges from <5% among patients <40 years to 35% for patients aged 70-79 years and >60% for patients aged 80-89 years (24).

Supportive care, including supplemental oxygen and mechanical ventilation, is the main treatment for severe/critical COVID-19 patients. However, recent clinical studies indicate that dexamethasone decreases mortality (subgroup analysis suggests benefit is limited to patients who require supplemental oxygen and who have symptoms for >7 days) and remdesivir improves time to recovery (subgroup analysis suggests benefit is limited to patients not receiving mechanical ventilation); both are currently recommended for treatment of COVID-19 patients (34), (35). Other classes of drugs are being assessed in clinical studies for treatment of COVID-19 (to either resolve ongoing viremia and/or to manage various COVID-19 manifestations), including antivirals (e.g., umifenovir), antibody-based therapies (e.g., COVID-19 convalescent

plasma), anti-inflammatory agents (e.g., statins), immunomodulatory therapies (e.g., tocilizumab, sarilumab, anakinra, ruxolitinib), anticoagulants [e.g., heparin; albeit, thromboprophylaxis with heparin is currently recommended for hospitalized COVID-19 patients (35)] and anti-fibrotics (e.g., tyrosine kinase inhibitors). Despite the enormous current efforts into clinical investigations of either repurposed drug therapies or development of new products, there are no approved therapeutic interventions to prevent SARS-CoV-2 infection or to treat COVID-19. Therefore, there still exists an unmet medical need for interventions that would resolve SARS-CoV-2 infection and improve clinical outcomes in COVID-19 patients.

1.2 Study Drug

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

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 US Food and Drug Administration (FDA)-licensed and/or registered plasma and/or blood collection centers from healthy, adult donors who have elevated levels of SARS-CoV-2 antibodies.

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. During the viral inactivation step of the manufacturing process, tri-n-butyl phosphate (TnBP) and Triton-X-100 (TX-100) are used and may be presented in trace amounts in the final product [≤1 parts per million (ppm) for TnBP and ≤5 ppm for TX-100].

The potency of the final product is determined by a validated immunoassay that measures concentration of binding SARS-CoV-2 antibodies (
) in relation to a standard; the final drug product is also characterized by a wild-type SARS-CoV-2 neutralization assay (refer to the most current version of the Investigator's Brochure).

COVID-HIGIV is provided as a sterile liquid for IV administration only. The product is a clear to slightly opalescent and colorless or pale-yellow liquid essentially free of foreign particles.

The active ingredient of COVID-HIGIV is human immunoglobulin (IgG), which is a normal constituent of the human body and therefore it is not expected to be toxic to humans. At the proposed COVID-HIGIV doses (≤100-400 mg/kg) for this study, exposure levels of excipients (proline, PS80) and residuals (TnBP, TX-100) are well below maximum tolerated doses in animals; hence, these substances are not expected to pose any clinically significant health risks to study subjects (refer to the most current version of the Investigator's Brochure for more details).

Emergent BioSolutions is developing COVID-HIGIV for post-exposure prophylaxis following SARS-CoV-2 exposure and for treatment of COVID-19.

1.2.2 COVID-HIGIV as a Therapeutic Intervention for SARS-CoV-2/COVID-19

COVID-HIGIV (code name: NP-028) is intended as a passive immunization therapy (i.e., passive transfer of antibodies) that would provide suitable levels of SARS-CoV-2 antibodies for binding and neutralization of SARS-CoV-2 preventing viral cellular entry and potentially augmenting the immune response.

Although no animal studies have been done to date with COVID-HIGIV, passive transfer of anti-SARS-CoV-2 antibodies with neutralizing activity [e.g., monoclonal antibodies (mAbs) isolated from recovered COVID-19 patients] has been shown to be effective at modulating SARS-CoV-2 infection and reducing viral load (including in the lung tissue) and disease burden in animals after exposure to SARS-CoV-2 (36), (37), (38). In addition, 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., 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 (39), (40), (41), (42), (43).

The overall safety profile of COVID-HIGIV is anticipated to be comparable to other commercially available human hyperimmune IGIV products, including those hyperimmune IGIV products manufactured by Emergent (VARIZIG®, HepaGam B®, ANTHRASIL®, WinRho® SDF, CNJ-016®-VIGIV) (44), (45), (46), (47), (48). The most common types of adverse reactions to hyperimmune IGIV products are non-anaphylactic infusion reactions, such as back or abdominal pain, nausea and vomiting within the first 30 minutes of infusion. Usually there is no dyspnea or other clinically significant changes in vital signs. Fever, headache, chills, rash, fatigue may begin at the end of the IV infusion and continue for several hours. More severe reactions of this type may require treatment with corticosteroids or acetaminophen and persist for several hours after the infusion. These may be treated symptomatically. The incidence of adverse reactions associated with IV administration of immunoglobulin products is reported by the manufacturers to be typically in the range of 1 to 15% (44), (45), (46), (47), (48), (49), (50), (51), (52). Infrequent events associated with IV immunoglobulin treatment have also been reported (mostly in individuals with risk factors for developing these events), such as hypersensitivity reactions, renal failure, aseptic meningitis syndrome (AMS), hemolysis, transfusion-related acute lung injury (TRALI) and thrombotic events (53). Potential risk of antibody-dependent enhancement (ADE) in COVID-19 patients following treatment with antibody-based therapies has not been clinically observed (e.g., in COVID-19 patients after transfusion of convalescent COVID-19 plasma); however, COVID-HIGIV recipients will be closely monitored for disease worsening throughout the study period.

Overall, there is currently proof-of-concept efficacy animal data with SARS-CoV-2 passive antibody transfer (with SARS-CoV-2 mAbs isolated from recovered COVID-19 patients) and some clinical experience with CCP in COVID-19 patients to suggest that an antibody therapeutic such as COVID-HIGIV would elevate SARS-CoV-2 neutralizing antibody levels sufficiently to impact SARS-CoV-2 viral load and to potentially improve clinical outcomes.

1.3 Clinical Study Rationale

This study is designed to evaluate safety and PK of three COVID-HIGIV dose levels administered IV as a single dose to healthy adults.

Like other human IGIV products, the hyperimmune products manufactured by Emergent (see Section 1.2.2) have been studied in several healthy adult volunteers and clinical studies with patients; the safety profile of these hyperimmune products is consistent with other commercial IGIV/hyperimmune products and the PK profile is typically similar to PK of licensed IGIV/hyperimmune products, with a half-life of approximately 24 to 30 days after IV administration. The proposed doses for this clinical study (≤100-400 mg/kg) are within the dose levels tested in clinical studies of other licensed IGIV/hyperimmune products and are expected to display similar safety and PK profile to those products.

Results from this clinical study will provide safety information on the intravenously administered COVID-HIGIV, as well as PK parameters such as peak COVID-HIGIV plasma levels, trough titers of SARS-CoV-2 antibodies and COVID-HIGIV half-life in healthy adults; the safety data and PK parameters from this study (along with data available from other ongoing or planned clinical studies with COVID-HIGIV) will be used for dose optimization/dose selection for the proposed COVID-HIGIV indications (treatment of COVID-19; post-exposure prophylaxis of COVID-19).

2 STUDY HYPOTHESIS, OBJECTIVES AND ENDPOINTS

2.1 Study Hypothesis

No statistically-powered hypothesis is tested in this Phase 1 study.

2.2 Study Objectives

2.2.1 Primary Objectives

The following primary objectives will be evaluated:

- To evaluate PK of three dose levels of COVID-HIGIV administered IV as a single dose to healthy adults.
- To evaluate safety of three dose levels of COVID-HIGIV administered as a single dose to healthy adults.

2.3 Study Endpoints

2.3.1 Primary Endpoints

The following primary safety endpoints will be evaluated:

- AEs within 72 hours post-dosing.
- AEs leading to discontinuation or temporary suspension of infusion.
- AEs and SAEs in healthy adults up to 84 days post- administration of a single COVID-HIGIV dose.

The following primary PK endpoints (based on PK sample test results of an immunobinding IgG assay and a pseudovirus neutralization assay) will be evaluated in healthy adults:

- Primary PK Endpoints (at each of the three COVID-HIGIV dose levels):
  - $AUC_{0\text{-last}}$: area under the concentration-time curve from time 0 to the last quantifiable concentration after dosing.
  - $AUC_{0\text{-inf}}$: $AUC_{0\text{-last}}$ plus the additional area extrapolated to infinity after dosing.
  - $AUC_{0\text{-14d}}$ after dosing.
  - $AUC_{0\text{-28d}}$ after dosing.
  - C_{max}: maximum observed concentration after dosing.
  - T_{max}: time at which C_{max} occurs after dosing.
  - C_{min28d}: observed or estimated concentration at 28 days after dosing.
  - λz: terminal elimination rate constant after dosing.
  - $T_{1/2}$: apparent terminal elimination half-life after dosing.

- CL: systemic clearance after dosing.
- V_Z: volume of distribution after dosing.

Secondary PK Endpoints: following body weight normalized PK parameters will be estimated as PK parameter divided by subject body weight (kg) at baseline.

- CmaxBWN: Body weight normalized Cmax
- Cmin28dBWN: Body weight normalized Cmin28d
- $AUC_{0\text{-}14d}$BWN: Body weight normalized $AUC_{0\text{-}14d}$
- $AUC_{0\text{-}28d}$BWN: Body weight normalized $AUC_{0\text{-}28d}$
- $AUC_{0\text{-}last}$BWN: Body weight normalized $AUC_{0\text{-}last}$
- $AUC_{0\text{-}inf}$BWN: Body weight normalized $AUC_{0\text{-}inf}$

3 INVESTIGATIONAL PLAN

3.1 Study Design

This study will be a Phase 1, single-center, randomized, double-blind, placebo-controlled design to assess safety and PK of COVID-HIGIV in healthy adults.

Healthy adult subjects are planned to be enrolled and randomized to receive a single dose; see Table 2 below.

Eligible subjects will be randomized 2:2:2:1 to four study treatment arms to receive a single IV infusion of one of three COVID-HIGIV dose levels (1-3) or saline placebo (4), respectively.

Table 2 Overview of Study Design

Study Arm	No. of Subjects	Dosing Schedule – Day 1 Visit
1	8	COVID-HIGIV dosage 1*
2	8	COVID-HIGIV dosage 2**
3	8	COVID-HIGIV dosage 3***
4	4	Placebo (saline)

* 100 mg/kg (≈1 mL/kg), with a maximum of 100 mL COVID-HIGIV for ≥100 kg body weight.
** 200 mg/kg (≈2 mL/kg), with a maximum of 200 mL COVID-HIGIV for ≥100 kg body weight.
*** 400 mg/kg (≈4 mL/kg), with a maximum of 400 mL COVID-HIGIV for ≥100 kg body weight.

Following randomization and dosing on Day 1, subjects will be kept in the inpatient unit and will be discharged the following day (Day 2 visit). Subjects will be followed for safety and PK up to 84 days (up to Day 85 visit) post-dosing.

Overall study duration for subjects will be up to 91 days (seven days of screening period and 84 days of follow-up post-randomization).

The enrollment/dosing of the first seven subjects (2:2:2:1 randomization) in the study will be staggered, wherein no more than three subjects will be dosed on the same day (dosing at least 1 hour apart). Principal Investigator (PI) and the Sponsor's Medical Monitor (MM) will review blinded data (up to 24 hours after end of IV infusion) before proceeding with dosing subsequent set of staggered subjects. Available safety (blinded) data will be reviewed by Study Monitoring Committee (SMC) (consisting of at least three independent external medical monitors) after seven subjects have completed at least 72 hours of safety follow-up. If unblinding of the safety data is required, closed session by the SMC will be held. An overall decision by the SMC will be made to proceed with full randomization (2:2:2:1) and dosing of the remaining study subjects (n=21). The SMC will perform overall ongoing review of safety data during the study. Study enrollment and administration of study treatments may be temporarily paused by the SMC for safety review, if required (see Section 8.11 for study safety-pausing rules).

Subjects who become positive for SARS-CoV-2 at any time post-dosing follow-up period will be withdrawn from the study (no further specimen collections), but will be followed up for safety only via telemedicine until their originally scheduled last follow-up visit. Subjects who report

clinical signs/symptoms of COVID-19 during telephone contact follow-ups will be classified in severity by site staff as grade 1-4 (see Appendix II – Grading of COVID-19 Symptoms), while overall clinical status of the subjects with COVID-19 will be assessed by the site staff using modified WHO ordinal scale as outlined (see Appendix I – Modified WHO Ordinal Scale).

3.2 Study Center(s)

This study will be conducted at a single center in the US.

3.3 Sample Size

There was no formal sample size calculation for this Phase 1 study. However, based on previous experience with hyperimmune globulin products manufactured by Emergent (see Section 1.2.2) in Phase 1 clinical studies with healthy adults, Emergent deems that the number of subjects planned to receive COVID-HIGIV is sufficient to descriptively assess safety and PK of three COVID-HIGIV dose levels administered by IV to healthy adults.

In total, 28 subjects are planned for the study(8 subjects/dose level, and 4 placebo subjects).

3.4 Randomization

Randomization/dosing of the first seven subjects in the study will be staggered; seven subjects will be randomized 2:2:2:1 (two subjects at COVID-HIGIV dosage level 1, two subjects at COVID-HIGIV dosage level 2, two subjects at COVID-HIGIV dosage 3 and one placebo subject). After the SMC review of the safety data from the first seven subjects, and if the enrollment is recommended to proceed, the remaining subjects (n=21) will be randomized 2:2:2:1.

Randomization list will be generated by a Randomization and Trial Supply Management (RTSM) system vendor. The designated individual at the site receiving the randomization codes will be unblinded (pharmacist). Details on the randomization procedures will be provided in the Pharmacy Manual.

3.5 Blinding

The pharmacy staff assigned to this Phase 1 clinical study will be unblinded to access the randomization assignment and prepare the study treatments. All doses of study treatments will be prepared in the same total volume in the IV infusion bags; in addition, bag covers will be used to mask the bags to maintain the blind.

There will be designated (subcontracted) unblinded clinical study monitors and an independent unblinded Quality Assurance (QA) representative (if needed). In addition, designated personnel at the bioanalytical laboratory who will be assigned to perform PK sample testing may indirectly become unblinded due to nature of test results; however, measures will be implemented not to disseminate bioanalytical laboratory results until required. Other personnel involved in the conduct of the clinical study will remain blinded until database lock and final unblinding.

Access to information in electronic data capture (EDC) system will be blinded using role-based permissions. Randomization group and study treatment dispensing data will be provided to Emergent after database lock and unblinding. Dosing data will be reconciled with the randomized treatment group for each subject by the unblinded monitor, and any deviations will be reported in the Clinical Study Report (CSR).

Upon request, subjects who received placebo will be informed of their treatment assignment after all subjects have completed the Day 29 to follow current COVID-19 vaccine recommendations. Placebo recipients will be kept in the study for safety follow-up, but no PK samples will be drawn.

While this is a double-blind study, an unscheduled unblinding may occur at any point after the infusion. Details on the reasons for unblinding and the associated unblinding procedures will be described in the Pharmacy Manual. In an event of unblinding, Emergent must be notified.

4 SELECTION OF STUDY SUBJECTS

4.1 Subject Inclusion Criteria

Subjects must meet the following inclusion criteria to participate in the study:

1. Able and willing to provide written informed consent (voluntarily signed by the subject) prior to performing any study procedures.
2. Females or males, 18-60 years of age, inclusive.
3. Body mass index (BMI) less than or equal to 35.0 kg/m^2.
4. Women who are either:
   A) Not of childbearing potential: surgically sterile (at least six weeks post bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or post-menopausal (defined as ≥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) Women of childbearing potential (WOCBP) who are not planning to be pregnant during the study period and meet all of the following criteria:

   Negative pregnancy test prior to randomization/dosing at Day 1; **and**

   Use of a highly effective contraception during the study period:

   - Hormonal contraceptives (e.g., implants, pills, patches) initiated ≥30 days prior to Day 1; or
   - Intrauterine device (IUD) inserted ≥30 days prior to Day 1; or
   - Double barrier type of birth control (e.g., male condom with female diaphragm, male condom with cervical cap).
5. Subject understands and agrees to comply with planned study procedures.
6. Healthy as determined by principal investigator based on medical history, physical exam, vital signs, urinalysis, blood chemistry and hematology test results at Screening and no evidence of prior exposure to SARS-CoV-2 (i.e., RT-PCR negative for SARS-CoV-2 and negative for SARS-CoV-2 antibodies) at Screening.

4.2 Subject Exclusion Criteria

Subjects who have any of the following exclusion criteria will be excluded from the study:

1. Use of any investigational product within 30 days prior to Screening or use of any SARS-CoV-2 vaccines or monoclonal antibodies, or COVID-19 convalescent plasma at any time prior to Screening or during study follow-up period, or subject plans to participate in another clinical study during the study period.

2. Screening clinical laboratory test result greater than the laboratory's upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), random glucose, total and/or bilirubin, blood urea nitrogen (BUN), or creatinine. Other serum chemistry parameters that are not within the reference range will not be considered exclusionary unless deemed clinically significant by the principal investigator.
3. History of hypersensitivity to blood or plasma products or to COVID-HIGIV excipients (proline, PS80).
4. History of allergy to latex or rubber.
5. History of hemolytic anemia.
6. History of IgA deficiency.
7. Receipt of any blood product within the past 12 months.
8. Plasma donation within 7 days or significant blood loss or blood donation within 56 days of randomization/dosing.
9. History of known congenital or acquired immunodeficiency or receipt of immunosuppressive therapy (e.g., prednisone or equivalent for more than two consecutive weeks within the past three months).
10. History of thrombosis or hypercoagulable state with increased risk of thrombosis.
11. History of clinically significant chronic illness (e.g., requiring hospitalization in the past three months) such as cardiac, pulmonary, renal, hepatic or other chronic conditions.
12. Receipt of a live vaccine within 28 days prior to screening or anticipated receipt of a live vaccine during the study period.
13. Currently pregnant, breastfeeding, or planning to become pregnant during the study.
14. History of, or suspected substance abuse problem (including alcohol).
15. Other medical condition which may place subject at increased risk due to participation in the study as determined by the investigator.
16. Any planned elective surgery or procedure during the follow-up period that impacts study compliance.
17. An opinion of the investigator that it would be unwise to allow the individual to be randomized into the study.

4.3 Subject Withdrawal

The subjects must be available, without coercion, for all parts of the study. If continued participation jeopardizes the subject’s health, the subject should be withdrawn from the study. The investigator is encouraged to consult Emergent prior to the withdrawal of any subject, except in the event of a medical emergency. The reason for withdrawal of any subject must be

clearly documented on the study source documents and the appropriate Electronic Case Report Form (eCRF).

4.3.1 Subject Withdrawal Criteria

All subjects 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 subject is otherwise entitled. In addition, subjects may be withdrawn from the study for any of, but not limited to, the following reasons:

- The subject develops an intercurrent illness that prevents completion of the study.
- The subject becomes positive for SARS-CoV-2 at any time post-dosing.
- It is the opinion of the principal investigator that it is unwise for the subject to continue in the study.
- The subject is not compliant with the requirements of the study to the satisfaction of the investigator and/or sponsor (e.g., non-cooperative, misses appointments, unreported use of concomitant medications).
- The subject is lost to follow-up.

If a subject is withdrawn from the study, they will not be re-entered into the study for any reason.

4.3.2 Subject Replacement

Subjects withdrawn from the study or who withdraw consent after randomization will not be replaced.

4.3.3 Follow-up for Withdrawn Subjects

Every attempt will be made to ensure that subjects who are withdrawn, or who withdraw from the study during the active treatment or follow-up period, will complete all safety and available assessments for the Withdrawal Visit (WV) visit as outlined in this protocol; see Table 1 or Section 6.3.3 for a list of recommended WV assessments. The investigator should inform the subjects that these assessments are for their own safety.

5 INVESTIGATIONAL PRODUCT INFORMATION

5.1 COVID-HIGIV

5.1.1 Packaging and Formulation

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 (target 100 mg/mL), of which at least 90% is human IgG. COVID-HIGIV 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 25.0 mL. Each vial is intended for single use. The vials will be provided in shelf cartons (4 vials per shelf carton).

For more information, please refer to the most current version of the Investigator's Brochure for COVID-HIGIV.

5.1.2 Labeling

COVID-HIGIV vial and shelf carton labels will include information that will comply with US regulations, in the appropriate language(s).

For dispensing labels for secondary receptacles, refer to Section 5.1.5.

5.1.3 Shipment

COVID-HIGIV will be shipped to the site 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 assessment of the shipping temperature including upload of temperature data from the electronic temperature monitoring device, as well as returning of the shipping container and all required documentation to Emergent or designate. Study treatment will be released for use by the site only after the data logger results are reviewed and written authorization has been issued to the investigator/designate by Emergent. Temperature excursions during shipment must be reported to Emergent 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 Investigator's Brochure and the Pharmacy Manual.

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.

Subject identifier (subject ID number) must be recorded on the labels of the vial(s) used to prepare the dose. The 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 (note: all doses are to be prepared to maximum volume of 400 mL; refer to Pharmacy Manual for details around dose preparation). 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 25.0 mL per vial) into a sterile syringe (that can accommodate up to 25.0 mL) using standard aseptic techniques and transfer the content into an appropriately sized and labeled IV infusion bag.
- If multiple transfers of content from COVID-HIGIV vials are needed to prepare the total dose in the IV infusion bag, use aseptic techniques to prevent contamination.

Once punctured, use the vial contents to prepare the infusion bag promptly. COVID-HIGIV contains no preservative. 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: subject ID, expiry date of the prepared dose (i.e., <24 hours after dose preparation), the investigator's name, protocol code (EBS-CVH-003) 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.

Record date of the infusion, start/stop times and the total volume infused. For further details, refer to the Pharmacy Manual.

5.1.6 Administration

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 1.0 mL/min for the first 30 minutes. If the infusion is well tolerated, double the infusion rate to 2.0 mL/min for the next 30 minutes, and if tolerated, double the rate to 4.0 mL/min (maximum rate) which should be used for the remainder of the infusion.

For example, at the recommended infusion rates above (with no interruptions or reduction in the infusion rates), dose volume of 400 mL should be infused within 2.5 hours.

Monitor subjects closely during infusion and within 24 hours after completion of COVID-HIGIV infusion.

If AEs occur during the IV infusion, such as grade 1 (mild) events of flushing, headache, chills, fatigue, nausea, slight changes in pulse rate or blood pressure, slow the rate of infusion or temporarily stop the infusion until symptoms subside (at discretion of the investigator). Once the AEs resolve, resume the infusion at a rate that is comfortable to the subject (e.g., start the infusion at half of the last tolerated infusion rate and increase gradually). If the recipient experiences 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 if serious AEs develop (e.g., anaphylaxis, severe hypersensitivity reactions) and administer appropriate medical management. Do not restart the infusion.

5.1.7 Drug Accountability

The investigator is responsible for maintaining accurate inventory records of COVID-HIGIV. The pharmacist or pharmacy staff designate will inventory all COVID-HIGIV shipments upon receipt, acknowledge possession by signing all required documentation, and returning these to the sponsor. The investigator must ensure that all drug supplies are kept in a secure location in the site pharmacy in accordance with recommended storage conditions. A site pharmacist (unblinded) or a designated individual (unblinded) not involved in study treatment administration/study assessments will maintain a current inventory and ongoing record of test material supplies using the Drug Accountability Form provided by the sponsor. This inventory record for the COVID-HIGIV 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/Re-test date
- Number of vials dispensed, date and time of dispensing and study subject for whom product was dispensed
- Product balance
- Name and title of qualified individual dispensing product.

These records will be reviewed by unblinded representatives contracted out by the sponsor and may be reviewed by regulatory agencies.

5.2 Description of Reference Treatment, Comparator and/or Placebo

This study is not using a reference treatment or a comparator; rather a placebo control will be used. The intended placebo is a normal saline (0.9% w/v sodium chloride) liquid solution suitable for IV administration. In general, placebo will be prepared at the same volume as COVID-HIGIV doses, and administration of placebo will be the same as for COVID-HIGIV (e.g., IV infusion, starting infusion rates/incremental increases in infusion rates). Refer to the Pharmacy Manual for details on the placebo.

6 STUDY PROCEDURES

6.1 Screening

Screening period is within seven days prior to Day 1.

Eligible subjects will first undergo informed consent counselling. Once informed consent has been obtained, subjects will undergo a screening visit in the clinic to ascertain their eligibility for the study.

Perform the following screening visit assessments:

- Informed consent.
- Eligibility.
- Collection of demography information (age, gender, race/ethnicity, height, body weight, BMI).
- NP swab sample for SARS-CoV-2 point-of-care RT-PCR test.
- Medical history and ongoing medications.
- Complete physical exam (to include assessment of general appearance, and the following body systems: head/eyes/ears/nose/throat, respiratory, cardiovascular, gastrointestinal, dermatological, lymphatic/hematological, musculoskeletal, neurological, metabolic/endocrine).
- For WOCBP: instruct on use of contraception from the time of Screening through end of study period (up to Day 85 visit).
- Vital signs including body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate.
- Safety laboratory assessments:
    - Chem 7 panel [sodium (Na+), potassium (K+), chloride (Cl^-), bicarbonate ($HCO3^-$), BUN, creatinine, glucose], total and direct bilirubin, ALT, AST, LDH,
    - CBC (red blood cells, white blood cells, hemoglobin, hematocrit) with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
    - Urinalysis.
- Viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody).
- SARS-CoV-2 antibody (IgM, IgG) point-of-care rapid test.
- Provide counselling to subjects on precautions/measures to prevent contracting SARS-CoV-2 infection.

6.2 Day 1 – Randomization and Dosing

Perform the following assessments on Day 1:

- If WOCBP, perform UPT.
- If required, update medical history and ongoing medications.
- Inquire if the subject has had a suspected or confirmed exposure to SARS-CoV-2 in the period of Screening visit to Day 1.
- Confirm eligibility.
- Vital signs [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]; within 2 hours prior to dosing.
- Collect NP swab sample for SARS-CoV-2 point-of-care PCR test.
- Collect pre-dose serum sample (within 4 hours prior to dosing) for SARS-CoV-2 antibody PK assessment.
- Randomize.
- Administer randomized study treatment via IV infusion.
- Monitor/assess AEs during the infusion and after the end of infusion for the time period the subject is in the clinic (i.e., for at least 24 hours after end of the infusion).
- Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate] at 30 minutes (±5 mins) and 1 hour (±10 mins) after end of IV infusion.
- Serum samples for PK assessment of SARS-CoV-2 antibodies at 1 hour (±15 mins), 2 hours (±15 mins), 4 hours (±30 mins), 8 hours (±1 hour) and 12 hours (±1 hour) after end of IV infusion.
- Keep the subject in the inpatient unit overnight (i.e., for 24 hours after end of IV infusion).
- Record any concomitant medications (if applicable).

6.3 Post-Dosing Assessments

6.3.1 Day 2 – Discharge

Day 2 (in-clinic visit) will occur 24 hours (±2 hours) after end of IV infusion on Day 1. Perform the following:

- Assessment of AEs and concomitant medications.
- Serum sample for SARS-CoV-2 antibody PK assessment.
- Safety laboratory assessments (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential).
- Urinalysis.
- Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate].

- Targeted physical exam (if clinically indicated).
- Assessment of clinical status based on modified WHO ordinal scale. Note: perform this assessment ONLY if the subject's prior RT-PCR test (i.e., Day 1) returned as positive.
- Remind the subjects of the precautions/measures to prevent SARS-CoV-2 infection.
- Discharge the subject.

6.3.2 Days 4, 8, 15, 22, 29, 43 and 57

Visits are conducted as in-clinic or telemedicine/home healthcare follow-ups.

Visit windows are as follows (in relation to end of IV infusion):

Day 4: 3 days±12 hours; Day 8: 7±1 days; Day 15: 14±2 days; Day 22: 21±2 days; Day 29: 28±2 days; Day 43: 42±3 days; Day 57: 56±3 days.

Perform the following in-clinic or via telemedicine follow-up:

- Assessment of AEs and concomitant medications.
- Targeted physical exam, if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medications during telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if immediate medical attention is required.
- Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessments (via a telephone contact) ONLY if the subject became positive at any time post-dosing during the study period.
- Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection.

In-clinic staff or home healthcare attendant to perform the following:

- NP swab sample for SARS-CoV-2 point-of-care RT-PCR test.
- Serum sample for SARS-CoV-2 antibody PK assessment.
- Blood sample for safety laboratory assessments (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential) at Day 4 only; at other follow-ups, collect sample only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- Urinalysis at Day 4 only; at other follow-ups, collect sample only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]. Note: perform vital signs assessment at Day 4 only; at other visits perform if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).

6.3.3 Day 85

Visit conducted as telemedicine/home healthcare follow-up.

Visit window for Day 85: 84±3 days (in relation to Day 1 visit).

Perform the following in-clinic or via telemedicine follow-up:

- Assessment of AEs and concomitant medications.
- Targeted physical exam if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medications during telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if immediate medical attention is required.
- Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessments (via telemedicine) ONLY if the subject became positive at any time post-dosing during the study period.
- Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection.

In-clinic staff or home healthcare attendant to perform the following:

- NP swab sample for SARS-CoV-2 point-of-care RT-PCR test.
- Serum sample for SARS-CoV-2 antibody PK assessment.
- Blood sample for safety laboratory assessments (Chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential), if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- Sample for urinalysis, if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody).
- Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]. Note: perform vital signs assessment only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- If WOCBP, perform UPT.

6.3.4 Withdrawal Visit (WV)

Visit can be conducted as in-clinic or telephone/home healthcare follow-up.

Perform if withdrawal occurs at any time during the follow-up period, but outside of scheduled visits / visit windows.

Perform in-clinic or via telemedicine follow-up:

- Assessment of AEs and concomitant medications.

- Targeted physical exam if clinically indicated. Based on the investigator's assessment of adverse events/concomitant medications during telemedicine follow-up, an unscheduled visit (in-clinic) can be arranged to conduct a targeted physical exam. The investigator can also refer the subject to their healthcare provider or urgent care if immediate medical attention is required.
- Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessments (via telemedicine) ONLY if the subject became positive at any time post-dosing during the study period.
- Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection.

In-clinic staff or home healthcare attendant to perform the following;

- NP swab samples for SARS-CoV-2 point-of-care RT-PCR test.
- Serum sample for SARS-CoV-2 antibody PK assessment.
- Safety laboratory assessments:
  - Blood sample for Chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential) if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
  - Sample for urinalysis if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate]. Note: perform vital signs assessment only if clinically indicated (as per investigator's discretion during in-clinic or telemedicine follow-up).
- If WOCBP, perform UPT.

6.3.5 Unscheduled Visit(s)

Visit is conducted in-clinic or as telephone/home healthcare follow-up.

Subjects can be evaluated during an unscheduled visit if the investigator deems it necessary to further follow-up on subject's safety.

Any unscheduled visit(s) must be recorded on the Unscheduled Visit eCRF.

The following may be performed at an unscheduled visit at investigator's discretion in-clinic or via telemedicine follow-up:

- Assessment of AEs and concomitant medications.
- Targeted physical exam.
- Assessment of clinical status based on modified WHO ordinal scale and COVID-19 symptoms (if reported). Note: perform the assessments (via telemedicine) ONLY if the subject became positive at any time post-dosing during the study period.

- Remind the subjects of precautions/measures to prevent contracting SARS-CoV-2 infection.

In-clinic staff or home healthcare attendant to perform the following:

- NP swab samples for SARS-CoV-2 point-of-care RT-PCR test.
- Blood sample for safety laboratory assessments (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential).
- Sample for urinalysis.
- Vital signs [body temperature, blood pressure (seated), pulse, SpO_2 (pulse oximetry) and respiratory rate].

Subjects may be referred for emergency medical care (i.e., to emergency room, for hospitalization), if clinically indicated. Subjects will inform the site of any emergency medical care (either by phone call or at the next in-clinic visit). Any healthcare emergency encounter will be documented in the eCRF.

6.4 Handling of Samples for PK and SARS-CoV-2 Viral Samples

For details around sample handling/processing for PK (serum samples) and SARS-CoV-2 testing (NP swabs) refer to the Laboratory Manual.

In general, each sample will be labelled with the following information:

- Study Protocol Number (EBS-CVH-003)
- Subject ID
- Study Visit and nominal time point (e.g., D1, 2h: Day 1 visit, 2 hour sampling time point)
- Sample Code (e.g., bar code)

6.5 Shipment of Samples for PK Testing

For details on sample shipment of samples for PK testing refer to the Laboratory Manual.

6.6 Pharmacokinetic Sample Analysis

The PK sample testing will be performed using validated immunobinding IgG PK assay and a pseudovirus neutralization assay. The primary PK analysis will be based on a validated PK immunobinding IgG assay and a pseudovirus neutralization assay test results generated by Emergent BioSolutions facility.

6.7 Concomitant Medications

The use of concomitant medication that the investigator considers unnecessary will be discouraged. No pre-infusion pre-medication will be permitted. Medications to treat minor ailments (headache, nausea, etc.) will be allowed at the discretion of the investigator. Study subjects will be questioned about all concomitant medications during in-clinic follow-up visits

including all herbal preparations and non-prescription medications that they are receiving. This information will be recorded on the appropriate eCRF.

Concomitant medications taken in relation to adverse events and/or COVID-19 will be noted.

Elective blood- or plasma-derived products/plasma exchange procedures during the study are not allowed. If these are required for medical emergency reasons; the use of these types of products/procedures and the reason for such use will be recorded by the investigator (or designate) in the eCRF.

7 ASSESSMENT OF PK

7.1 PK Parameters

PK parameters of three dose levels of COVID-HIGIV administered IV as a single dose will be determined in healthy adults (see Section 9.3.1). The assessments described below will be used to derive serum concentrations of SARS-CoV-2 antibodies (by testing PK samples with validated immunobinding IgG and pseudovirus neutralization assays) to calculate the PK parameters.

7.1.1 Assessment of PK Parameters

For subjects that receive a single IV infusion of one of three COVID-HIGIV dose levels, analysis of PK will include PK sample test results (from samples collected by assigned site staff) from pre-dose on Day 1 and post-dose timepoints at Day 1, including 1 hour (±15 mins), 2 hours (±15 mins), 4 hours (±30 mins), 8 hours (±1 hour) and 12 hours (±1 hour) after end of IV infusion. In addition, the following post-dose timepoints will be included (brackets indicate time after end of IV infusion): Day 2 (24±2 hours), Day 4 (3±0.5 days), Day 8 (7±1 days), Day 15 (14±2 days), Day 22 (21±2 days), Day 29 (28±2 days), Day 43 (42±3 days), Day 57 (56±3 days) and Day 85 (84±3 days).

8 ASSESSMENT OF SAFETY

The safety of COVID-HIGIV will be assessed by collection of adverse events (AEs), laboratory test results (blood chemistry and hematology, urinalysis), concomitant medications, medical history updates, vital signs and physical exam results.

The occurrence of AEs will be monitored throughout all phases of the study and will cover all participating subjects. Any medical history changes that occur after baseline (Day 1) but before dosing will be updated as medical history. Capture of AEs starts during IV infusion of study treatment and until the end of study period (up to Day 85 visit). Unanticipated problems related to study procedure may be collected following enrollment.

Adverse events are to be elicited by the investigator (or designate) by asking the subject non-leading questions. The association of the AE to COVID-HIGIV is to be judged by the investigator as related or unrelated (see Section 8.3 below).

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

NOTE: A diagnosis should be preferentially captured as an adverse event term and signs and symptoms should be captured only in the absence of a unifying diagnosis. In the event that there are multiple diagnoses, then all diagnoses should be captured. The worsening of an existing sign, symptom or disease is also considered to be an AE. An abnormal laboratory finding deemed by the Principal Investigator as not clinically significant will not be captured as an AE, but an abnormal laboratory finding that worsens after dosing with the study drug, from not clinically significant to clinically significant, is considered an AE. Surgical procedures are not AE's. 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

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 subject 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 SAE.

8.1.3 Adverse Drug Reaction

Any noxious and unintended response to a medicinal (investigational) product related to any dose.

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., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

8.1.3.2 Unexpected Adverse Drug Reaction/Events

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

8.2 Assessment of Severity

All AEs (clinical and laboratory abnormalities) irrespective of relationship to study treatment, including those that are not of a serious nature and those that are expected, will be documented by the investigators (or designate) in the source documents and appropriately recorded on AE eCRF. All AEs will be examined by the investigator or sub-investigator(s) for assessment of AE severity using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Appendix III – Grading of Adverse Events). For AEs that are not included in the DAIDS AE Grading Table, use the following generic scale is:

Table 3 Generic AE Grading Scale

Grade 1 (mild)	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
Grade 2 (moderate)	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
Grade 3 (severe)	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
Grade 4 (potentially life-threatening)	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability
Grade 5 (death)	Death

8.3 Assessment of Causality

The Investigator is responsible for the assessment of the causality of an AE. Emergent's Medical Monitor will also assess SAE causality, independent of the Investigator.

The following guidelines are provided for assessment of causality:

- **Unrelated:** No relationship between the investigational product and the reported event.
- **Possibly related:** The event follows a reasonable temporal sequence from the time of administration of investigational product and/or follows a known response pattern to the investigational product 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 investigational product, known or previously reported adverse reactions to the investigational product or similar products, or in the Investigator's (or designee) clinical judgment the association of the event with the investigational product seems likely.
- **Definitely related:** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to investigational product 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 investigational product (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 investigational product is determined to be "definitely", "possibly" or "probably," the event will be considered to be "related" to the investigational product.

8.4 Description of Known Adverse Event Profile for COVID-HIGIV

For general description of safety profile for COVID-HIGIV, see Section 1.2.2. For more details, refer to the most current version of the Investigator's Brochure.

8.5 Eliciting Adverse Events

AEs reported spontaneously by the subject and/or in response to an open question from the Investigator (or designee) or revealed by observation (e.g., during physical exam or from a clinical laboratory test result) 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 investigational product.

All AEs reported from the signing of the ICF until immediately before dosing of investigational product on Day 1, will be recorded as signs and symptoms on the Medical History eCRF.

Reporting of AEs is required for any new observation presenting during and after investigational product dosing or for a deterioration of baseline condition (e.g., increased severity/frequency).

Occurrence of AEs will be monitored throughout the study and will cover all participating subjects. Study subjects will be provided with a 24-hour telephone number to contact study personnel in case of an untoward reaction.

8.6 Requirements for Immediately Reportable Events

8.6.1 Principal Investigator's Reporting Requirements

The investigator will report all SAEs and confirmed pregnancies to Emergent within 24 hours of the investigator's knowledge of occurrence. The PV SAE and pregnancy forms are available within the EDC system. Pharmacovigilance is notified of SAEs and pregnancies through a 'trigger' email which is delivered to
However, safety information may also be provided directly from the site via email to

The details of the SAE report should be completed within three days of the investigator's knowledge of occurrence of the SAE.

For SAEs, the Serious Adverse Event Report Form will be completed (abbreviated hereafter SAE Report Form). The SAE Report Form is NOT the same as the AE eCRF. Subject 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 Report Form.

All SAEs that are unexpected must be reported to the IRB/IEC/REB by the Investigator (or designee) as required by ICH GCP E6.

While pregnancy itself is not considered an AE, pregnancy outcomes of spontaneous miscarriage, congenital anomaly, or birth defect are considered to be SAEs and must be reported. Elective abortions without complications will not be handled as AEs.

If a subject becomes pregnant during a study, Emergent will be notified. All pregnancies where conception occurred after first exposure to the investigational product 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 subject 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 investigational product, then the guidelines for expedited reporting of serious, unexpected adverse drug reactions should be followed.

Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy forms ("Pregnancy Notification Form" and "Pregnancy Follow-up Form"). To ensure subject 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 an SAE.

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

The Investigator is responsible to notify their IRB/IEC/REB according to their policy for SAE or pregnancy reporting.

8.6.2 Emergent's Reporting Requirements

Emergent will report suspected unexpected serious adverse drug reactions (SUSARs) to the FDA and to the principal investigator in an individual case safety report as soon as possible, no later than 15 calendar days after Emergent becomes aware of the SUSAR.

Unexpected fatal or life-threatening suspected adverse reactions will be reported to the FDA as soon as possible but in no case later than seven calendar days after Emergent's initial receipt of the information.

8.7 Reporting of Other Information - Unanticipated Problems

For investigational sites in the United States, 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:
    - Procedures that are described in the study-related documents, such as the IRB/IEC/REB approved research protocol and informed consent document.
    - The characteristics of the subject population being entered into the study.
- Related or possibly 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 subjects 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 subjects or others. Only a small subset of AEs occurring in human subjects participating 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 subjects 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 subjects or others is identified. Also, the Investigator should notify the Emergent of unanticipated problem(s), as well as to the US Army Medical Research and Development Command (USAMRDC) Office of Research Protections (ORP) – Human Research Protection Office (HRPO).

8.8 Follow-up of Adverse Events

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

8.8.1 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 AEs 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. Subjects will be interviewed at the study visits to determine if any previously on-going AEs are resolved.

8.8.2 Follow-up of Serious Adverse Events

Confirmed SAEs will be recorded on the AE eCRF.

The Investigator will provide or arrange appropriate care for subjects 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 subject is referred to a specialist or other physician for treatment and follow-up. The Principal Investigator (or designee) will follow the subject's condition even if the subject 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:

- Subject withdraws consent.
- Subject is referred to appropriate long-term medical care.
- Subject 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 SAE 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 . Additional information received related to any SAE must be forwarded within 24 hours of awareness to the Emergent Global PV Department

8.9 Study Monitoring Committee

An independent Study Monitoring Committee (SMC) will provide on-going review of safety data during the study. The SMC (consisting of at least three independent external members) 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/stopping of the study (see Section 8.11) as it relates to safety and risk to the study subject population as outlined in the SMC Charter.

8.10 Breaking the Blind for Individual Subjects

While this is a double-blind study, the blind may be broken if a subject's health or safety is at risk and knowledge of the study arm may be beneficial to the medical management of the subject. In an event of unblinding, Emergent must be notified.

If the Investigator determines that knowledge of a subject's treatment assignment is urgently needed in order to guide treatment or ensure the subject's safety, the Investigator may perform emergency unblinding via RTSM system. The Investigator may not delegate this responsibility. The Investigator must attempt to notify Emergent's Medical Monitor prior to unblinding and must notify Emergent's study MM within 24 hours after unblinding at the latest.

If a subject's study treatment assignment is unblinded for safety reasons, or if a subject becomes accidentally unblinded for any reason, the subject will be requested to remain in the study for safety follow-up. Documentation of breaking the blind must be entered in the study subjects' 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 Emergent's study MM.

8.11 Study Safety-Pause Rule

Study enrollment and administration of study treatments may be temporarily paused by the SMC for safety review, if any of the following occur after study treatment administration and during the study's follow-up period:

- One or more SAE(s).
- Three or more of the same AEs classified as grade 3 severity.
- Five or more of the same AEs classified as grade 2 severity.

These events will be reviewed by the SMC and a recommendation will be made. The procedures will be outlined in the SMC Charter.

9 STATISTICAL CONSIDERATIONS

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

Subject disposition will be provided for all who sign and date the ICF.

9.1 Sample Size Calculation

There was no formal sample size calculation for this Phase 1 study. However, based on previous experience with hyperimmune globulin products manufactured by Emergent (see Section 1.2.2) in Phase 1 clinical studies with healthy adults, Emergent deems the number of subjects planned to receive study treatments (one of three dose levels of COVID-HIGIV or saline placebo) in the study [N=28; n=8 COVID-HIGIV dosage 1; n=8 COVID-HIGIV dosage 2; n=8 COVID-HIGIV dosage 3, n=4 placebo] is sufficient to descriptively assess COVID-HIGIV safety and PK of a single dose in healthy adults.

9.2 Analysis Sets

The following analysis sets will be evaluated in the study:

- Safety Set (SS): all randomized subjects who receive any amount of COVID-HIGIV or placebo, analyzed according to the actual study treatment arm.
- PK Set (PKS): all subjects who are randomized and received COVID-HIGIV according to the protocol and with evaluable PK data (i.e., no major protocol deviations affecting PK sampling and results, adequate number of PK sample test results).

9.3 Study Endpoints

9.3.1 Primary Safety Endpoints

The following primary safety endpoints will be evaluated:

- Frequency and severity of AEs within 72 hours post-dosing.
- AEs leading to discontinuation or temporary suspension of infusion.
- AEs and SAEs in healthy adults up to 84 days post-administration of a single dose.

The primary safety endpoints will be evaluated using the following safety assessments over the 84-day follow-up period after administration of a single COVID-HIGIV dose:

- Adverse events.
- Physical exams (complete and/or targeted physical exams).
- Safety laboratory tests (chem 7 panel, total and direct bilirubin, ALT, AST, LDH, CBC with differential, urinalysis).
- Vital signs (oral temperature, seated blood pressure, resting heart rate, pulse oximetry and respiratory rate).

- Concomitant medications.

9.3.2 Primary PK Endpoints

The following primary PK endpoints will be evaluated in healthy adults:

- Primary PK Endpoints (at each of the three COVID-HIGIV dose levels):
    - $AUC_{0\text{-last}}$: area under the concentration-time curve from time 0 to the last quantifiable concentration after dosing.
    - $AUC_{0\text{-inf}}$: $AUC_{0\text{-last}}$ plus the additional area extrapolated to infinity after dosing.
    - $AUC_{0\text{-14d}}$ after dosing.
    - $AUC_{0\text{-28d}}$ after dosing.
    - C_{max}: maximum observed concentration after dosing.
    - T_{max}: time at which C_{max} occurs after dosing.
    - C_{min28d}: observed or estimated concentration at 28 days after dosing.
    - λz: terminal elimination rate constant after dosing.
    - $T_{1/2}$: apparent terminal elimination half-life after dosing.
    - CL: systemic clearance after dosing.
    - V_Z: volume of distribution after dosing.

Secondary PK Endpoints: following body weight normalized PK parameters will be estimated as PK parameter divided by subject body weight (kg) at baseline.

- CmaxBWN: Body weight normalized Cmax
- Cmin28dBWN: Body weight normalized Cmin28d
- $AUC_{0\text{-14d}}$BWN: Body weight normalized $AUC_{0\text{-14d}}$
- $AUC_{0\text{-28d}}$BWN: Body weight normalized $AUC_{0\text{-28d}}$
- $AUC_{0\text{-last}}$BWN: Body weight normalized $AUC_{0\text{-last}}$
- $AUC_{0\text{-inf}}$BWN: Body weight normalized $AUC_{0\text{-inf}}$

The PK endpoints will be based on serum concentrations of SARS-CoV-2 binding and neutralizing antibodies after IV administration of a single COVID-HIGIV dose (up to 84 days post-dosing). Serum concentrations of SARS-CoV-2 binding and neutralizing antibodies will be measured by validated immunobinding (IgG) and pseudovirus neutralization PK assays and the results will be used to calculate the primary PK endpoints.

9.4 Handling of Missing Data

When calculating summary statistics, including geometric mean and 95% confidence intervals (CIs) and PK (SARS-CoV-2 binding and/or neutralizing antibody) concentrations below the assay's limit of quantitation (LOQ) and/or detection (LOD) will be imputed as half of LOQ/LOD values. If the lower bounds of the CIs are below lower LOQ (LLOQ), it will be replaced by "<LLOQ" in the output. Unless otherwise specified, no imputation will be made for missing data and complete data analysis will be used. Missing data due to the COVID-19 pandemic will be indicated.

9.5 Interim Analyses

The SMC will perform blinded review of the safety days after the first seven subjects have completed at least 72 hours of safety follow-up.

9.6 Planned Method of Analyses

In general, continuous endpoints will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum and maximum. Logarithmic transformation will be used when appropriate, coefficient of variation (CV), geometric mean, and geometric CV will also be summarized. Categorical endpoints will be summarized by the total number of subjects, frequencies and percentages. Unless otherwise specified, CIs are two-sided with 95% confidence. Non-compartment method will be used for estimating PK parameters.

9.6.1 Subject Disposition, Demographics, Medical History and Study Treatment Exposure

Subject disposition, including early termination reasons, will be summarized by study treatment for all subjects. Major protocol deviations will be presented for the safety population. Subject demographics, medical history, and study treatment dosing data will be tabulated for the ITT population and the safety population. Study disruption due to the COVID-19 pandemic will be indicated in the listing of subject disposition.

9.6.2 Safety Analyses

All safety analyses will be conducted on the safety population by treatment group..

Adverse Events (AE)/Serious Adverse Events (SAE):

AE will be coded to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), using the most current version at the time of coding. AEs 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.

- AE within 72 hours post-dosing will be summarized by SOC and preferred term.

- AEs and SAEs within 84 days post-dosing will be summarized in the same manner as described above in the first bullet.
- Discontinuation or temporary suspension of infusion will be summarized by treatment group.

Clinical Laboratory Test Results:

Laboratory test results and change from baseline will be summarized by time point and study treatment. The clinical significance of abnormality will be assessed by the Investigator. Abnormal laboratory results will be graded with severity grade 1 to 4 (grade 1=mild, through grade 4=potentially life-threatening) according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Appendix III). For severity not specifically listed in the severity grading criteria, the PI or designee will use the grading criteria for "illness or clinical AE" to assign the AE severity grading.

Values not meeting criteria for severity of at least grade 1 will be considered as grade 0.

Shift table of abnormality (Low, Normal, High) will be provided for selective laboratory parameters by treatment groups and timepoints.

Shift table of severity grade (0, 1-2, ≥3) will be provided for selective laboratory parameters by treatment groups and timepoints.

Vital Signs:

Vital signs include the following parameters: oral temperature, seated blood pressure, resting heart rate, pulse oximetry and respiratory rate. Vital sign results and change from baseline will be summarized by time point and study treatment.

Abnormal vital sign results will be assessed and assigned a severity grade 1 to 4 (see Appendix IV – Grading of Vital Signs). Grade 0 includes all values not meeting criteria for severity of at least Grade 1.

Normality/Abnormality shift from baseline, and severity grade shift from baseline will be summarized by treatment group and timepoints in the same manner as for laboratory data.

Concomitant Medications:

Concomitant medications will be coded using the WHO Drug Dictionary and displayed by treatment group for the safety population. Concomitant medications for COVID-19 treatment will be summarized separately, if applicable.

Clinical Status based on Modified WHO Ordinal Scale:

For subjects that become SARS-CoV-2 positive during the study period (at any time post-dosing on Day 1 and up to last follow-up visit/contact) and report COVID-19 symptoms, maximum score on the modified WHO ordinal scale (see Appendix I – Modified WHO Ordinal Scale) will be provided, as well as the score at the last follow-up visit/contact.

COVID-19 Symptoms:

For subjects that become SARS-CoV-2 positive during the study period (at any time post-dosing on Day 1 and up to last visit/contact) and report COVID-19 symptoms, the frequencies and percentages of subjects reporting COVID-19 symptoms will be presented by treatment arm. A summary of COVID-19 symptoms by maximum severity (see Appendix II – Grading of COVID-19 Symptoms) will be performed, for each symptom and for any symptoms.

9.6.3 PK Analyses

PK analysis will be conducted using the results of binding IgG and pseudovirus neutralization antibody assays (primary PK analysis) for each dose level of COVID-HIGIV. Binding IgG and neutralizing SARS-CoV-2 antibody serum concentrations versus time will be plotted and summarized by treatment groups. PK parameters will be estimated using standard non-compartmental method (i.e., trapezoidal method). Actual times and not nominal times will be used in the analysis, and concentrations below the assay's limit of quantitation (LOQ) and/or detection (LOD) will be imputed as half of LOQ/LOD values. Calculated PK parameters will include those listed in Section 9.3.1. Subjects with elevated baseline levels of SARS-CoV-2 antibodies or subjects with inadequate number of PK time-points (e.g., no pre-dose sample, or no measurable post-dose samples) may be excluded from the PK analysis. Baseline correction may be implemented, if necessary.

10 DATA HANDLING PROCEDURES

10.1 Recording of Data

Per ICH guidelines, study documents will be retained for one of the following periods:

- A period of at least two years after the date of the last approval of a marketing application in an ICH region until there are no pending or contemplated marketing applications;
- A period of at least two years after Emergent has notified the regulatory authority(ies) that clinical investigation with this product is discontinued.

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 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 remotely, 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 arrange for the retention of the subject identification codes for at least 25 years after the completion or discontinuation of the study (Revised Canadian CTA Regulations, September 2001). Subject 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 subject will be confidential except that they may be inspected by Emergent representatives for the study, the IRB/EC, 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.

10.4 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).

10.4.1 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 Data Management Plan (DMP).

10.4.2 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.

10.5 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.

10.6 Protocol Deviations

The Principal 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.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

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

The occurrence of protocol deviations will be routinely monitored for evaluation of Investigator compliance with the protocol, GCP, and regulatory requirements. Emergent will review all protocol deviations on an ongoing basis and will be responsible for determining if the deviation should be categorized as an Important Protocol Deviation (IPD). IPDs may require additional documentation as requested by Emergent.

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

Protocol deviations due to the COVID-19 pandemic will be recorded, assessed, and indicated.

11 REGULATORY AND ETHICAL ISSUES

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 subject data and completing eCRFs, the Investigator and investigational site staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject identification number will be used to identify each subject.

11.2 Informed Consent

Informed consent is a process that is initiated prior to the subject'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 ICF must be in compliance 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 course of the study.

The subject 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 Independent Ethics Committee/Institutions Review Board

Before the start of the study, the Investigator's Brochure, the protocol, proposed informed consent form(s), subject compensation (if any), Emergent-approved study materials and advertisements, and any other written information to be provided to the subject, will be

submitted to a properly constituted IRB for review. Emergent must receive a copy of the written approval from the IRB for all of the above applicable documents prior to recruitment of subjects into the study and shipment of COVID-HIGIV.

The IRB 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 in addition to other information as required by the IRB.

The names (or title, if IRB procedures prohibit publishing of names) and associated backgrounds of the members of IRB (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 Informed Consent Form and, where applicable, any other document listed above, have been approved by them.

All correspondence between the investigator and the IRB will be available for review by Emergent (or designate), 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 subjects' participation in the study, including details but not limited to signed and dated notes on consenting, eligibility, medical history, study assessments, Investigational Product administration, adverse events, concomitant medications, subject 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 subject 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 Clinical 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-approved informed consent form.
- Copy of the written IRB approval for the protocol, Investigator's Brochure, informed consent form(s), subject compensation (if any), any study materials and advertising, and any other written information to be provided to the subject.
- Current Curriculum Vitae and a photocopy of medical license (if applicable) of the principal 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 in regard to this protocol.
- Laboratory normal ranges and documentation of laboratory certification.
- Signed site contract agreement.

12.3 Clinical Study Registration

Emergent is responsible for registration of EBS-CVH-003 study to Clinicaltrials.gov in accordance with applicable regulations.

12.4 Liability and Insurance

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

12.5 Subject Identification and Confidentiality

The investigator must ensure the anonymity of each subject is maintained at all times. Subjects should only be identified by their initials and Subject Study ID number on the CRF, or on any other study documents provided to Emergent or their designate(s). Any documents that identify the subject should be kept in strict confidence by the principal investigator.

12.6 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 Principal 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 in the course of data monitoring are resolved appropriately.

12.7 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 Principal 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.

12.8 Use of Study 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 principal investigator.

12.9 Future Use of Stored Samples

Stored specimens (e.g., PK samples) will be identified by subject ID/sample numbers/codes for future testing after unblinding. Subjects will be asked to consent to the future use of the samples as part of the informed consent process. Samples may be retained until at least 2 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 2 years have elapsed since the formal discontinuation of clinical development.

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APPENDIX I – MODIFIED WHO ORDINAL SCALE

Modified WHO Ordinal Scale for COVID-19:

Ordinal Category	Categorical Description	Categorical Definition
1	No limiting symptoms due to COVID-19.	Subject can independently undertake usual activities with minimal or no symptoms
2	Limiting symptoms due to COVID-19.	Subject is symptomatic and currently is unable to independently undertake usual activities.
3	Moderate end-organ dysfunction.	Subject requires supplemental oxygen <4 liters/min, or <4 liters/min above pre-morbid requirements*.
4	Serious end-organ dysfunction.	Subject currently requires supplemental oxygen (≥4 liters/min, or ≥4 liters/min above pre-morbid requirements*), but not high-flow oxygen OR Subject has any symptoms or signs of the following extra-pulmonary conditions: Stroke (NIH Stroke Scale/Score [NIHSS] ≤14), meningitis, encephalitis, or myelitis, acute coronary syndromes (myocardial infarction, unstable angina), myocarditis, pericarditis, or New York Heart Association Class III or IV congestive heart failure, arterial or deep venous thrombosis including pulmonary embolism.
5	Life-threatening end-organ dysfunction.	Subject currently requires non-invasive assisted ventilation or high-flow oxygen OR Extra-pulmonary condition: Symptoms and signs of an acute stroke (NIHSS > 14).
6	End-organ failure.	Subject currently requires invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy.
7	Death.	Fatality due to COVID-19.

APPENDIX II – GRADING OF COVID-19 SYMPTOMS

Use the table below to grade severity of COVID-19 symptoms:

COVID-19 Related Symptom	**Response Options (Scoring/Grade)**
For items 1-10, what was the severity of your symptom at its worst over the last 24 hours?	
Stuffy or runny nose	None (0) Mild = defined as no interference with daily activity (1) Moderate = Interference with activity (2) Severe= prevents daily activity (3) Serious = life threatening or requires hospitalization (4)
Sore throat	
Shortness of breath (difficulty breathing)	
Cough	
Low energy or tiredness	
Muscle or body aches	
Headache	
Chills or shivering	
Nausea (feeling like you wanted to throw up)	
Fever	None= (0) Mild =100.4-102°F (1) Moderate 102.1-104°F (2) Severe >104°F (3)
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) Life threatening/requires hospitalization (4)
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) Life threatening/requires hospitalization (4)
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)
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)

Responses will be scored on a 1 point scale. (e.g., My sense of taste is the same as usual (0 points); My sense of taste is LESS than usual (1 point); I have NO sense of taste (2 points).

Note: Score values will not be provided within the response options presented to subjects.

APPENDIX III – GRADING OF ADVERSE EVENTS

The severity of adverse events 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, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

APPENDIX IV – GRADING OF VITAL SIGNS

Use the following criteria to grade vital signs:

Grading Scale*	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (potentially life-threatening)**
Temperature (C°) (F°)	 38.0-38.4 100.4-101.1	 38.5-38.9 101.2-102.0	 39.0-40.0 102.1-104.0	 >40.0 >104
Tachycardia (beats/min)	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia (beats/min)	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Hypertension systolic (mmHg)	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension diastolic (mmHg)	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension systolic (mmHg)	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths/min)	17-20	21-25	>25	Intubation
SPO_2 (%)	92 - <95	90 - <92	85 - <90	<85 or ER visit or hospitalization for hypoxia

***** Taken from Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials {CBER, 2007}, except SPO_2.

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