EMERGENT®

# CLINICAL STUDY PROTOCOL

# A Phase 1, Open-Label, Randomized Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin (Human) Investigational Product (COVID-HIG) Administered through Intramuscular, Subcutaneous or Intravenous Routes as a Single Dose Regimen to SARS-CoV-2 Uninfected Adults

## EBS-CVH-006

## Version 3.0

## 18 Feb 2022

**Funding Source:** The United States Department of Defense

**Study Sponsor:** Emergent BioSolutions Canada Inc.

# DOCUMENT HISTORY

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.0 | 12 Oct 2021 | n/a | Initial version of the protocol |
| 2.0 | 23 Nov 2021 | Substitution for a comparable antibody assay for screening, simplified randomization scheme, and administrative changes | Modified due to logistical challenges and to improve clarity. |
| 3.0 | 18 Feb 2022 | Decreased study follow-up to 56 days post-dosing (Day 57) and stopped enrollment at 23 of 36 subjects enrolled. Primary endpoints were updated to remove pseudoviral neutralization assay testing and some administrative changes were made. | Study follow-up period was decreased, and enrollment was stopped due to the impact of the COVID-19 pandemic and logistical difficulties of enrolling and retaining SARS-CoV-2 negative participants. The pseudoviral neutralization assay was eliminated due to assay limitations related to low sensitivity. Other minor changes were made to improve clarity. |

# SPONSOR SIGNATORY

**Signatory:** *See electronic signature page*

Date (dd/mmm/yyyy)

# KEY STUDY CONTACT INFORMATION

**Sponsor's Medical Monitor:**

**Immediately Reportable Adverse Events:** Emergent Global Pharmacovigilance
Email: productsafety@ebsi.com

For all other contact information please refer to study contact list.

# INVESTIGATOR SIGNATORY

**Compliance Statement:** This study is to be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements, as applicable.

| | |
|---|---|
| **EBS_CVH-006, Version 3.0:** | A Phase 1, Open-Label, Randomized Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin (Human) Investigational Product (COVID-HIG) Administered through Intramuscular, Subcutaneous or Intravenous Routes as a Single Dose Regimen to SARS-CoV-2 Uninfected Adults |
| | QPS Holdings, LLC (Phase I units) |
| | Newark, DE 19711, USA |

My signature below verifies that I have read and agree to this protocol. I am aware of my responsibilities as a Principal Investigator (PI) under the current ICH GCP Guidelines, the Declaration of Helsinki, and applicable laws and regulations of the country of the investigational site for which I am responsible. I agree to conduct the study according to these regulations.

I have read this protocol in its entirety and agree to conduct this study accordingly. Any changes in procedure will only be made if necessary, to protect the safety, rights and welfare of study subjects.

I agree to conduct in person and/or to supervise staff assigned to specific study responsibilities. I will ensure that all staff who assist me in the conduct of the study have access to the protocol and all pertinent information. I will ensure that all assigned staff are trained and qualified and are fully informed of their responsibilities regarding the conduct of the study.

I agree to abide by the terms of the confidentiality disclosure agreement and/or contract with the Sponsor and/or its representatives.

**Miami Site Principal Investigator:**

| | |
|---|---|
| Principal Investigator Name (print) | Title (print) |
| Principal Investigator Signature | Date dd/mmm/yyyy) |

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**Springfield Site**
**Principal Investigator:**

| | |
|---|---|
| Principal Investigator Name (print) | Title (print) |
| Principal Investigator Signature | Date dd/mmm/yyyy) |

# PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:<br>Emergent BioSolutions Canada Inc. (Emergent)<br><br>Winnipeg, MB, R3T 5Y3, CANADA</td></tr>
<tr><td colspan="2">Name of Investigational Product: COVID-HIG</td></tr>
<tr><td colspan="2">Name of Active Ingredient(s): Anti-SARS-CoV-2 Immunoglobulin Injection (Human) [COVID HIG] is a purified liquid immunoglobulin G (IgG) preparation</td></tr>
<tr><td colspan="2">Protocol No.: EBS-CVH-006</td></tr>
<tr><td colspan="2">Title of Study: A Phase 1, Open-Label, Randomized Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin (Human) Investigational Product (COVID-HIG) Administered through Intramuscular, Subcutaneous, or Intravenous Routes as a Single Dose Regimen to SARS-CoV-2 Uninfected Adults</td></tr>
<tr><td colspan="2">Study Center(s): two sites in the United States (US)</td></tr>
<tr><td>Study Duration for Each Subject: 56 days<br>Estimated Study Duration: 3.5 months<br>Estimated Enrollment Period: 1.5 months<br>Anticipated Start Date: Q4 (December) 2021<br>Estimated End Date: Q1 2022</td><td>Phase of Development: Phase 1</td></tr>
<tr><td colspan="2">Primary Objectives:<br>• To evaluate safety of COVID-HIG administered intramuscularly (IM) or subcutaneously (SC) as a single dose<br>• To evaluate pharmacokinetics (PK) of COVID-HIG administered IM or SC as a single dose<br>Secondary Objectives:<br>• To compare PK of COVID-HIG IM to COVID-HIG IV<br>• To compare PK of COVID-HIG SC to COVID-HIG IV<br>• To compare PK of COVID-HIG SC to COVID-HIG IM<br>Exploratory Objectives<br>• To evaluate the effects of COVID-HIG in participants that become Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) positive</td></tr>
<tr><td colspan="2"></td></tr>
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## Methodology

### Study Design:

This will be a Phase 1, two-center, open-label, randomized study to evaluate one dose level of COVID-HIG administered IM or SC for safety and PK in healthy adults compared to COVID-HIG administered intravenously (IV). Up to 36 adult participants will be targeted to be enrolled in the study. The study has been truncated to 23 randomized participants due to the impact of high circulating SARS-CoV-2 omicron cases on enrollment and participant retention. The sample size with 7-8 participants per study arm will allow for assessment of the primary safety and PK objectives.

**Table 1 Study Design**

| Group | Study Arm | No. of Participants | Dosing Schedule – Day 1 |
|---|---|---|---|
| Intramuscular | 1 | Up to 12 | ≈250,000 AU COVID-HIG[1] |
| Subcutaneous | 2 | Up to 12 | ≈250,000 AU COVID-HIG[1] |
| Intravenous | 3 | Up to 12 | ≈250,000 AU COVID-HIG[1] |

[1]Exact dose volumes (mL) was determined based on potency of COVID-HIG clinical lot as defined in Alliance Units (AU) using the wild-type neutralization assay (Clinical lot potency: 29,282 AU/mL, 8.5 mL volume; target protein concentration: 100 mg/mL).

Up to thirty-six participants will be enrolled and assigned equally to one of three study arms to receive a single IM, SC, or IV dose of COVID-HIG, respectively (see the table above). Randomization will be separate for Cohort 1 (12 subjects) and Cohort 2 (up to 24 subjects), but both randomization ratios will be 1:1:1 for each administration route. Subjects will be stratified based on their SARS-CoV-2 detectable antibody status (>LLOQ, but ≤80 AU/mL on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG assay) and undetectable antibody (≤LLOQ) at screening.

Enrollment into the study will be staggered, wherein no more than three participants will be randomized and dosed on the first day with at least one hour between dosing of each participant. On the second day, up to two more subjects will be randomized and dosed. The remaining participants will be randomized and dosed, with no more than 5 participants dosed per day. Safety data will be reviewed by a Safety Monitoring Committee (SMC) (consisting of at least three independent external members) after all 12 participants in Cohort 1 have completed at least 72 hours of safety follow-up. An overall decision by the SMC will be made whether to proceed with full randomization (1:1:1) and dosing of the remaining study participants (Cohort 2, up to n=24).

Participants will be admitted to the inpatient unit one day prior to dosing (Day -1), and following dosing on Day 1, each participant will stay overnight in the inpatient unit for close observation and PK sample collection. Each dosed participant will be discharged from the inpatient unit once all assessments at the 24 hours post-dosing timepoint (i.e., Day 2) are completed. Participants will be followed for safety and PK up to 56 days post-dosing (Day 57; see Table 2 for Schedule of Events). Follow-up visits to collect required samples and/or safety assessments can occur in-clinic or at-home as indicated in Table 2.

Study enrollment and administration of study treatments may be paused by the PI or medical monitor for safety review by the SMC if any of the following occur after study product administration and during the enrollment period:

- One or more serious adverse event(s) [SAE(s)].
- Three or more of the same Grade 3 adverse events (AEs)
- Three or more Grade 2 hypersensitivity AEs

Adverse event severity will be graded according to the DAIDS Severity Grading Scale (Appendix I).

If any participants become positive for SARS-CoV-2 during the study follow-up period, they will be assessed using an Ordinal Outcome Scale (Appendix II) until symptom resolution and will be followed until they complete their last scheduled follow-up visit (via telemedicine). Participants who test positive for SARS-CoV-2 will be excluded from PK analyses. As such, all subsequent visits should be done via telemedicine following SARS-CoV-2 positive status (except the Day 57 or the withdrawal visit), unless an in-person visit is deemed clinically necessary by the PI. Any in-person visits should be scheduled in a manner that reduces the risk of SARS-CoV-2 transmission, according to local rules and regulations. As the Day 57 or withdrawal visit necessitates in-person safety assessments, this visit should proceed in-person, if possible. If a participant tests positive for SARS-CoV-2 immediately prior to or at the in-person Day 57 visit, reasonable efforts will be made to collect as many of the required samples from the Day 57 visit in a manner that reduces the risk of SARS-CoV-2 transmission, according to local rules and regulations.

**Number of Subjects (Planned):** Up to 36 participants (truncated at 23 participants randomized)

**Study Population:** Healthy adult (18-59 years of age) non-pregnant females and males, without clinical symptoms of Coronavirus Disease 2019 (COVID-19) and without evidence of SARS-CoV-2 infection (negative RT-PCR result for SARS-CoV-2 RNA) at screening.

**Criteria for Study Participation**

**Inclusion Criteria:**

1. Able and willing to provide written informed consent (voluntarily signed by the participant) prior to performing study procedures.
2. Females and males 18-59 years of age.
3. Have a body mass index (BMI) less than or equal to 35.0 $kg/m^2$.
4. Healthy, based on medical history (no chronic disease, no chronic therapy, no ongoing acute condition within four weeks prior to dosing), normal physical examination (no clinically significant findings in the opinion of the investigator), and screening laboratory assessments (no clinically significant findings in the opinion of the investigator).

5. No clinical symptoms suspicious for COVID-19 infection, as well as SARS-CoV-2 IgM antibody negative and no laboratory evidence of current SARS-CoV-2 infection (i.e., RT-PCR negative for SARS-CoV-2) at Screening.
6. Females must not be pregnant, or trying to become pregnant as demonstrated by either of the following A or B:

A. Not of childbearing potential: surgically sterile (at least six weeks post bilateral salpingectomy, bilateral oophorectomy, or hysterectomy); or post-menopausal (history of ≥12 consecutive months without menses prior to randomization in the absence of other pathologic or physiologic causes and confirmed by follicle stimulating hormone [FSH] level ≥40 mIU/mL); OR

B. Women of childbearing potential (WOCBP) who are not planning to be pregnant during the study period and who meet all of criteria i–iii:

i. Negative serum pregnancy test at the Screening Visit.

ii. Negative urine pregnancy test on Day 1 (a positive test will result in discontinuation from intervention).

iii. Using one of the following highly effective methods of contraception during the study:

- Combined estrogen and progestogen, or progestogen-only hormonal contraception associated with inhibition of ovulation (e.g., implants, pills, patches) initiated ≥30 days prior to Study Day 1.
- Intrauterine device (IUD) or hormone releasing intrauterine system (IUS) inserted ≥30 days prior to Study Day 1.

7. Participant understands and agrees to comply with planned study procedures.

**Exclusion Criteria:**

1. Use of any investigational product within 30 days or SARS-CoV-2 monoclonal antibodies and COVID-19 convalescent plasma within 90 days prior to Screening or anticipated receipt during the study follow-up period, or participant plans to participate in another clinical study during the study period.
2. Receipt of 1 or 2 doses COVID-19 vaccine within 60 days prior to screening or anticipated receipt during the study follow-up period.
3. SARS-CoV-2 IgG antibody levels >80 AU/mL as determined by the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay.
4. 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 direct 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.

5. Positive laboratory evidence of current infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). Note: Positive anti-HCV antibody result along with a negative HCV PCR would NOT be exclusionary.
6. History of allergy or hypersensitivity to blood or plasma products or to COVID-HIG excipients (proline, PS80).
7. History of allergy to latex or rubber.
8. History of hemolytic anemia.
9. History of IgA deficiency.
10. Receipt of any blood product within the past 12 months.
11. Plasma donation within 7 days or blood loss/donation (>450 mL) within 56 days of dosing.
12. 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).
13. History of thrombosis or hypercoagulable state with increased risk of thrombosis.
14. Receipt of a live vaccine within 30 days prior to screening or anticipated receipt of a live vaccine during the study period.
15. Currently pregnant, breastfeeding, or planning to become pregnant during the study.
16. History of, or suspected substance abuse problem (including alcohol).
17. Any planned elective surgery or procedure during the follow-up period that impacts study compliance.
18. Other condition which may place participant at increased risk due to participation in the study or may impact study compliance as determined by the investigator.
19. An opinion of the investigator (or designee) that it would not be in the best interest of the individual to participate in the study.

**Investigational Product (IP), Dosage and Mode of Administration:** COVID-HIG is a purified liquid IgG preparation containing antibodies (including neutralizing antibodies) to SARS-CoV-2. COVID-HIG is intended for IM, SC or IV administration. COVID-HIG product contains a target of 100 mg/mL protein and is formulated with 250 mM proline and polysorbate 80 (0.03% w/w) target pH 5.8 COVID-HIG potency against SARS-CoV-2 will be expressed in AU/mL as assessed using the NIAID neutralization assay.

**Reference Therapy, Dosage and Mode of Administration:**

There is no reference product for this study.

**Study Endpoints/Outcome Measure(s)**

**Primary:**

The following primary safety endpoints will be evaluated:

- Adverse events within 72 hours post-dosing.
- Adverse events leading to discontinuation or temporary suspension of study treatment administration
- Adverse events and serious adverse events up to 56 days post-administration of a single dose.

The following primary COVID-HIG PK endpoints (based on PK sample test results by an immunobinding IgG assay) will be evaluated:

- $AUC_{0\text{-}inf}$: $AUC_{0\text{-}last}$ plus the additional area extrapolated to infinity after dosing.
- $AUC_{0\text{-}last}$: area under the concentration-time curve from time 0 to the last quantifiable concentration after dosing.
- $C_{max}$: maximum observed concentration after dosing.
- $T_{max}$: time at which $C_{max}$ occurs after dosing.
- C28d: observed or estimated concentration at 28 days after dosing.

**Secondary:**

The following additional COVID-HIG PK endpoints (based on PK sample test results by an immunobinding IgG assay) will be calculated, when data permit:

- $AUC_{0\text{-}inf}$ ratios (bioavailability) will be compared between routes for comparable dose levels (COVID-HIG SC to IV; IM to IV; and SC to IM).
- $AUC_{0\text{-}14d}$ after dosing.
- $AUC_{0\text{-}28d}$ after dosing.
- $\lambda_z$: 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.

**Exploratory:**

- COVID-19 disease severity among SARS-CoV-2 positive participants as assessed by an Ordinal Outcomes scale (Appendix II).

**Procedures and Assessments:**

For a tabular summary of visits/assessments refer to Table 2 Schedule of Events at the end of the synopsis.

**Screening:** in-clinic visit; within 14 days prior to randomization.

- Informed consent.
- Eligibility assessment.
- Demography (age, sex, race/ethnicity, height, body weight, BMI).
- Perform rapid SARS-CoV-2 IgM/IgG antibody test and SARS-CoV-2 antigen test prior to collecting other samples. Only proceed further with screening if negative for SARS-CoV-2 IgM and antigen.
- Nasopharyngeal (NP) swab sample for SARS-CoV-2 RT-PCR test.
- Medical history and ongoing medications.
- Complete physical exam (to include assessment of general appearance, and the following body systems: head-neck, respiratory, cardiovascular, gastrointestinal, dermatological, lymphatic/hematological, musculoskeletal, neurological, metabolic/endocrine).
- For WOCBP: assess contraception use (>30 days prior to dosing) and instruct on use of contraception from the time of Screening through end of study (up to Day 57).
- Vital signs (resting ≥10 minutes) 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.
  - Complete blood count (CBC) (red blood cells, white blood cells, hemoglobin, hematocrit) with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
  - Urinalysis.
- Viral marker testing [Human immunodeficiency virus 1/2 (HIV 1/2) antibody, HBV surface antigen, HCV antibody].
- Urine drug screening (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine opioids)
- Serum sample for the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody test.
- Serum pregnancy test for WOCBP and follicle stimulating hormone (FSH) testing for post-menopausal women.
- Provide counselling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.

- Assess for any COVID-19 symptoms or SARS-CoV-2 exposure.
- Monitor/assess AEs related to study procedures.

**Pre-Dosing – Day -1**: in-clinic overnight stay

- If required, update medical history and ongoing medications.
- Inquire if the participant has had a suspected or confirmed exposure to SARS-CoV-2 or developed COVID-19 symptoms in the period of Screening visit to Day 1.
- Perform rapid SARS-CoV-2 IgM/IgG antibody test.
- If WOCBP, perform urine pregnancy test (UPT).
- If WOCBP, confirm use of contraceptives.
- Alcohol breath test
- Confirm eligibility.
- Collect serum sample for SARS-CoV-2 antibody PK assessment.
- Collect NP swab sample for SARS-CoV-2 RT-PCR test.
- Targeted physical exam, if clinically indicated.
- Assess for any COVID-19 symptoms or SARS-CoV-2 exposure.
- Monitor/assess AEs related to study procedures.

**Dosing – Day 1:** in-clinic overnight visit.

- Collect pre-dose serum sample (within 2 hours prior to dosing) for SARS-CoV-2 antibody PK assessment.
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, $SpO_2$ (pulse oximetry) and respiratory rate]; within 2 hours prior to dosing.
- Randomize.
- Administer randomized study treatment.
- Monitor/assess AEs before, during injection and post-administration in the clinic overnight.
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, $SpO_2$ (pulse oximetry) and respiratory rate] at 30 minutes (±5 mins) and 1 hour (±10 mins) post-administration.
- Serum samples for post-dosing assessment of SARS-CoV-2 antibodies for PK at 1 hr ±10min, 2 hrs ±15min, 4 hrs ±15min, 8 hrs ±30min, and 12 hrs ±30min (from end of infusion/injection).
- Targeted physical exam, if clinically indicated.

- Record any concomitant medications (if applicable).

**Post-Dosing Assessments (Days 2-57)*:**

**Day 2 (1±0.5 days) – in-clinic discharge visit**

**Day 3 (2±0.5 days), Day 4 (3±0.5 days), Day 6 (5±0.5 days), Day 8 (7±1 day), Day 15 (14±2 days), Day 29 (28±2 days), Day 43 (42±3 days): – visit can be conducted in-clinic or as home healthcare/telemedicine follow-up**.

If randomized to IV group (Arm 3), omit visits on Day 3 and Day 6.

* Visits are indicated as calendar days, while the time post-dosing 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.
- If WOCBP, confirm use of contraceptives.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2 at any time post-dosing during the study period: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

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

- 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) at Day 2 and Day 4 only. At other follow-ups, collect sample only if clinically indicated (as per investigator's discretion during in-clinic or home healthcare/telemedicine follow-up).
- Sample for urinalysis at Day 2 and Day 4 only. At other follow-ups, collect sample only if clinically indicated (as per investigator's discretion during in-clinic or home healthcare/telemedicine follow-up).
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate] at Day 2 and Day 4 only. At other follow-ups perform only if clinically indicated (as per investigator/sub-investigator's assessment of the participant in-clinic or during the home healthcare/telemedicine follow-up).

- NP swab sample for SARS-CoV-2 RT-PCR test on Day 8, Day 15 Day 29, and Day 43. At other follow-ups perform only if clinically indicated (as per investigator/sub-investigator's assessment of the participant in-clinic or during the home healthcare/telemedicine follow-up).

**Day 57 (±3 days)*:** visit can be conducted in-clinic or as 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.
- If WOCBP, confirm use of contraceptives.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

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

- Serum sample for SARS-CoV-2 antibody PK assessment.
- Safety laboratory assessments (e.g., ALT, AST, LDH, CBC, urinalysis), if clinically indicated.
- Blood sample for viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody).
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion).
- Nasopharyngeal swab sample for SARS-CoV-2 RT-PCR test.

If any participants become positive for SARS-CoV-2 at any point during the study follow-up period, all subsequent visits should be done via telemedicine (except for the Day 57 or the withdrawal visit), unless an in-person visit is deemed clinically necessary by the PI. As the Day 57 or withdrawal visit necessitates in-person safety assessments, this visit should proceed in-person, if possible. In-person visits should be performed after the infectious period has passed to reduce the risk of transmission and should follow local rules and regulations. If a participant tests positive for SARS-CoV-2 immediately prior to or at the in-person Day 57 visit, reasonable efforts will be made to collect as many of the required samples from the Day 57 visit in a manner that reduces the risk of SARS-CoV-2 transmission, according to local rules and regulations.

**Withdrawal Visit (WV):** visit can be conducted in-clinic or as 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.
- If WOCBP, confirm use of contraceptives.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

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

- Serum sample for SARS-CoV-2 antibody PK assessment.
- Safety laboratory assessments (e.g., ALT, AST, LDH, CBC, urinalysis), if clinically indicated.
- Blood sample for viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody).
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion).
- Nasopharyngeal swab sample for SARS-CoV-2 RT-PCR, if clinically indicated (as per investigator/sub-investigator's assessment).

**Unscheduled Visit(s):** in-clinic or telemedicine/home healthcare follow-up.

Participants can be evaluated during an unscheduled visit if the investigator deems it necessary to further follow-up on participant's safety. The following may be performed at an unscheduled visit at investigator's discretion.

Perform the following in-clinic, at-home, or via telemedicine follow-up. If telemedicine follow-up requires sample collection or in-person assessments, an in-clinic or at-home follow-up should be scheduled:

- Assessment of AEs and concomitant medications.
- Targeted physical exam, if clinically indicated.
- Nasopharyngeal swab samples for SARS-CoV-2 RT-PCR test (as per investigator's discretion assessing COVID-19 symptoms/exposure).
- Safety laboratory assessments: (e.g., ALT, AST, LDH, CBC, urinalysis), if clinically indicated.

- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion).
- If WOCBP, confirm use of contraceptives.
- If WOCBP and only if clinically indicated, perform serum pregnancy test.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

**Statistical Methods**

**Sample Size Considerations:** 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 1.3.1) in Phase 1 clinical studies, Emergent deems the number of participants planned to receive study treatments in the study is sufficient to descriptively assess COVID-HIG safety and PK administered IM, SC, and IV. Even with the truncation to 23 randomized participants due to the COVID-19 pandemic case surge, 7-8 participants per study arm should be sufficient to meet study objectives, similar to the previous PK study EBS-CVH-003 with 7-8 participants per arm.

**Analysis Populations:**

The following analysis populations will be evaluated in the study:

- Safety Population: All randomized participants who receive any amount of COVID-HIG IM, COVID-HIG SC or COVID-HIG IV, analyzed according to the actual study treatment arm.
- PK Population: All participants who are randomized and received COVID-HIG IM, COVID-HIG SC or COVID-HIG IV according to the protocol and with evaluable PK data (i.e., no major protocol deviations affecting PK sampling and results including COVID-19 infection, adequate number of PK sample test results), analyzed according to actual study treatment arm.
- SARS-CoV-2 Positive Population: Any randomized participant (whether or not dosed with COVID-HIG) who tests positive for SARS-CoV-2 during the study period and for whom data are available, analyzed according to randomized study treatment arm.

**Considerations for Endpoints**:

In general, continuous endpoints will be summarized by descriptive statistics including number of participants, 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 participants, frequencies, and percentages. Non-compartmental methods will be used for estimating PK parameters.

Bioavailability will be compared between administration routes, if data permit. An analysis of variance (ANOVA) model will be used with $AUC_{0\text{-inf}}$ as the dependent variable and administration route as the fixed effect. The adjusted least square means will be used to estimate ratios of $AUC_{0\text{-inf IM}}$ / $AUC_{0\text{-inf IV}}$ * 100%, $AUC_{0\text{-inf SC}}$ / $AUC_{0\text{-inf IV}}$ * 100%, and $AUC_{0\text{-inf IM}}$ / $AUC_{0\text{-inf SC}}$ * 100% along with corresponding two-sided 90% confidence intervals (CIs) calculated based on the ANOVA. The width of the 90% CIs will be examined relative to the standard of [80%, 125%] for comparative bioavailability.

# SCHEDULE OF EVENTS

**Table 2 Schedule of Events**

| | In-clinic | In-clinic overnight stay | | | In-clinic or home healthcare/telemedicine visit | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Day -1** | **Day 1** | **Day 2** | **Day 3*** | **Day 4** | **Day 6*** | **Day 8** | **Day 15** | **Day 29** | **Day 43** | **Day 57** | **Withdrawal Visit (WV)** | **Unsched-uled** |
| **Visit Window (days in relation to Day 1)** | **≤14 days** | **≤1 day** | | **1±0.5** | **2±0.5** | **3±0.5** | **5±0.5** | **7±1** | **14±2** | **28±2** | **42±3** | **56±3** | | |
| Informed consent | X | | | | | | | | | | | | | |
| Eligibility | X | X[2] | | | | | | | | | | | | |
| Demography (age, sex, race/ethnicity, height, body weight, BMI) | X | | | | | | | | | | | | | |
| Medical history & ongoing medications[1] | X | X | | | | | | | | | | | | |
| Complete physical exam[3] | X | | | | | | | | | | | | | |
| Targeted physical exam | | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] |
| Randomization and dosing | | | X | | | | | | | | | | | |
| Vital signs[4] | X | | X[5] | X | X[13] | X | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] |
| Safety laboratory tests[6] | X | | | X | X[13] | X | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] |
| Urinalysis[7] | X | | | X | X[13] | X | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] |
| Serum pregnancy test, if WOCBP | X[8] | | | | | | | | | | | | | X[13] |
| Urine pregnancy test, if WOCBP | | X[8] | | | | | | | | | | | | |
| FSH test, if postmenopausal female | X[8] | | | | | | | | | | | | | |
| Urine drug screen | X | | | | | | | | | | | | | |
| Alcohol breath test | | X | | | | | | | | | | | | |
| Viral markers (HBV surface Ag, HCV Ab, HIV 1/2 Ab)[9] | X | | | | | | | | | | | X | X | |
| NP sample for SARS-CoV-2 RT-PCR | X | X | | X[13] | X[13] | X[13] | X[13] | X | X | X | X | X | X[13] | X[13] |
| Rapid SARS-CoV-2 IgM/IgG test | X | X | | | | | | | | | | | | |
| Rapid SARS-CoV-2 antigen test | X | | | | | | | | | | | | | |
| Serum sample for Diasorin LIAISON SARS-CoV-2 S1/S2 IgG assay | X | | | | | | | | | | | | | |
| Serum sample for SARS-CoV-2 Ab PK | | X | X[10] | X | X | X | X | X | X | X | X | X | X | |
| AEs & concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Confirm use of contraceptives (if appropriate) | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Counselling on precautions to prevent SARS-CoV-2 infection and assess COVID-19 symptoms/exposure.[11] | X | X[12] | | X[12] | X | X | X | X | X | X | X | X | X | X |

* Visits on Day 3 and Day 6 are not necessary for the IV arm (Arm 3)

[1] Medical history information will be collected from participants at the Screening Visit and confirmed (and updated, if required) at the Day -1 Visit and will include (but not be limited to) demographic information (date of birth, race, ethnicity, and sex of participant), current and past medical conditions, prior and concomitant medications.

[2] Review and confirm eligibility.

[3] A complete physical examination will be performed on participants during the Screening Visit. The examination should include, general appearance, eyes-ears-nose-throat, head-neck, lungs-chest, heart, abdomen, musculoskeletal, lymph nodes, skin, extremities, and neurological assessment. A targeted physical exam may be performed on participants at additional time points if indicated by AE or SAE reporting.

[4] Vital signs collected from participants will include blood pressure, heart rate, $SpO^2$ (pulse oximetry), respiratory rate, and temperature. Vital signs must be taken after ≥10 minutes resting. Vital signs can be repeated twice if grade 3 or higher to verify the severity. Body weight, height for BMI calculations will be obtained at Screening Visit.

[5] Collect resting vital signs within 2 hours prior to dosing and at 30±5 mins and 1 hour±10 mins postdosing (from end of infusion/injection).

[6] Clinical chemistry assessments will include the Chem 7 panel [Na+, K+, Cl-, HCO3-, BUN, creatinine, glucose], total and direct bilirubin, ALT, AST, LDH, and CBC with differential.

[7] Urinalysis will include appearance and color, specific gravity, protein, glucose, pH, occult blood. Initial analysis will be by dipstick, with further testing and microscopic examination only if clinically indicated.

[8] Serum pregnancy tests will be performed at Screening for all females of childbearing potential. Urine pregnancy tests will be performed on Day -1 visit for all females of childbearing potential. Pregnancy tests are not required for female participants who are postmenopausal ≥12 months, or surgically sterilized. Follicle stimulating hormone levels will be evaluated for females who are postmenopausal for ≥12 months.

[9] Viral markers include: HBsAg, HCV antibody, HIV-1/2. HCV RNA will be performed in HCV antibody positive individuals only.

[10] Collect serum PK samples at pre-dose (within 2 hrs prior to dosing) and postdose (from end of infusion/injection) at 1 hr ±10min, 2 hrs ±15min, 4 hrs ±15min, and 8 hrs±30min, and 12 hrs ±30min.

[11] If COVID-19 symptoms are present or high-risk exposure has occurred based on investigator's discretion, an NP sample can be collected for SARS-CoV-2 RT-PCR. If participant tests positive for SARS-CoV-2 prior to dosing, they are no longer eligible to be enrolled.

[12] At Day -1 visit, participants will be assessed for COVID-19 symptoms/exposure only. At Day 2 visit, prior to discharge, participants will be counselled on precautions/measures to prevent SARS-CoV-2 infection.

[13] Assessment to be performed only if clinically indicated (as per investigator's discretion during in-clinic, home healthcare or telemedicine follow-up).

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## APPENDIX

# LIST OF TABLES



# LIST OF FIGURES

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ADE | Antibody-dependent enhancement |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALT | Alanine aminotransferase |
| AMS | Aseptic meningitis syndrome |
| ANOVA | Analysis of variance |
| anti-HCV | antigen (HBsAg), Hepatitis C virus antibody |
| AST | Aspartate aminotransferase |
| AU | Alliance units |
| BARDA | Biomedical Advanced Research and Development Authority |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CCP | COVID-19 convalescent plasma |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| $Cl^-$ | Chloride |
| CNJ-016® | Vaccinia immune globulin intravenous (Human) |
| COVID-19 | Coronavirus disease 2019 |
| COVID-HIG | Anti-SARS-CoV-2 Immunoglobulin Injection (Human) |
| CRO | Contract research organization |
| CRF | Case Report Form |
| CSF | Cerebrospinal fluid |
| CV | Coefficient of variation |
| DAIDS | Division of Acquired Immunodeficiency Syndrome (AIDS) |
| DMC | Data Monitoring Committee |
| DMP | Data management plan |
| DoD | Department of Defense |
| EAP | Expanded access program |
| EC | Ethics committee |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| Emergent | Emergent BioSolutions Canada Inc. |
| FDA | US Food and Drug Administration |
| GCP | Good clinical practices |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B Virus |
| $HC03^-$ | Bicarbonate |

| | |
|---|---|
| HCV | Hepatitis C Virus |
| HepaGam B® | Hepatitis B immune globulin (human) |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International conference on harmonization |
| ICU | Intensive care unit |
| ID | Identification |
| IEC | Independent ethics committee |
| IgA | Immunoglobulin A |
| IgG | Immunoglobulin G (gamma globulin) |
| IgM | Immunoglobulin M |
| IGIV | Immunoglobulin intravenous |
| IM | intramuscular |
| IP | Investigational product |
| IPD | Important protocol deviation |
| IRB | Institutional review board |
| ITT | Intent-to-Treat Set |
| IUD | Intrauterine device |
| IUS | Intrauterine system |
| IV | Intravenous |
| K+ | Potassium |
| KM | Kaplan-Meier |
| LDH | Lactate dehydrogenase |
| LLOQ | Lower limit of quantitation |
| LSLV | Last subject last visit |
| mAb | Monoclonal antibody |
| MM | Medical monitor |
| Na+ | Sodium |
| NHP | Non-human primate |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NP | Nasopharyngeal |
| NP-028 | Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) |
| OHRP | Office for Human Research Protection |
| OR | Odds ratios |
| PD | Protocol deviation |
| PE | Physical exam |
| PEP | Postexposure prophylaxis |
| PI | Principal investigator |
| PK | Pharmacokinetics |

| | |
|---|---|
| ppm | Parts per million |
| PS80 | Polysorbate 80 |
| PV | Pharmacovigilance |
| REB | Research ethics board |
| RTSM | Randomization and trial supply management |
| RT-PCR | Reverse transcriptase polymerase chain reaction |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SC | subcutaneous |
| SD | Standard deviation |
| SMC | Safety Monitoring Committee |
| SOC | Standard of Care |
| SOC | System Organ Class |
| SS | Safety Set |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment emergent adverse event |
| 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) |
| ULN | Upper limit of normal |
| UPT | Urine pregnancy test |
| US | United States of America |
| USG | United States Government |
| VARIZIG® | Varicella zoster immune globulin intravenous (human) |
| VIGIV | Vaccinia immune globulin intravenous (human) |
| WinRho® SDF | Rho (D) immune globulin intravenous (human) |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |

# 1 BACKGROUND INFORMATION

## 1.1 Name and Description of Investigational Product(s)

### 1.1.1 Indication

COVID-HIG is being developed for treatment of COVID-19 caused by the SARS-CoV-2 virus to be administered as a single dose following diagnosis.

### 1.1.2 Description of Investigational Product

Anti-SARS-CoV-2 Immunoglobulin Injection (Human), also referred to as COVID-HIG (code name: NP-028), is a hyperimmune product that consists of purified IgG fraction of human plasma containing antibodies (including neutralizing antibodies) to SARS CoV-2. COVID-HIG 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.

COVID-HIG is prepared from pooled plasma collected at US Food and Drug Administration (FDA) licensed and/or registered plasma and/or blood collection centers and Health Canada licensed/US FDA licensed and/or registered plasma collection centers from healthy, adult donors who have elevated levels of SARS-CoV-2 antibodies.

COVID-HIG (85-115 mg/mL protein) is provided as a sterile liquid for IV, SC, or IM administration.

For IP details, refer to Section 5.1 and the most current version of the Investigator's Brochure (IB).

## 1.2 Summary of Findings from Nonclinical and Clinical Studies

Animal studies in a variety of species have shown that both polyclonal and monoclonal (mAb) antibodies administered intravenously are efficacious against SARS-CoV-2. Passive transfer of COVID-19 convalescent serum reduced lung virus load in both non-human primates (NHP) and hamsters when administered one day post-infection, with complete protection (sterile immunity) when treated one day before infection (1, 2). Several mAbs showed a protective effect by reducing the duration and/or degree of body weight loss, tissue virus load and lung pathology when given within a window of one day before or one day post-infection in adenovirus transduced mice, NHPs and hamsters (3, 4, 5, 6, 7, 8, 9). Evidence to date demonstrates that administration of antibodies in NHP and hamsters infected with a human SARS-CoV-2, significantly reduces the virus replication in the respiratory system and prevents the development of lung pathology.

Preclinical studies demonstrated the efficacy of COVID-HIG in hamsters and adenovirus transduced ACE2 expressing mice when administered in a post-exposure prophylaxis setting. COVID-HIG in these models reduced the lung viral burden and reduced the duration and/or degree of infection related transient body weight loss.

In human clinical trials in recently tested SARS-CoV-2 positive patients, mAb treatments showed a reduction in viral load in upper respiratory samples, with the greatest effect seen in patients treated earlier in disease course (10, 11). These data suggest that antibody therapeutics have the potential to impact SARS-CoV-2 viral replication which may result in reduced disease severity.

COVID-19 convalescent plasma rapidly became an intervention for hospitalized patients after initial reports from open label treatment studies (12, 13) supported use under an expanded access program (EAP) in the US. Data emerging from the EAP and other published studies have demonstrated the safety and suggested the benefit of passive immunotherapy with COVID-19 convalescent plasma (CCP) (14, 15, 16, 17) which supported emergency use authorization (EUA) for CCP in hospitalized COVID-19 patients (18). Contrary to EAP experience, randomized controlled studies in India and Argentina have failed to demonstrate efficacy of CCP in patients hospitalized with COVID-19 (19, 20). Limitations to CCP include the 1:1 donor to recipient treatment and a lack of consistent neutralizing potency from unit to unit. Despite limitations, analyses of over 3000 patients treated with CCP in the US, has shown a mortality benefit for treatment with CCP with high neutralizing antibody titers in comparison to low titer CCP as well as benefit with intervention earlier in disease course prior to the need for mechanical ventilation (21). These data speak both to the importance of a threshold of antibody levels and to the timing of intervention prior to a hyperinflammatory state. Selection of high titer CCP combined with early intervention has also been supported by a randomized placebo-controlled trial of high titer CCP in older adults treated within 72 hours of symptom onset mild COVID-19 (22). Despite stopping early due to a decrease in the regional COVID-19 incidence in Argentina, this study showed a 48% reduction in the incidence of severe COVID-19 in patients infused with high titer CCP.

Neutralizing mAbs and antibody cocktails have also demonstrated the benefit of early treatment in the prevention of COVID-19 disease progression. The combination of casirivimab and imdevimab (REGN-CoV2) and sotrovimab (VIR-7831) have received EUA for the treatment of mild to moderate COVID-19 in patients at high risk of disease progression (23, 24), with REGN-CoV2 recently being granted EUA for post-exposure prophylaxis as well (23). Although bamlanivimab plus etesevimab has received an EUA for treatment as well (10), there are concerns about its efficacy against certain neutralization-escaping variants (25). Both REGN-COV2 and sotrovimab similarly demonstrated a decrease in hospitalizations with antibody treatment in ambulatory patients (11, 26) yet have maintained resilience against emerging variants (27). These studies also demonstrated the benefit of early antibody seroconversion, as outpatients who were seropositive at baseline had lower viral load and a trend for faster alleviation of symptoms than seronegative patients (28). In line with this, the RECOVERY trial observed a survival benefit only in hospitalized severe COVID-19 patients that were seronegative at baseline (29). Additional studies are underway in hospitalized patients with COVID-19; however, mAbs may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Thus, evidence currently suggests that mAb use provides benefit primarily in seronegative patients, which typically represents those early in disease course or certain hospitalized patients.

Currently three clinical trials with Emergent's COVID-HIG product are ongoing. Emergent has partnered with the US Government (USG) to advance this program by working closely with Biomedical Advanced Research and Development Authority (BARDA) and National Institute of Allergy and Infectious Diseases (NIAID) for participation in randomized controlled trials with COVID-HIG for treatment of hospitalized COVID-19 patients [INSIGHT 013] and high-risk outpatients [INSIGHT 012]. The INSIGHT 013 trial [NCT04546581] was an international, multi-center, adaptive, randomized, double-blind, placebo-controlled trial of the safety, tolerability, and efficacy of a single dose infusion (up to 400 mL) of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin (hIVIG) for the treatment of adult recently hospitalized COVID-19 patients (N=593). Participants received one of four hIVIG products (from different manufacturers) or placebo in addition to standard of care (SOC). Although the trial did not meet the primary efficacy endpoint to provide clinical benefit when compared to SOC plus placebo, there were no significant safety issues reported with Emergent's COVID-HIG product (n=80).

INSIGHT 012 [NCT04910269] is an international, multi-center, randomized, double-blind, placebo-controlled trial of the safety, tolerability and efficacy of hIVIG in high-risk adult outpatients in early stages of COVID-19. Participants will receive one of two hIVIG products (from two different manufacturers) or placebo in addition to SOC. The primary efficacy endpoint is an ordinal outcome (ranging from death to asymptomatic COVID-19) based on the participant's clinical status at Day 7. As of 06Aug2021, recruitment has been initiated.

EBS-CVH-003, funded by the US Department of Defense (DoD) was a Phase 1 double-blind, randomized, placebo-controlled study conducted by Emergent in healthy adults to assess the safety and pharmacokinetics of three dose levels of COVID-HIG IV [NCT04661839]. Study enrollment (n=28) has been completed with all participants being followed up to study completion. Thus far, one SAE has occurred not related to study treatment.

## 1.3 Summary of Known and Potential Risks and Benefits

### 1.3.1 Risks Related to Study Intervention

The overall safety profile of COVID-HIG is anticipated to be comparable to other commercially available human hyperimmune products, including those hyperimmune products manufactured by Emergent (VARIZIG®, HepaGam B®, ANTHRASIL®, WinRho® SDF, CNJ-016®-VIGIV) (30, 31, 32, 33, 34). The most common types of adverse reactions to hyperimmune products are local injection reactions (e.g., pain, redness, swelling) and non-anaphylactic infusion reactions, such as back or abdominal pain, nausea and vomiting during longer IVIG infusions. Usually there is no dyspnea or other clinically significant changes in vital signs. Fever, headache, chills, rash, fatigue may begin during the injection 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 injection. These may be treated symptomatically. The incidence of adverse reactions associated with IM/SC/IV administration of immunoglobulin products is reported by the manufacturers to be typically in the range of 1 to 15% (30, 31, 32, 33, 34, 35, 36, 37, 38, 39). 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 (40). 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) (15).

The risk assessment for COVID-HIG and mitigation strategies for EBS-CVH-006 are summarized in Table 3.

**Table 3 Risk Assessment for COVID-HIG**

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Potential for injection-related local (e.g., pain, redness, tenderness or swelling) and systemic (back or abdominal pain, nausea and vomiting, fever, headache, myalgia, chills, rash, or fatigue) reactions. | These are common adverse reactions seen with other human hyperimmune products (VARIZIG, HepaGam B, ANTHRASIL, WinRho SDF, CNJ-016-VIGIV, BIVIGAM®, GAMMAPLEX®, Privigen®, GAMUNEX®-C, Hizentra®) (30, 31, 32, 33, 34, 35, 36, 37, 38, 39). | The IM dose will be administered to the thigh muscle and will be split between both thigh muscles to mitigate discomfort. All study participants will stay overnight in the inpatient unit for close observation for approximately 24 hours post injection. Injection stopping rules and study stopping rules are provided (Pharmacy Manual and Sections 3.4). |
| Potential for hypersensitivity reactions within six hours after the injection. | Hypersensitivity reactions are rare. Severe immediate hypersensitivity reactions to plasma-derived products occur in individuals with IgA deficiency or hypersensitivity to human globulin. | Participants will be monitored overnight after injection in a setting with appropriate equipment, medication and personnel trained in the management of hypersensitivity, anaphylaxis, and shock. Participants at risk of hypersensitivity reactions are excluded from the study. |
| Potential for renal dysfunction/acute renal failure. | Renal dysfunction has been associated with HIG products containing sucrose as a stabilizer. | COVID-HIG does not contain sucrose.<br>Serum blood urea nitrogen and creatinine will be monitored at Screening and at Day 2 and Day 4 post-administration. |
| Potential for hematologic complications such as hemolytic anemia and thrombotic complications. | Rare thrombotic events have been associated with presence of activated factor XI resulting in elevated procoagulant activity in some immunoglobulin products.<br>High doses (>1–2 g/kg) are associated with an increased risk of hemolysis. | COVID-HIG has been tested for procoagulant activity and has met the product release specification. The COVID-HIG doses being administered are well below 1 g/kg.<br>Hemoglobin will be monitored at Screening and at Day 2 and Day 4 post-administration.<br>Participants with pre-existing thrombotic or procoagulant disorders are excluded from the study. |
| Potential for AMS or TRALI | AMS and TRALI rarely occurs in association with high doses (1–2 g/kg) of IGIV therapy. AMS begins within several hours to two days following | The COVID-HIG doses being administered are well below 1 g/day.<br>Participants will be monitored overnight after injection, with safety tests at Days 2 and 4 post injection. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | IGIV treatment, while TRALI occurs one to six hours post infusion. | |
| Potential for transmission of infectious diseases | Human plasma is used in the manufacture of COVID-HIG. Plasma is collected in accordance with regulatory requirements and donors are screened to assess the risk of exposure. Plasma donations are tested for HIV 1/2, HCV, and Hepatitis B. | Manufacturing processes include viral filtration and inactivation steps with quality control testing to eliminate risk of viral infection from COVID-HIG. Viral markers for Hepatitis B, Hepatitis C, and HIV 1/2 will be obtained from participants at Screening to document baseline status and at End of Study visit. Additional follow-up tests will be performed only if clinically indicated. |
| Potential for immunologic interference with live attenuated virus vaccine or the COVID-19 vaccine | Antibody therapies may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella.<br>Concomitant administration of antibody therapies and the COVID-19 vaccine could theoretically result in immunologic interference. | The use of live virus vaccination before or after COVID-HIG should follow current recommendations.<br>COVID-19 vaccination must occur at least 60 days prior to screening to be eligible. COVID-19 vaccination after the study should be deferred for 90 days post-administration as per current ACIP recommendations post-administration of passive antibody therapies (41)414141 |

The active ingredient of COVID-HIG is human IgG, which is a normal constituent of the human body and therefore it is not expected to be toxic to humans. A no-observed-adverse-effect level of 2000 mg/kg total protein was determined for product manufactured on the same platform and formulated identically to COVID-HIG administered IV to rats in a Good Laboratory Practice compliant single dose acute toxicology study conducted by Emergent (42). At the proposed COVID-HIG doses (~2-10 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 participants (refer to the most current version of the IB for more details).

The available clinical safety and efficacy data from immune based therapies such as convalescent plasma and mAbs that have been granted EUA support early intervention to prevent serious outcomes associated with COVID-19. Preclinical efficacy data with COVID-HIG, related preclinical safety data with product manufactured on the same platform as COVID-HIG and safety data from ongoing COVID-HIG studies (INSIGHT 013 and EBS-CVH-003) in 180 participants to date support the further development of COVID-HIG as a COVID-19 therapeutic.

### 1.3.2 Risks Related to the Study

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Participants may have in-clinic visits which could involve attendance at healthcare facilities during the global SARS-CoV-2 pandemic. | There is a potential for increased exposure/transmission of SARS-CoV-2. | Participants will have the opportunity to have a home visit for vital signs and collection of study specimens followed by a telemedicine appointment with the investigator if required. Participants will be counseled on precautions for reducing transmission of COVID-19. |
| Participants will undergo nasopharyngeal swab testing. | There is a potential for discomfort, risk of gagging during the test. Participants may have a minor nosebleed afterwards. Rarely cerebrospinal fluid (CSF) leak has been reported following COVID-19 testing (43). | Only appropriately qualified personnel will obtain the NP swab. Individuals at risk for serious complications following nasopharyngeal swab testing (e.g., CSF leak) are excluded from participation in the study (healthy participants only). |
| Blood draws will be performed during the study. | There is a risk of bleeding, bruising, hematoma formation and infection at the venipuncture site. | Only appropriately qualified personnel will obtain the blood draw. |
| Unauthorized exposure or release of confidential information. | As with any procedure that collects protected personal identifiable information, there is a risk of inappropriate exposure to unauthorized individuals or unapproved use of information. | Only approved personnel will be able to access participant information. Participant data and samples will only be used as consented by the participant. Procedures and safeguards to maintain integrity of confidential information are outlined in Section 12. |

### 1.3.3 Benefits

There are no proven benefits of the study intervention that participants in this study should expect. Clinical data derived from participants in this study will contribute to the development of COVID-HIG for treatment of COVID-19.

## 1.4 Population to be Studied

COVID-HIG will be evaluated in healthy non-pregnant female and male adults 18–59 years of age.

Refer to Section 3.1 for Study Description and Section 4 for Subject Inclusion and Exclusion criteria.

## 1.5 Literature and Data Relevant to the Trial

### 1.5.1 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 (44). Due to the spread of SARS-CoV-2, first identified in December 2019, causing a sudden increase in COVID-19 cases throughout the world, a pandemic was declared by World Health Organization (WHO) in March 2020. As of early August 2021, >200 million COVID-19 cases and >4.2 million COVID-19 attributed deaths have been reported to the WHO. In the US and Canada, COVID-19 cases continue to rise prompting public health authorities to continue active monitoring and focus on containment of the outbreak to prevent further spread (45).

### 1.5.2 Natural History of COVID-19

The incubation period for SARS-CoV-2 is approximately four to five days (range: two to seven days) (46, 47), and most individuals who develop symptoms (~98%) will do so within 11.5 days post-infection (46). Acute manifestations of COVID-19 include the following signs and symptoms: fever, cough, shortness of breath, fatigue, myalgia, nausea/vomiting or diarrhea, headache, rhinorrhea, anosmia, and ageusia. (48).

Many COVID-19 patients present with mild disease (approximately 80%). Although mild, symptomatic COVID-19 often resolves five to seven days (and up to 14 days) after symptom onset, there is growing recognition of the occurrence of postinfectious sequelae lasting for months in individuals, including young, physically fit individuals who initially experienced mild acute illness (49). Fatigue, dyspnea, cough, arthralgia, and chest pain are among the most commonly reported. Based on current available evidence, postinfectious sequelae may also include serious outcomes: cardiac (myocardial inflammation, ventricular dysfunction), respiratory (pulmonary function abnormalities), renal (acute kidney injury), dermatologic (rash, alopecia), neurologic (altered cognition, memory impairment, olfactory and gustatory dysfunction, sleep dysregulation), and psychiatric (depression and changes in mood).

Approximately 20% of patients will progress to more severe COVID-19 characterized by worsening dyspnea and hypoxia, severe pneumonia with >50% lung involvement on imaging. The median time from symptom onset to hospitalization is seven days; range: three to nine days post-symptom onset (50). Five percent of patients progress to critical COVID-19 manifested as acute respiratory distress syndrome, septic shock and/or multiorgan system dysfunction (47, 51, 52, 53). Cardiac, neurologic, hepatic, renal and hematologic complications may occur (54). Mortality in hospitalized COVID-19 patients ranges from 15% to 40% (55).

Reports of reinfection and vaccine breakthrough infections have become more frequent with emerging novel variants, but still remain relatively infrequent, with vaccination post-infection yielding a greater than two-fold reduction in reinfection risk (56).

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

General methods to prevent COVID-19 based on current guidance are to wear a mask in public settings, practice social distancing and avoid crowds and poorly ventilated indoor spaces (57). In December 2020, regulatory agencies in both the US and Canada authorized emergency use of the Moderna® and Pfizer-BioNTech® vaccines for pre-exposure prophylaxis of COVID-19 (58, 59, 60, 61). Although these vaccines are widely available in the U.S. and Canada, as of mid-July 2021, less than 60% of each country's population has been fully vaccinated (62). With emerging variants of increased transmissibility and severity (63), COVID-19 remains an urgent public health threat.

Individuals with mild to moderate COVID-19 disease not requiring supplemental oxygen are currently provided with symptomatic treatment if needed and instructed to follow public health protocols for self-isolation and return to the hospital if symptoms worsen. Several SARS-CoV-2 mAb (casirivimab plus imdevimab, bamlanivimab plus etesevimab or sotrovimab) are available under EUA for outpatients who are at high risk of disease progression and as post-exposure prophylaxis in high risk individuals (casirivimab plus imdevimab and bamlanivimab plus etesevimab) (64, 65, 66). The current standard of care for hospitalized patients with severe disease requiring supplemental oxygen includes dexamethasone with or without remdesivir in addition to supportive care. Current NIH treatment guidelines (updated 15Sep2021) recommend these mAbs for a broad range of high-risk patients ≥12 years of age that are likely to progress to more severe disease, however they are not considered SOC for all that test positive for SARS-CoV-2 (67).

## 1.6 Hypothesis

No statistically-powered hypothesis is tested in this Phase 1 study. It is hypothesized that COVID-HIG in all three routes of administration (IM, SC, and IV) is well-tolerated and that concentrations of SARS-CoV-2 antibodies will be measurable over time, with derived PK parameters in line with immunoglobulin product class kinetics.

# 2 STUDY OBJECTIVES AND PURPOSE

## 2.1 Study Purpose

This study is designed to evaluate safety and PK of COVID-HIG administered as IM, SC, or IV routes as a single dose in healthy adults.

Like other human immunoglobulin products, the hyperimmune products manufactured by Emergent (see Section 1.3.1) 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 hyperimmune products and the PK profile is typically similar to the PK of licensed hyperimmune products, with a half-life of approximately 24 to 30 days after IV administration.

Results from this clinical study will provide safety information on intramuscularly and subcutaneously administered COVID-HIG, as well as PK parameters such as peak COVID-HIG plasma levels, trough titers of SARS-CoV-2 antibodies, and COVID-HIG 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-HIG) will be used for dose optimization/dose selection for the proposed COVID-HIG indications (treatment of COVID-19; post-exposure prophylaxis of COVID-19).

### 2.1.1 Dose Rationale

The proposed dose for this clinical study (approximately 8–16 mg/kg based on an estimated participant weight of 50–100 kg) is within the dose levels tested in clinical studies of other licensed hyperimmune products and is expected to display similar safety and PK profile to those products. The selected dose for this clinical study is ≈250,000 Alliance Units (AU), based on COVID-HIG product lot potency of 29,282 AU/mL in the wild-type neutralization assay (performed at the NIAID analytical laboratory), resulting in a dose volume of 8.5 mL. The COVID-HIG lot potency is derived using an internal standard that has been established in the NIAID sponsored treatment study INSIGHT-013 (clinical lot potency of COVID-HIG is 29,282 AU/mL). The selected dose is based on antibody titer data available from treatment studies with COVID-19 convalescent plasma (CCP) and SARS-CoV-2 antibody-based therapeutics and vaccine trials as well as emerging literature on protective antibody levels (17, 21, 22, 68, 69, 70). The proposed dose potency is within the range of COVID-HIG doses that have been used for treatment of hospitalized COVID-19 patients (INSIGHT-013; NCT04546581) and for early treatment of high-risk COVID-19 patients (INSIGHT-012; NCT04910269).

As part of Emergent's manufacturing process for COVID-HIG, identification and screening of convalescent plasma donors is performed to select plasma as source material for manufacturing of COVID-HIG from COVID-19 convalescent donors that have been vaccinated against COVID-19. Plasma screening is primarily with an in-house immunobinding assay to SARS-CoV-2 Spike protein, however several assays including viral (wild type and pseudovirus) neutralization and external binding assays including the Ortho VITROS and the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG immunoassays, have been assessed for correlation. This experience has identified a range of neutralizing titers in non-vaccinated convalescent donors, which are typically around 20-50 AU/mL (data on file). Plasma testing data generated by Emergent allow a high-level comparison of COVID-HIG neutralizing antibody potency to that of CCP used in therapeutic clinical trials. COVID-19 convalescent plasma treatment in hospitalized patients from the US National registry demonstrated that higher titers of binding and neutralizing antibodies were associated with decreased 30-day mortality (21). Extrapolating based on our calculations of COVID-HIG and high-titer CCP potency, COVID-HIG is estimated to be at least 60 times as potent as high titer CCP based on the Ortho VITROS assay. Informal comparison of COVID-HIG potency to the high titer CCP in an early treatment study in elderly patients Argentina (22), suggest that COVID-HIG contains approximately 100-fold higher neutralizing antibody levels than CCP. Thus, a dose of 250 mL high titer CCP in the aforementioned study that was associated with a reduction in incidence of severe disease, is expected to be equivalent to approximately 2.5 mL of COVID-HIG.

Vaccine studies also provide an early estimate of antibodies levels that correlate with protection, especially as vaccine studies include results comparing convalescent plasma control samples with samples from vaccinated subjects (69, 70). Antibody levels achieved post-vaccination after

two doses of vaccine are toward the higher high end of the CCP neutralizing antibody range and remain relatively stable for at least 6 months following vaccination.

Based on cumulative considerations presented above, the selected dose of ≈250,000 AU is expected to provide substantially higher antibody levels than high titer CCP that was used therapeutically in most clinical trials. Although this study will be performed in healthy, uninfected adults for safety and PK analyses, this dose level will inform future dose optimization/dose selection for future COVID-HIG studies.

## 2.2 Study Objectives

### 2.2.1 Primary Objective(s)

The following primary objectives will be evaluated:

- To evaluate safety of COVID-HIG administered IM or SC as a single dose
- To evaluate PK of COVID-HIG administered IM or SC as a single dose

### 2.2.2 Secondary Objective(s)

The following secondary objectives will be evaluated:

- To compare PK of COVID-HIG IM to COVID-HIG IV
- To compare PK of COVID-HIG SC to COVID-HIG IV
- To compare PK of COVID-HIG SC to COVID-HIG IM

### 2.2.3 Exploratory Objective

The following exploratory objective will be evaluated:

- To evaluate the effects of COVID-HIG in participants that become Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) positive.

# 3 STUDY DESIGN

## 3.1 Study Description

This will be a Phase 1, two-center, open-label, randomized study to evaluate one dose level of COVID-HIG administered IM, SC, or IV for safety and PK in healthy adults. Up to 36 adult participants will be targeted to be enrolled in the study. The study has been truncated to 23 randomized participants due to the impact of high circulating SARS-CoV-2 omicron cases on enrollment and participant retention. The sample size with 7-8 participants per study arm will allow for assessment of the primary safety and PK objectives.

Subjects that provide written informed consent and meet eligibility criteria will be stratified based on their SARS-CoV-2 detectable antibody status (>LLOQ, but ≤80 AU/mL on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay) and undetectable antibody

(≤LLOQ) at screening, and randomized in two cohorts. If the proportion of subjects in one stratum is high, that stratum may be closed to allow for enrollment in the other stratum.

**Table 4 Study Design**

| Group | Study Arm | No. of Participants | Dosing Schedule – Day 1 |
|---|---|---|---|
| Intramuscular | 1 | Up to 12 | ≈250,000 AU COVID-HIG IM[1] |
| Subcutaneous | 2 | Up to 12 | ≈250,000 AU COVID-HIG SC[1] |
| Intravenous | 3 | Up to 12 | ≈250,000 AU COVID-HIG IV[1] |

[1]Exact dose volumes was determined based on the potency of the COVID-HIG clinical lot as defined in Alliance Units (AU) through the wild-type neutralization assay (Clinical lot potency: 29,282 AU/mL, 8.5 mL volume; target protein concentration: 100 mg/mL).

Up to thirty-six participants will be enrolled and assigned equally to one of three study arms to receive a single IM, SC, or IV dose of COVID-HIG, respectively (see the table above). Cohort 1 will consist of 12 subjects; Cohort 2 will comprise up to 24 subjects.

Enrollment into the study will be staggered, wherein no more than three participants will be randomized and dosed on the first day with at least one hour between dosing of each participant. On the second day, up to two more subjects will be randomized and dosed. The remaining participants will be randomized and dosed, with no more than 5 participants dosed per day. Safety data will be reviewed by an SMC (consisting of at least three independent external members) after all 12 participants in Cohort 1 have completed at least 72 hours of safety follow-up. An overall decision by the SMC will be made whether to proceed with full randomization (1:1:1) and dosing of the remaining study participants (Cohort 2, up to n=24).

Participants will be admitted to the inpatient unit one day prior to dosing (Day -1), and following dosing on Day 1, each participant will stay overnight in the inpatient unit for close observation and PK sample collection. Each dosed participant will be discharged from the inpatient unit once all assessments at 24 hours post-dosing timepoint (i.e., Day 2) are completed. Participants will be followed for safety and PK up to 56 days post-dosing (Day 57; see Table 2 for Schedule of Events). Follow-up visits to collect required samples and/or safety assessments can occur in-clinic or at-home as indicated in Table 2.

Study enrollment and administration of study treatments may be paused by the PI or medical monitor for safety review if any of the following occur after study product administration and during the enrollment period:

- One or more SAE(s)
- Three or more of the same AEs classified as Grade 3 severity
- Three or more hypersensitivity AEs classified as Grade 2

AE severity will be graded according to the DAIDS Severity Grading Scale (Appendix I).

Participants will be followed for 56 days post-dose.

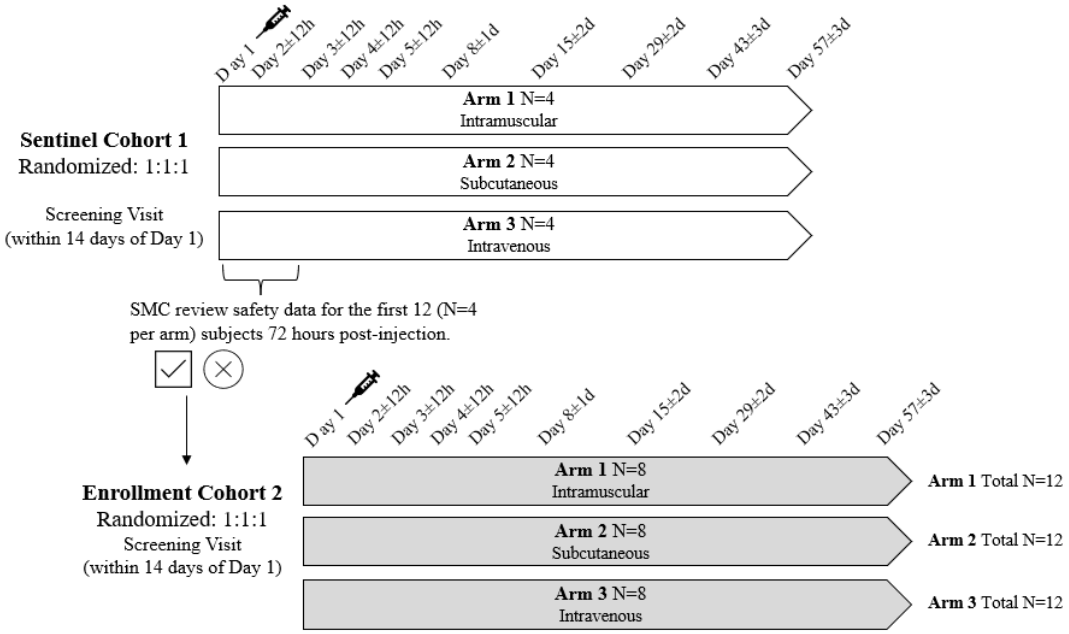
If any participants become positive for SARS-CoV-2 during the study follow-up period, they will be assessed using an Ordinal Outcome Scale (Appendix II) until symptom resolution and

will be followed until they complete their last scheduled follow-up visit (via telemedicine). Participants who test positive for SARS-CoV-2 will be excluded from PK analyses. As such, all subsequent visits should be done via telemedicine following SARS-CoV-2 positive status (except the Day 57 or the withdrawal visit), unless an in-person visit is deemed clinically necessary by the PI. Any in-person visits should be scheduled in a manner that reduces the risks of SARS-CoV-2 transmission, according to local rules and regulations. As the Day 57 or withdrawal visit necessitates in-person safety assessments, this visit should proceed in-person, if possible. If a participant tests positive for SARS-CoV-2 immediately prior to or at the in-person Day 57 visit, reasonable efforts will be made to collect as many of the required samples from the Day 57 visit in a manner that reduces the risk of SARS-CoV-2 transmission, according to local rules and regulations.

For details on schedule of events, refer to Table 2 Schedule of Events.

### 3.1.1 Schematic Diagram of Study Design, Procedures, and Stages

**Figure 1 Schematic of Study Design and Procedures.**




### 3.1.2 Study Center(s)

This study will be conducted at two centers in the US.

## 3.2 Study Endpoints

### 3.2.1 Pharmacokinetic Endpoints

#### 3.2.1.1 Primary Pharmacokinetic Endpoints

The following primary PK endpoints (based on PK sample test results of an immunobinding IgG assay) will be evaluated in healthy adults belonging to both strata, detectable SARS-CoV-2 antibody and undetectable antibody (≤LLOQ) at screening:

- $AUC_{0\text{-}inf}$: $AUC_{0\text{-}last}$ plus the additional area extrapolated to infinity after dosing.
- $AUC_{0\text{-}last}$: area under the concentration-time curve from time 0 to the last quantifiable concentration after dosing.
- $C_{max}$: maximum observed concentration after dosing.
- $T_{max}$: time at which $C_{max}$ occurs after dosing.
- $C_{28d}$: observed or estimated concentration at 28 days after dosing.

#### 3.2.1.2 Secondary Pharmacokinetic Endpoints

The following additional COVID-HIG PK endpoints (based on PK sample test results by an immunobinding IgG assay) will be calculated when data permit:

- $AUC_{0\text{-}inf}$ ratios (bioavailability) will be compared between routes for comparable dose levels (COVID-HIG SC to IV; IM to IV; and SC to IM).
- $AUC_{0\text{-}14d}$ after dosing.
- $AUC_{0\text{-}28d}$ after dosing.
- $\lambda_z$: 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.

### 3.2.2 Exploratory Endpoints

Descriptive analyses of COVID-19 disease severity among SARS-CoV-2 positive subjects as assessed by an Ordinal Outcomes scale (Appendix II).

### 3.2.3 Safety Endpoints

#### 3.2.3.1 Primary Safety Endpoints

The following primary safety endpoints will be evaluated:

- AEs within 72 hours post-dosing.

- AEs and SAEs in healthy adults up to 56 days post- administration of a single COVID-HIG dose.

## 3.3 Measures Taken to Minimize/Avoid Bias

### 3.3.1 Masking/Blinding Procedures

As this is an open label study, no masking/blinding procedures are necessary.

### 3.3.2 Treatment Assignment/Randomization

Enrollment into the study will be staggered. In the sentinel Cohort 1 a total of 12 participants will be randomized 1:1:1 to each study arm. As part of the sentinel cohort, the first three participants will be randomized and dosed on the first day with at least one hour between dosing of each participant. Another nine participants will then be randomized and dosed at least 24 hours after the first three participants have been dosed, with no more than 5 participants dosed per day in this set. Following randomization/dosing of the first four participants in each of the three arms (Cohort 1, n=12), safety data will be reviewed by the SMC once these 12 participants have completed at least 72 hours of safety follow-up. An overall decision by the SMC will be made whether to proceed with full randomization (1:1:1) and dosing of the remaining study participants (Cohort 2, up to n=24). Due to the impact of the COVID-19 pandemic surge in cases affecting enrollment and participant retention, the study has been truncated to 23 participants randomized, with 7-8 participants per study arm.

Subjects will be stratified based on their SARS-CoV-2 detectable antibody status (>LLOQ, but ≤80 AU/mL on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay) and undetectable antibody (≤LLOQ) at screening. If the proportion of subjects in one stratum is high, that stratum may be closed to allow for enrollment in the other stratum.

Randomization lists will be generated by a Randomization and Trial Supply Management (RTSM) system vendor. Details on the randomization procedures will be provided in the Pharmacy Manual. Sites will not be permitted to view the randomization list, and subjects will be assigned to treatment arm according to their stratum and randomization order.

## 3.4 Description of Stopping Rules

As described in Section 3.3.2, the SMC will evaluate safety data for sentinel participants to determine if the study can proceed to enroll remaining participants. The following related safety stopping rules apply throughout the entire study and will be managed by the SMC:

Study enrollment and IP administration will be temporarily held by the Sponsor if any of the following occur, pending further evaluation:

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

These events will be reviewed by the SMC and a recommendation will be made regarding IP administration, continuation of study, or study termination. The procedures for SMC notification and review of AEs will be outlined in the SMC Charter.

## 3.5 Accountability Procedures

The investigator (or designee) is responsible for maintaining accurate inventory records of the investigational product.

Refer to Section 5.1.5 for Investigational Product Accountability.

## 3.6 Maintenance of Study Intervention Randomization

As this study will be open label, there are no procedures for breaking randomization codes. Refer to Section 3.3.2 for Treatment Assignment/Randomization.

## 3.7 Data Directly Recorded on the Case Report Form

There are no planned data to be recorded directly on the eCRF that would be considered source data.

Refer to Section 9.3.

## 3.8 End of Study

End of study is defined as the last subject's last visit (LSLV). An individual participant is considered to have completed the study after completing the last study visit, Day 57 and all AEs have been followed to resolution or diagnosis. The study could be terminated early if stopping rules are triggered and the SMC or Emergent determines the study should be stopped.

### 3.8.1 Terminating the Study

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

Any decision to voluntarily suspend or terminate a clinical study will be carefully reviewed and fully justified. The Sponsor will notify the applicable regulatory authority country regulatory agency of any suspension or termination, along with justification for terminating the study.

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

### 3.8.2 Terminating the Study at an Individual Investigational Site

An investigational site may be terminated from the study at the discretion of the Sponsor or IRB/IEC/REB for reasons such as non-compliance, lack of recruitment, fraud or blacklisting by the regulatory authorities, etc.

The Sponsor may decide to replace a terminated investigational site.

# 4 SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1 Subject Inclusion Criteria

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

1. Able and willing to provide written informed consent (voluntarily signed by the participant) prior to performing study procedures.
2. Females and males 18–59 years of age.
3. Have a BMI less than or equal to 35.0 kg/$m^2$.
4. Healthy, based on medical history (no chronic disease, no chronic therapy, no ongoing acute condition within four weeks prior to dosing), normal physical examination (no clinically significant findings in the opinion of the investigator), and screening laboratory assessments (no clinically significant findings in the opinion of the investigator).
5. No clinical symptoms suspicious for COVID-19 infection, as well as SARS-CoV-2 IgM antibody negative and no laboratory evidence of current SARS-CoV-2 infection (i.e., RT-PCR negative for SARS-CoV-2) at Screening.
6. Females must not be pregnant, or trying to become pregnant as demonstrated by either of the following A or B:
   A. Not of childbearing potential: surgically sterile (at least six weeks post bilateral salpingectomy, bilateral oophorectomy, or hysterectomy); or post-menopausal (history of ≥12 consecutive months without menses prior to randomization in the absence of other pathologic or physiologic causes and confirmed by follicle FSH level ≥40 mIU/mL); OR
   B. Women of childbearing potential who are not planning to be pregnant during the study period and who meet all of criteria i–iii:
      i. Negative serum pregnancy test at the Screening Visit.
      ii. Negative urine pregnancy test on Day 1 (a positive test will result in discontinuation from intervention).
      iii. Using one of the following highly effective methods of contraception during the study:
         - Combined estrogen and progestogen, or progestogen-only hormonal contraception associated with inhibition of ovulation (e.g., implants, pills, patches) initiated ≥30 days prior to Study Day 1.
         - Intrauterine device or hormone releasing IUS inserted ≥30 days prior to Study Day 1.

7. Participant understands and agrees to comply with planned study procedures.

## 4.2 Subject Exclusion Criteria

Participants who meet any of the following criteria cannot be enrolled:

1. Use of any investigational product within 30 days or SARS-CoV-2 monoclonal antibodies and COVID-19 convalescent plasma within 90 days prior to Screening or anticipated receipt during the study follow-up period, or participant plans to participate in another clinical study during the study period.
2. Receipt of 1 or 2 doses COVID-19 vaccine within 60 days prior to screening or anticipated receipt during the study follow-up period.
3. SARS-CoV-2 IgG antibody levels >80 AU/mL as determined by the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay.
4. Screening clinical laboratory test result greater than the laboratory's ULN for ALT, AST, random glucose, total and/or direct bilirubin, 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 PI.
5. Positive laboratory evidence of current infection with HIV, HCV, or HBV. Note: Positive anti-HCV antibody result along with a negative HCV PCR would NOT be exclusionary.
6. History of allergy or hypersensitivity to blood or plasma products or to COVID-HIG excipients (proline, PS80).
7. History of allergy to latex or rubber.
8. History of hemolytic anemia.
9. History of IgA deficiency.
10. Receipt of any blood product within the past 12 months.
11. Plasma donation within 7 days or blood loss/donation (>450 mL) within 56 days of dosing.
12. 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).
13. History of thrombosis or hypercoagulable state with increased risk of thrombosis.
14. Receipt of a live vaccine within 30 days prior to screening or anticipated receipt of a live vaccine during the study period.
15. Currently pregnant, breastfeeding, or planning to become pregnant during the study.
16. History of, or suspected substance abuse problem (including alcohol).
17. Any planned elective surgery or procedure during the follow-up period that impacts study compliance.

18. Other condition which may place participant at increased risk due to participation in the study or may impact study compliance as determined by the investigator.
19. An opinion of the investigator (or designee) that it would not be in the best interest of the individual to participate in the study.

## 4.3 Subject Withdrawal Criteria

### 4.3.1 Withdrawal of Consent

All participants are free to withdraw from participation in this study at any time, for any reason. The PI will request (but cannot require) such participants to provide the reason(s) for withdrawal of consent.

Outreach will be made to ensure that participants who withdraw from the study during the active treatment or follow-up period will complete all safety and available assessments for the Early Withdrawal visit as outlined in this protocol. The PI should inform the participant that these assessments are for their own well-being and, if possible, for study purposes. Additional information regarding ongoing adverse events may be provided as a follow-up report.

The participant must first agree to the collection of early withdrawal and safety assessments prior to the assessments, and this agreement must be documented in the source documents.

Safety follow-up for adverse events should occur for all participants.

### 4.3.2 Discontinuation of Intervention

If applicable based on randomized route of administration, the injection(s) can be stopped if Grade 2 or higher or serious AE (anaphylaxis or hypersensitivity reaction) are observed. All participants should still be followed-up for the duration of the study for safety. Refer to Section 5.1.4 for further information related to AEs and administration of IP.

### 4.3.3 Subject Withdrawal Criteria

The PI may withdraw a participant from further IP administration or participation in the study, at their discretion, if medically necessary or for reasons of noncompliance. The reason for withdrawal of any participant must be clearly documented on the study source documents and the appropriate electronic Case Report Form (eCRF). The PI is encouraged to consult the Sponsor prior to the withdrawal of any participant, except in the event of a medical emergency.

The PI (and/or the Sponsor) may withdraw a participant from further IP administration or participation in the study for any of, but not limited to, the following reasons:

- Lost to Follow-up
  - Lost to follow-up determination requires documentation of at least 3 unsuccessful attempts to contact participants.
- Adverse Event

- Protocol Deviation
- Pregnancy
- Physician (i.e., PI) Decision
- Withdrawal by Subject
- Participant contracts COVID-19
- Participant receives prohibited COVID-19 vaccination
- Other

Safety follow-up for adverse events should occur for all participants.

Reasons for withdrawal of individual participants from the study prior to final protocol required visit and/or final safety follow-up are to be recorded on the CRF and subject source documents.

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

### 4.3.4 Subject Replacement

Participants who are discontinued or withdraw consent prior to baseline/randomization after signing consent will be replaced. Participants withdrawn from the study or who withdraw consent after randomization will not be replaced, regardless of whether they have been dosed. The study sample size determination has included consideration for some participants to be lost to follow-up or withdraw consent.

## 5 STUDY INTERVENTION

### 5.1 Investigational Product(s)

Anti-SARS-CoV-2 Immunoglobulin Injection (Human), also referred to as COVID-HIG, is a hyperimmune product that consists of purified IgG fraction of human plasma containing antibodies (including neutralizing antibodies) to SARS CoV-2. The product is a clear to slightly opalescent and colorless or pale, yellow liquid essentially free of foreign particles. The final sterile liquid product contains 85-115 mg/mL of human plasma proteins (target 100 mg/mL), of which at least 90% is human IgG. COVID-HIG 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 potency of the final product is determined by a validated immunoassay that measures concentration of binding SARS-CoV-2 antibodies (with SARS-CoV-2 trimeric S protein as the antigen) in relation to a reference standard; the final drug product is also characterized by a wild-type SARS-CoV-2 neutralization assay (refer to the most current version of the IB).

COVID-HIG will be administered as a single ≈250,000 AU dose through an IM, SC, or IV route of administration. Based on a calculated potency of 29,282 AU/mL as assessed using a wildtype neutralization assay, this will equate to an 8.5 mL (~850 mg, based on a target protein

concentration of 100 mg/mL) dose that may be split across several sites, depending on route of administration.

For additional information, refer to the IB and Pharmacy Manual for dose preparation instructions.

### 5.1.1 Packaging and Labeling

The final COVID-HIG product will be supplied in 6 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 5.0 mL. Each vial is intended for single use. The vials will be provided in shelf cartons (35 vials per shelf carton).

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

For dispensing labels for secondary receptacles, see Section 5.1.3 Preparation.

For more information, please refer to the most current version of the IB for COVID-HIG.

### 5.1.2 Storage Conditions

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

Once at the site, COVID-HIG 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-HIG IB and the Pharmacy Manual.

### 5.1.3 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.

The pharmacy staff assigned to this study will prepare COVID-HIG 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-HIG at the required dosage as per Pharmacy Manual instructions. 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 using standard aseptic techniques and transfer the content into an appropriately sized receptacle.

Once punctured, use the vial contents to prepare the dose promptly. COVID-HIG 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 label on final dispensed dose will capture at a minimum: participant identification (ID), expiry date of the prepared dose (i.e., <24 hours after dose preparation), the investigator's name, protocol code (EBS-CVH-006) and caution statement "For investigational use only".

Record date of the injection, start/stop times (where applicable) and the total volume administered. For further details, refer to the Pharmacy Manual.

### 5.1.4 Investigational Product Administration

Investigational product is to be administered only under the direct supervision of the PI or qualified investigational site personnel. An acute observation period after IP administration will occur (Section 6.5.1) where the participant will be monitored by study staff for signs of an acute adverse reaction after administration.

Participants will be monitored in-clinic closely during injection and overnight in-clinic. A detailed safety follow-up for participants will occur one day and three days post-dose (Days 2 and 4).

If AEs occur during or immediately after the injection, such as grade 1 (mild) events of flushing, headache, chills, fatigue, nausea, slight changes in pulse rate or blood pressure, slow the rate of injection until symptoms subside or until dose is completely administered (at discretion of the investigator). If the recipient experiences grade 2 (moderate) or higher AEs such as chest pain, difficulty breathing, vomiting, arthralgia, or severe headache, unresponsive to slowing or stopping the injection, halt the injection and wait until symptoms subside to determine whether to resume injection.

Depending on the route of administration, the participant may receive multiple injections of COVID-HIG to achieve the full dose in the study arm. Stop the injection if serious AEs develop (e.g., anaphylaxis, severe hypersensitivity reactions) and administer appropriate medical management. Do not complete the injection.

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

#### 5.1.4.1 Intramuscular Administration

COVID-HIG should be warmed to room temperature before use. The dose can be split into multiple injections to be administered slowly in both thigh muscles to reduce discomfort. All injections should be administered over approximately two minutes or as directed by the PI. Additional details will be provided in the Pharmacy Manual.

Date, time and locations of injections of COVID-HIG will be documented in the source documents and captured in eCRF.

#### 5.1.4.2 Subcutaneous Administration

COVID-HIG should be warmed to room temperature before use. The dose can be split into multiple injections with a maximum of 3 mL per injection. Each injection should be administered slowly at a different injection site in the abdomen (except for 2 inches (5 cm) around the navel), thigh or back of the upper arm. The waistline should be avoided. It is recommended to use different quadrants of the abdomen or upper thighs or back of upper arms to space apart each dose. All injections should be administered over approximately two minutes or as directed by the PI. Additional details will be provided in the Pharmacy Manual.

Date, time and locations of injections of COVID-HIG will be documented in the source documents and captured in eCRF.

#### 5.1.4.3 Intravenous Administration

COVID-HIG should be warmed to room temperature before use. Administer COVID-HIG by IV infusion through a dedicated IV line as a bolus IV injection. Administer the prepared dose slowly over five minutes at a rate of 1.7 mL/min or as directed by the PI. Additional details will be provided in the Pharmacy Manual.

Date and time of COVID-HIG administration will be documented in the source documents and captured in eCRF.

### 5.1.5 Investigational Product Accountability

The investigator is responsible for maintaining accurate inventory records of COVID-HIG bulk product. The pharmacist or pharmacy staff designee will inventory all COVID-HIG 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 or a designated individual 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-HIG 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 participant for whom product was dispensed
- Product balance
- Name and title of qualified individual dispensing product.

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

#### 5.1.5.1 Investigational Product Resupply

Resupply of IP may be requested through the study monitor.

#### 5.1.5.2 Used or Partially Used Investigational Product

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 with a record of disposition maintained, as directed by Emergent.

### 5.2 Prior and Concomitant Medications

Participants should not take prescription medications at the time of enrollment (with the exception of hormonal contraceptives for WOCBP). Participants must abstain from alcoholic beverages for at least 48 hours prior to baseline assessments.

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 participants will be questioned about all concomitant medications during in-clinic follow-up visits including all herbal preparations and non-prescription medications that they are consuming. This information will be recorded on the appropriate source documents and captured in the eCRF.

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

#### 5.2.1 Prohibited and/or Restricted Medications

Prescription medications (with the exception of hormonal contraceptives for females) and certain concomitant medications are prohibited and/or restricted for at least 30 days before Day 1 and during the study. Over-the-counter drugs, supplements, vitamins, and herbal preparations will be assessed and documented in medical history.

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 source documents and captured in the eCRF.

Participants must be advised to abstain from alcoholic beverages for at least 48 hours prior to screening assessments. The following are prohibited/restricted medications:

- Any commercially available live vaccine is prohibited from at least 30 days prior to dosing and through to the end of the study follow-up (Day 57).
- Any COVID-19 vaccination dose is prohibited at least 60 days prior to Screening and through to the end of the study follow-up (Day 57).

The use of medications considered prohibited is not allowed. Medications to treat minor ailments (headache, nausea, etc.) are allowed at the discretion of the investigator. Study participants will be questioned about all concomitant medications including all herbal preparations and non-prescription medications. All concomitant medication will be recorded on the CRF, including whether the medication is taken in relation to an adverse event.

The Medical Monitor (MM) should be consulted for any questions about prohibited or restricted medication usage.

### 5.3 Rescue Medications

Not applicable.

### 5.4 Procedures for Monitoring Subject Compliance

Participants will be monitored for study compliance through solicited responses to questions regarding any changes to concomitant medications and vaccinations at each visit. Counselling regarding preventing SARS-CoV-2 infection and contraceptive use (if WOCBP) will occur at each visit to help ensure the participant remains eligible for study participation.

## 6 STUDY PROCEDURES AND ASSESSMENTS PER VISIT

### 6.1 Screening

Screening period is within 14 days prior to Day 1.

Eligible participants will first undergo informed consent counseling. Once informed consent has been obtained, participants will undergo a screening visit to ascertain their eligibility in this study. The Screening visit assessments will include:

- Written informed consent.
- Collection of demography information (date of birth, sex, race/ethnicity, height, body weight, BMI).
- Review of inclusion/exclusion criteria.
- Medical history and ongoing medications.

- Perform rapid SARS-CoV-2 IgM/IgG antibody test and SARS-CoV-2 antigen test prior to collecting other samples. Only proceed further with screening assessments if negative for SARS-CoV-2 IgM and antigen.
- Complete physical examination: to include assessment of general appearance, and the following body systems: head-neck, respiratory, cardiovascular, gastrointestinal, dermatological, lymphatic/hematological, musculoskeletal, neurological, metabolic/endocrine.
- For WOCBP: assess contraception use (>30 days prior to dosing) and instruct on use of contraception from the time of Screening through end of study (up to Day 57).
- Serum pregnancy test for WOCBP and FSH testing for post-menopausal women.
- Vital signs (resting ≥10 minutes) include body temperature, pulse, respiratory rate, sitting blood pressure, and $SpO_2$ (pulse oximetry).
- Local safety laboratory assessments:
    - Chem 7 panel [Na+, K+, $Cl^-$, $HCO3^-$, 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 [Human immunodeficiency virus 1/2 (HIV 1/2) antibody, HBV surface antigen, HCV antibody].
- Urine drug screening (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine opioids).
- Nasopharyngeal swab sample for SARS-CoV-2 RT-PCR test.
- Serum sample for the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody test.
- Provide counselling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Assess for any COVID-19 symptoms or SARS-CoV-2 exposure.
- Monitor/assess AEs related to study procedures.

### 6.2 Re-Screening

Participants may be re-screened once at the discretion of the investigator in consultation with the sponsor's MM. Re-screened participants outside the screening period will be assigned a new subject identification number.

### 6.3 Pre-dosing (Day -1) – In-patient overnight assessment

- If required, update medical history and ongoing medications.

- Inquire if the participant has had a suspected or confirmed exposure to SARS-CoV-2 or developed COVID-19 symptoms in the period of Screening visit to Day 1.
- Perform rapid SARS-CoV-2 IgM/IgG antibody test.
- If WOCBP, perform UPT.
- If WOCBP, confirm use of contraceptives.
- Alcohol breath test.
- Confirm eligibility.
- Collect pre-dose serum sample for SARS-CoV-2 baseline antibody PK assessment.
- Collect NP swab sample for SARS-CoV-2 RT-PCR test.
- Targeted physical exam, if clinically indicated.
- Monitor/assess AEs related to study procedures.

### 6.4 Baseline (Visit 1, Day 1) Assessments – Randomization and Dosing

Perform the following assessments on Day 1 as an in-clinic overnight visit:

- Collect pre-dose serum sample (within 2 hours prior to dosing) for SARS-CoV-2 baseline antibody PK assessment.
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, $SpO_2$ (pulse oximetry) and respiratory rate]; within 2 hours prior to dosing.
- Randomize. Stratification will be based on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody status (positive/negative) from screening visit.
- Administer randomized study treatment.
- Monitor/assess AEs before, during and post-administration of the injection in the clinic overnight.
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, $SpO_2$ (pulse oximetry) and respiratory rate] at 30 minutes (±5 mins) and 1 hour (±10 mins) post-administration (from end of infusion/injection).
- Serum samples for post-dosing assessment of SARS-CoV-2 antibodies for PK at 1 hr ±10min, 2 hrs ±15min, 4 hrs ±15min, 8 hrs ±30min, and 12 hrs ±30min (from end of infusion/injection).
- Targeted physical exam, if clinically indicated.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Record any concomitant medications (if applicable).

## 6.5 Investigational Product Administration (Visit 1, Day 1)

The participant must receive COVID-HIG on the Day 1 visit which much occur within 14 days after screening. Participants will be randomized to receive a single dose of ≈250,000 AU of COVID-HIG as either an IM, SC, or IV infusion following confirmation of eligibility and collection of samples outlined in Section 6.3.

COVID-HIG is to be administered only under the direct supervision of the PI or a qualified sub-investigator identified on the Form FDA 1572. Under no circumstances will the PI allow COVID-HIG to be used other than as specified in the protocol.

Refer to Section 5.1.4 for details on Investigational Product Administration.

### 6.5.1 Acute Observation After Investigational Product Administration

The participant will be monitored by study staff for signs of an acute adverse reaction overnight in-clinic. Vital signs (resting ≥10 minutes) will be assessed at 30 minutes (±5 mins) and 1 hour (±10 mins) after administration.

## 6.6 Scheduled Study Visits

**Day 2, 3, 4, 6, 8, 15, 29, 43**

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

Visit windows are as follows (in relation to Day 1):

Day 2: (1±0.5 days), Day 3: (2±0.5 days), Day 4: (3±0.5 days), Day 6: (5±0.5 days), Day 8: (7±1 day), Day 15: (14±2 days), Day 29: (28±2 days), Day 43: (42±3 days).

*Visits are indicated as calendar days, while the time post-dosing and the visit windows are indicated in the brackets.

If randomized to IV group (Arm 3), omit visits on Day 3 and Day 6.

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

- Assessment of AEs and concomitant medications (in-clinic or telemedicine).
- Targeted physical exam, if clinically indicated. Based on the investigator's assessment of AEs/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.
- If WOCBP, confirm use of contraceptives.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2 at any time post-dosing during the study period: assess clinical status based on an Ordinal Outcome scale (Appendix II). Perform assessments via telemedicine if possible.

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

- 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) at Day 2 and Day 4 only. At other follow-ups, collect sample only if clinically indicated (as per investigator's discretion).
- Sample for urinalysis at Day 2 and Day 4 only. At other follow-ups, collect sample only if clinically indicated (as per investigator's discretion).
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate] at Day 2 and Day 4 only. At other follow-ups perform only if clinically indicated (as per investigator/sub-investigator's assessment).
- NP swab sample for SARS-CoV-2 RT-PCR test on Day 8, Day 15 Day 29, and Day 43. At other follow-ups perform only if clinically indicated (as per investigator/sub-investigator's assessment).

If any participants become positive for SARS-CoV-2 at any point during the study follow-up period, all subsequent visits should be done via telemedicine (except for the Day 57 or the withdrawal visit), unless an in-person visit is deemed clinically necessary by the PI.

### 6.7 Unscheduled Visits

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

Participants can be evaluated during an unscheduled visit if the investigator deems it necessary to further follow-up on participant'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. If telemedicine follow-up requires sample collection or in-person assessments, an in-clinic or at-home follow-up should be scheduled:

- Assessment of AEs and concomitant medications.
- Targeted physical exam, if clinically indicated.
- Nasopharyngeal swab samples for SARS-CoV-2 RT-PCR test (as per investigator's discretion assessing COVID-19 symptoms/exposure).
- 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 (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion).
- If WOCBP, confirm use of contraceptives.
- If WOCBP and only if clinically indicated, perform serum pregnancy test.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2 at any time post-dosing during the study period: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

Participants may be referred for emergency medical care (i.e., to emergency room, for hospitalization), if clinically indicated. Participants 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 source documents and captured in the eCRF.

### 6.8 End of Study Visit (Visit 10, Day 57)

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

Visit window for Day 57: 56±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.
- If WOCBP, confirm use of contraceptives.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

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

- 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).
- Blood sample for viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody).

- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion).
- Nasopharyngeal swab sample for SARS-CoV-2 RT-PCR test.

If a subject tests positive for SARS-CoV-2 during the study: As the Day 57 visit necessitates an in-person safety assessment (viral marker testing), this visit should proceed in-person, if possible. In-person visits should be performed after the infectious period has passed to reduce risk of transmission and should follow local rules and regulations. If a participant tests positive for SARS-CoV-2 immediately prior to or at the in-person Day 57 visit, reasonable efforts will be made to collect as many of the required samples from the Day 57 visit in a manner that reduces the risk of SARS-CoV-2 transmission, according to local rules and regulations.

### 6.9 Early Withdrawal/Termination Visit

Early withdrawal visit procedures will be performed for participants who received study treatment and who withdrew from the study prior to Day 57. Collect as much of the safety data as possible. If a subject tests positive for SARS-CoV-2 during the study and a subject withdraws prior to Day 57, collect as much safety data as possible while reducing the risk of transmission and following local rules and regulations.

If the participant withdrew consent, the PI must get participant agreement to perform the early withdrawal assessments and document this agreement in the source documents.

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

- Assessment of AEs and concomitant medications.
- Targeted physical exam, if clinically indicated.
- If WOCBP, confirm use of contraceptives.
- Provide counseling to participants on precautions/measures to prevent contracting SARS-CoV-2 infection.
- Only if participant becomes positive for SARS-CoV-2: assess clinical status based on an Ordinal Outcome Scale (Appendix II). Perform assessments via telemedicine if possible.

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

- 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).

- Blood sample for viral marker testing (HIV 1/2 antibody, HBV surface antigen, HCV antibody).
- Vital signs (resting ≥10 minutes) [body temperature, blood pressure (seated), pulse, SpO2 (pulse oximetry) and respiratory rate]. Note: perform only if clinically indicated (as per investigator's discretion).
- Nasopharyngeal swab sample for SARS-CoV-2 RT-PCR, if clinically indicated (as per investigator/sub-investigator's assessment).

# 7 ASSESSMENT OF PHARMACOKINETICS

In this study, only pharmacokinetic assessments will be performed to evaluate study objectives. The assessments described below will be used to derive serum concentrations of SARS-CoV-2 antibodies (by testing PK samples with a validated immunobinding IgG assay) that will be used to calculate the PK parameters.

## 7.1 Description of Study Assessments

Assessments that will be performed according to standard practices as scheduled in the Schedule of Events are not described further in this section. The visit time points of these procedures and assessments can be found in the Schedule of Events (Table 2).

Specific procedures related to collection, processing, storage, and shipment of the samples are provided in the Laboratory Manual. For the timing of sample collection refer to the Schedule of Events (Table 2).

### 7.1.1 Efficacy Outcomes

Not applicable.

### 7.1.2 Pharmacokinetic Samples

Serum samples will be collected as described for all participants for PK analyses as described in Section 7.3. For duration of sample retention see Section 12.6.

All serum samples must be taken as closely as possible to the specified times in relation to the start of IP administration (visit windows provided in Section 6).

Refer to the Laboratory Manual for information regarding samples to be collected and tests to be completed.

### 7.1.3 Nasopharyngeal Samples

Nasopharyngeal swabs will be used to collect samples from the nasopharynx to measure if the participant is infected with SARS-CoV-2. Nasopharyngeal swab samples for SARS-CoV-2 RT-PCR test will be collected at Screening, Day -1, Day 8, Day 15, Day 29, Day 43, Day 57, and as clinically indicated (as per investigator/sub-investigator's assessment of the participant in-clinic or during the telemedicine follow-up) and tested by the Phase 1 unit.

### 7.1.4 Non-standard Safety Outcomes

There are no non-standard safety outcomes.

## 7.2 Specification of the Outcome Measures

Blood will be drawn to collect serum to measure SARS-CoV-2 antibodies and for safety laboratory assessments.

Refer to the Laboratory Manual for information regarding samples to be collected and tests to be completed.

## 7.3 Methods and Timing for Assessing and Recording of Outcome Measures

Pharmacokinetic parameters of COVID-HIG administered IM, SC, or IV as a single dose will be determined in healthy adults (see Section 9.4.2). The samples drawn at the time points described below will be used to derive serum concentrations of SARS-CoV-2 antibodies (by testing PK samples with a validated immunobinding IgG assay) that will be used to calculate the PK parameters. The immunobinding IgG assay will be performed at the facility outlined in the EBS-CVH-006 Laboratory Manual.

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: 1 hour (±10 mins), 2 hour (±15 mins), 4 hour (±15 mins), 8 hour (±30 mins) and 12 hour (±30 mins) post-infusion. In addition, the following post-dose timepoints will be included (brackets indicate days after injection on Day 1): Day 2 (1±0.5 days), Day 3 (2±0.5 days), Day 4 (3±0.5 days), Day 6: (5±0.5 days), Day 8 (7±1 day), Day 15 (14±2 days), Day 29 (28±2 days), Day 43 (42±3 days), and Day 57 (56±3 days). The IV arm (Arm 3) will not have data for post dose samples on Day 3 or Day 6 as these will not be collected.

# 8 SAFETY ASSESSMENTS AND REPORTING

The safety of COVID-HIG will be assessed by collection of AEs, laboratory test results (blood chemistry and hematology, urinalysis), concomitant medications, 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 screening but before dosing will be captured as an AE. Any AE that occurs after screening but before dosing will be documented in the source documents and captured in EDC if subject is randomized. Capture of treatment emergent adverse events (TEAEs) starts from the time of COVID-HIG administration and until the end of study period (up to Day 57 visit). Unanticipated problems related to study procedures may be collected following enrollment.

Adverse events are to be elicited by the investigator (or designate) by asking the participant non-leading questions. The association of the AE to COVID-HIG is to be judged by the investigator as related or unrelated (see Section 8.1.9 below).

## 8.1 Definitions

### 8.1.1 Adverse Event

An AE is 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.

*Notes:*

- *A diagnosis should be captured as an adverse event term and signs and symptoms should be captured only in the absence of a unifying diagnosis. If a diagnosis is ultimately made, it should replace the previous report based on signs and symptoms.*
- *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 PI (or designee) as not clinically significant will not be captured as an AE, but an abnormal laboratory finding that worsens after dosing with the investigational product, from not clinically significant to clinically significant, is considered an AE.*
- *Surgical procedures are not AEs. They are the action taken to treat a medical condition. Interventions that were planned prior to study entry for medical conditions that started prior to study entry but did not worsen during the clinical study are not reported as AEs.*

### 8.1.2 Serious Adverse Event

An SAE is any untoward medical occurrence that: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, 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 an 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.

*Notes:*

- *Death is an outcome and not an event. The condition leading to death is the event. If no other information regarding the cause of death is available, the event will be considered "Unspecified Adverse Event".*
- *Overnight stays at hospital/clinic that occurs during a trial for social reasons (e.g., transportation difficulties, respite care) is not considered to be a hospitalization event.*

### 8.1.3 Adverse Drug Reaction

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

### 8.1.4 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is the term used to refer to an AE that occurs in a clinical trial subject, which is assessed by the Sponsor and or PI as being unexpected, serious and as having a reasonable possibility of a causal relationship with the IP.

### 8.1.5 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs (serious or non-serious) that are of scientific and medical concern specifically related to the sponsor's product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. In this study, there are no AESIs.

### 8.1.6 Solicited Adverse Event(s)

A solicited adverse event (solicited AE) is a protocol-specified AE about which the PI (or designee) proactively asks the subjects during a protocol-specified time period. There are no solicited adverse events in this study.

### 8.1.7 Unsolicited Adverse Event

An unsolicited adverse event (unsolicited AE) is an AE that is spontaneously reported by the subject or discovered by the PI. Any newly reported/identified AE following dosing or an increase in the severity/frequency of a previously reported condition prior to dosing regardless of causal relationship with investigational product or procedure is considered an unsolicited/spontaneous event.

### 8.1.8 Severity of Adverse Events

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 I). For AEs that are not included in the DAIDS AE Grading Table, use the following generic scale is:

**Table 5 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 |

### 8.1.9 Causality of Adverse Events

The PI is responsible for the assessment of the causality of an adverse event and the Sponsor's MM will also assess SAE causality, independent of the PI.

The following guidelines are provided for this assessment.

- **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 IP or similar products, or in the PI's (or designee) clinical judgment the association of the event with the IP seems likely.
- **Definitely related**: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to IP administration, and which cannot be explained by concurrent disease or other drugs or chemicals (e.g., injection site pain, anaphylaxis, TRALI). The response to withdrawal of the IP (DECHALLENGE) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory RECHALLENGE procedure if necessary.

When possible, de-challenge and re-challenge should be considered to assess the causality of the relationship between the AE and the IP.

If the relationship between the AE and the IP is determined to be "possible" or "probable," the event will be considered to be "related" to the investigational product, otherwise it will be considered "not related" for reporting purposes.

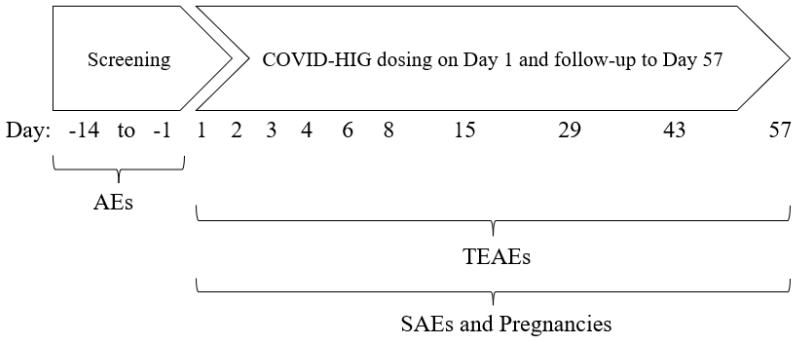
## 8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

All events that occur following screening until immediately before the first dose of IP on Day 1, will be recorded as an AE for randomized participants. Adverse event reporting is required for any new observation presenting after the first dose of IP or for a deterioration of baseline

condition (e.g., increased severity/frequency). Adverse events following first dose of IP will be considered TEAEs. Refer to Figure 1 below for timing of safety monitoring in this study.

Occurrence of AEs will be monitored until the end of the study (Day 57) and will cover all participants. Study participants will be provided with a 24-hour telephone number to contact study personnel in case of an untoward reaction. Adverse events reported spontaneously by the participant and/or in response to an open question from the PI (or designee) or revealed by observation (e.g., during physical exam or from a clinical test result) will be recorded by the PI (or designee) on the AE eCRF if they occurred during the study period, regardless of causal association with the IP.

**Figure 2 Reporting Periods for Adverse Events**




### 8.2.1 Solicited Adverse Events

There are no solicited adverse events in this study.

### 8.2.2 Safety Laboratory Tests

It is the responsibility of the PI or designee to review the results of all screening and safety laboratory tests (including unscheduled lab tests) as they become available, initially for the assessment of study eligibility (screening laboratory test results, if not otherwise specified in the inclusion/exclusion criteria, should be within the central laboratory's reference ranges, or, if outside such ranges, be assessed by the investigator as not clinically significant) and subsequently for the continuous safety monitoring of participants.

The following standard safety laboratory tests will be performed in the study:

- Blood chemistry: glucose, sodium, potassium, bicarbonate, chloride, BUN, creatinine, ALT, AST, LDH, bilirubin (direct, total).
- Blood hematology (CBC, with differential): red blood cells, white blood cells, hemoglobin, hematocrit, with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
- Urinalysis: appearance, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen, microscopic examination (only if protein, nitrite, leukocyte esterase, or occult blood results are positive).

For each abnormal laboratory test result, the PI or designee needs to ascertain if this is a clinically significant change from baseline for that individual. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The PI or designee may repeat the laboratory test and/or request additional tests to verify the results of the original laboratory tests. The PI (or designee) will inform the MM of any unscheduled clinical laboratory testing, including but not limited to confirmatory testing of laboratory samples, with the exception that notification is not required for confirmatory testing for pregnancy, HCV, and HIV.

Safety laboratory tests will be done at Screening, Day 2, and Day 4 visits, and can be done at any other visit if clinically warranted based on PI (or designee) discretion. The PI or designee may request the participant return to the clinic for an unscheduled visit for an assessment of clinical status. The decision to redraw laboratory tests will be made by the PI (with notification to the MM) and/or MM and will be based on the type and severity of the laboratory abnormality and the clinical status of the participant. If the original (retested sample) or repeat laboratory value is Grade 3 or higher, this will be considered an AE and will be recorded by the PI on the AE eCRF. Any other clinical laboratory abnormalities must also be reported as AEs if considered by the PI or designee to be a clinically significant change from baseline.

Refer to Table 2 (Schedule of Events) for timing of the safety laboratory tests and Appendix I for toxicity grading to determine which abnormal labs should be evaluated as AEs (Grade 3 or higher). If the lab analyte does not have toxicity grading criteria specified in Appendix I, then the PI or designee will use the grading criteria for “illness or clinical AE” in Appendix I to assign the AE toxicity grading. If an abnormal laboratory test result is a sign of a disease or syndrome, the disease or syndrome will be recorded as the AE/SAE and not the abnormal laboratory result.

#### 8.2.2.1 Drug Screen

Urine drug screening (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine opioids) will be performed at Screening visit.

#### 8.2.2.2 Alcohol Screen

An alcohol breath test will be performed on Day -1 in-clinic visit.

#### 8.2.2.3 Viral Testing

A blood sample will be collected for viral marker testing (HIV 1/2, HbsAg, HCV antibody, and HCV RNA only if positive for HCV antibody) to be performed at Screening visit and at the end of study visit (Day 57 or Early Withdrawal Visit). Viral marker testing may be performed at an unscheduled visit, as applicable.

### 8.3 Reporting Requirements for Immediately Reportable Events

#### 8.3.1 Principal Investigator’s Reporting Requirements

The investigator will report all SAEs and confirmed pregnancies to Emergent within the electronic data capture within 24 hours of the investigator’s knowledge of occurrence. The SAE report should include a medical summary of the SAE.

An email notification will be sent to EBCI pharmacovigilance (PV) team through Medidata RAVE to: productsafety@ebsi.com.

Applicable events must be entered into the validated EDC system. In the event of a system failure, paper forms may be used as a back-up method for reporting and sent via email to the following address:

The appropriate forms will be completed and sent by email to the following address:

| |
|---|
| **Global Pharmacovigilance Department**<br>Emergent BioSolutions Canada Inc.<br>Medical Monitor Phone: 1 (204) 230-6804<br>Email: productsafety@ebsi.com |
| Toll free fax: 1-800-768-2281 |

For SAEs, the Serious Adverse Event Form will be completed (abbreviated hereafter SAE 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.

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

If a participant becomes pregnant during a study, Emergent will be notified. All pregnancies where conception occurred after first exposure to the IP through the End of Study visit are to be followed to outcome (e.g., delivery, spontaneous/elective/therapeutic abortion) and up to 28 days post-birth, including after the study is completed and even if the participant is withdrawn from the study. If a pregnancy results in an abnormal outcome that the reporting health care professional considers might be due to the IP, then the guidelines for expedited reporting of SUSARs should be followed.

Any pregnancy that occurs during study participation must be reported on a clinical study pregnancy form in the EDC. To ensure participant safety, each pregnancy must be reported to Emergent within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child up to 28 days post-birth. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as a SAE.

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

The PI is responsible to notify their IRB/IEC/REB according to their policy.

### 8.3.2 Emergent's Reporting Requirements

As specified in 21 CFR 312.32, SUSARs will be reported by Emergent to the FDA and to all participating investigators in an individual case safety report as soon as possible, no later than 15

calendar days after Emergent becomes aware of the suspected adverse reaction (21 CRF 312.32). In addition, any unexpected fatal or life-threatening suspected adverse reaction 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 (21CRF 312.32).

## 8.4 Follow-up of Adverse Events

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

### 8.4.1 Follow-up of Nonserious Adverse Events

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

### 8.4.2 Follow-up of Serious Adverse Events

This study requires that participants be monitored for SAEs up to Day 57. From Study Day 1, confirmed SAEs will be recorded on the AE eCRF. The status of ongoing SAEs will be assessed at each clinic visit and at each quarterly safety phone contact to determine any new information and to update the resolution status in the AE eCRF.

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

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

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

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

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

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

information received related to any SAE must be forwarded within 24 hours of awareness to the Emergent Global PV Department (productsafety@ebsi.com).

### 8.4.3 Follow-up of Pregnancies

Any pregnancy, where conception occurred after first exposure to the IP through the End of Study visit of a female participant must be reported to the Sponsor within 24 hours of learning of its occurrence. Such pregnancies must be reported using a clinical study pregnancy form. All pregnancies are to be followed to outcome and status of mother and child (e.g., delivery, spontaneous/elective/therapeutic abortion), including up to when the infant is 28 days old. Any events following study closeout will be captured in the safety database.

If a pregnancy results in an abnormal outcome that the reporting health care professional considers might be due to the IP, then the guidelines for expedited reporting of serious, unexpected adverse drug reactions should be followed.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE.

Spontaneous abortions/miscarriage must be reported as an SAE.

### 8.4.4 Unanticipated Problems

For investigational sites in the US, 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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incidence, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the study or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

The PI should promptly notify the IRB/IEC/REB when an unanticipated problem involving risks to participants or others is identified. Also, the PI should notify the Sponsor of unanticipated problem(s).

### 8.5 Safety Data Monitoring

An independent SMC will provide on-going review of safety data during the study. In fulfilling these responsibilities, the SMC may make recommendations concerning continuation and/or stopping of the study as it relates to safety and risk to the participant population as outlined in the SMC Charter.

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

- ≥ one SAE regardless of relatedness to IP
- ≥ three of the same AEs classified as Grade 3 severity
- ≥ three Grade 2 hypersensitivity AEs

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

## 9 STATISTICAL CONSIDERATIONS

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

Tables will be displayed by administration route columns. Data from both study sites and both cohorts will be pooled.

### 9.1 Sample Size Rationale

There was no formal sample size calculation for this Phase 1 study. However, based on previous experience with hyperimmune globulin products manufactured by Emergent (30, 31, 32, 33, 34) in Phase 1 clinical studies with healthy adults, Emergent deems the number of participants planned to receive treatment in the study [N=up to 36; n=up to 12 per each treatment arm] is sufficient to descriptively assess COVID-HIG safety and PK of a single dose in healthy adults. Even with the truncation to 23 randomized participants due to high circulating SARS-CoV-2 omicron cases, 7-8 participants per study arm should be sufficient to meet study objectives, similar to the previous PK study EBS-CVH-003 with 7-8 participants per arm.

### 9.2 Statistical Methods

In general, continuous endpoints will be summarized by descriptive statistics including number of participants, mean, standard deviation (SD), median, minimum, and maximum. Logarithmic transformation will be used when appropriate, CV, geometric mean, and geometric CV will also be summarized. Categorical endpoints will be summarized by the total number of participants, frequencies, and percentages.

See Section 9.4.2 for statistical methods for PK analyses.

## 9.3 Handling of Missing Data

When calculating summary statistics, including geometric mean and 90% CIs and PK parameters, PK (SARS-CoV-2 antibody) concentrations below the assay's lower limit of quantitation (LLOQ) will be imputed as half of the LLOQ value. If the lower bound of the CIs is below the 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. Imputation rules for partial or missing dates will be described in the study SAP.

## 9.4 Planned Analyses

### 9.4.1 Analyses of Disposition, Demographic and Baseline Characteristics

Participant disposition, including early termination reasons, will be provided for all randomized participants by administration route. Demographic and baseline characteristics including age, sex, race, ethnicity, and BMI will be tabulated by administration route for all randomized participants and the safety and PK populations.

Medical history will be coded to System Organ Class (SOC) and Preferred Term (PT) using the MedDRA dictionary and summarized by administration route for the safety population. Protocol deviations (PDs) will be categorized as important or not important and evaluated for exclusion of data from PK analyses. Protocol deviations will be presented by administration route for the safety population.

Physical examination data will be listed by participant.

### 9.4.2 Pharmacokinetic Analyses

Pharmacokinetic parameters will be estimated using standard non-compartmental methods (i.e., log-linear trapezoidal method). Subjects will be stratified based on their SARS-CoV-2 detectable antibody status (>LLOQ, but ≤80 AU/mL on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG assay) and undetectable antibody (≤LLOQ) at screening, with analyses done by antibody status (if possible) and overall per each arm. Actual times and not nominal times will be used in the analysis; concentrations at nominal time points may be imputed using linear interpolation. Participants with elevated baseline levels of SARS-CoV-2 antibodies or participants with inadequate number of PK time points (e.g., no pre-dose sample, or no measurable post-dose sample) may be excluded from the PK analysis. Outliers will be examined for possible exclusion from analysis, such as spiking antibody levels during the study attributed to active infection. Baseline subtraction may be employed, if necessary and where possible, using the mean of individual subject's pre-dose antibody titers. For partial AUCs through a given time point, the partial AUC will be set to missing unless an actual time point occurs within ±10% of the nominal timepoint for a given profile.

Bioavailability will be compared between administration routes, if data permit. An ANOVA model will be used with $AUC_{0\text{-inf}}$ as the dependent variable and administration route as the fixed effect. The adjusted least square means will be used to estimate ratios of $AUC_{0\text{-inf IM}}$ / $AUC_{0\text{-inf IV}}$ * 100%, $AUC_{0\text{-inf SC}}$ / $AUC_{0\text{-inf IV}}$ * 100%, and $AUC_{0\text{-inf IM}}$ / $AUC_{0\text{-inf SC}}$ * 100% along with

corresponding two-sided 90% CIs calculated based on the ANOVA. The width of the 90% CIs will be examined relative to the standard of [80%, 125%] for comparative bioavailability. If the area extrapolated from the time of the last measured concentration to infinity is greater than 40% of the total AUC for a subject profile, then the observation will be excluded from bioavailability analyses. No adjustment for multiplicity will be applied, and no formal hypothesis testing will be performed.

Any anomalous concentration values observed prior to the first dose will be identified. Such values less than 5% of the observed $C_{max}$ for the affected PK profile will be set to 0 (zero) for the calculation of PK parameters. The original concentration values will be used in statistical summaries. If the pre-dose value is greater than 5% of $C_{max}$, the affected PK profile will be excluded from statistical summaries and analysis. Similarly, PK concentrations for the affected profile will be excluded from statistical summaries.

Pharmacokinetic analyses will be performed separately for each administration route for the PK population, using the results of the binding IgG antibody assay (see Section 0). Comparative bioavailability will be presented between administration routes (IM to IV; SC to IV; and IM to SC), if data permit. Derived PK parameters, including both primary and secondary PK endpoints, will be tabulated by administration route for the PK population. Binding IgG SARS-CoV-2 antibody serum concentrations versus time curves will be summarized and plotted by administration route for the PK population.

### 9.4.3 Safety Analyses

#### 9.4.3.1 Study Medication Exposure

Participant exposure to study medication (amount administered and administration per protocol yes/no) will be tabulated for the safety population by administration route and by baseline antibody level.

#### 9.4.3.2 Adverse Events and Serious Adverse Events

Treatment-emergent adverse events are defined as AEs that present after the initiation of study IP or any AEs already present that worsen in either intensity or frequency following treatment. The incidences of TEAEs and SAEs will be summarized by administration route for the PK population using the MedDRA coded terms for SOC and PT and by event severity.

#### 9.4.3.3 Clinical Laboratory Test Results

Hematology and clinical chemistry laboratory test results and change from baseline to Day 2 and Day 4 will be summarized by time point and administration route for the safety population. The clinical significance of any 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 (Appendix I). Values within the normal range as well as out of range laboratory values not meeting criteria for severity of at least grade 1 will be considered grade 0. Shift tables of laboratory abnormalities (Low, Normal, High) and/or severity grade (0,

1-2, ≥3) will be provided for selected laboratory parameters summarized by time point and administration route for the safety population.

Results for urinalysis, pregnancy tests, and viral markers will be listed by participant.

#### 9.4.3.4 Vital Signs Test Results

Vital signs test results (including temperature, blood pressure, pulse, pulse oximetry, and respiratory rate) and change from baseline to Day 1 post-dose (from end of injection/infusion) time points, Day 2, and Day 4 will be summarized by time point and administration route for the safety population. The clinical significance of any abnormality will be assessed by the investigator, any abnormal vital signs results will be graded per Appendix III. Vital signs can be repeated twice if grade 3 or higher to verify the severity. Values within the normal range as well as out of range vital signs values not meeting criteria for severity of at least grade 1 will be considered grade 0. Shift tables of vital signs severity grade (0, 1-2, ≥3) may be provided for selected parameters summarized by time point and administration route for the safety population.

#### 9.4.3.5 Nasopharyngeal Swab Results

Nasopharyngeal swabs at Days 8, 15, 29, 43, and 57 will be analyzed for SARS-CoV-2 by RT-PCR and results will be reported by time point and administration route for the safety population.

In addition, the frequency and percentage of participants testing positive for COVID-19 will be reported for the safety population. The maximum COVID-19 symptom severity per participant using an Ordinal Outcome grading scale (Appendix II) will be tabulated for the SARS-CoV-2 positive population.

### 9.4.4 Subgroup Analyses

No subgroup analyses are planned for this phase 1 study.

### 9.4.5 Planned Interim Analyses and Criteria for Study Termination

No interim analysis is planned for the study.

The SMC will review safety data after the first 12 participants have completed at least 72 hours of safety follow-up. Stopping rules are provided in Section 3.4 and will be explained futher in the SMC Charter.

## 9.5 Analysis Populations

Analysis will be based on the following study populations:

**Safety Population:** All randomized participants who receive any amount of COVID-HIG IM, COVID-HIG SC, or COVID-HIG IV, analyzed according to the actual study treatment arm.

**PK Population:** All participants who are randomized and received COVID-HIG IM, COVID-HIG SC, or COVID-HIG IV according to the protocol and with evaluable PK data (i.e., no major protocol deviations affecting PK sampling and results including COVID-19 infection, adequate number of PK sample test results), analyzed according to actual study treatment arm.

**SARS-CoV-2 Positive Population:** Any randomized participant (whether or not dosed with COVID-HIG) who tests positive for SARS-CoV-2 during the study period and for whom data are available, analyzed according to randomized study treatment arm. This population is used for the COVID-19 symptom severity exploratory endpoint.

# 10 DATA HANDLING AND RECORD KEEPING

## 10.1 Source Documents and Access

Source data are all information, original records of clinical findings, and observations in a clinical trial necessary for the reconstruction and evaluation of the trial. 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 PI/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, IP administration, AEs, concomitant medications, participant follow-up information, and other relevant observations.

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

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

Records from the study that identify the participant will be confidential except that they may be given to and inspected by the Sponsor (or designee), the IRB/IEC/REB, the FDA, other government agencies as appropriate, and will not otherwise be released except as required by law. Refer to Section 12.5 Subject Confidentiality. All information provided to the PI by the Sponsor is to be considered confidential unless otherwise stated.

## 10.2 Data Management

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

## 10.3 Data Collection and Discrepancy Management

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

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

### 10.4 Laboratory Data

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

### 10.5 File Management at the Investigational Site

The PI 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 PI/Institution will take measures to prevent accidental or premature destruction of these documents.

### 10.6 Records Retention at the Investigational Site

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 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.

The PI 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 PI 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 PI 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.

### 10.7 Deviations from the Protocol

The PI agrees to conduct the clinical study in compliance with the protocol agreed to by the Sponsor and approved by the investigational site's IRB/IEC/REB.

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

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

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

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

# 11 QUALITY CONTROL AND ASSURANCE

## 11.1 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 PI must make source documentation accessible to the study monitor as needed to verify the information in the eCRF. The PI 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.

## 11.2 Auditing

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

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

# 12 ETHICS AND RESPONSIBILITY

This study must be conducted in accordance with the ethical principles described in the current 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 PI and investigational site staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID number will be used to identify each subject.

## 12.1 Informed Consent/Assent

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

Emergent (or the designee) will generate and provide a master Informed Consent Form (ICF) template to each investigational site for development of a site-specific ICF.

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

The participant will be asked to read and review the document. The PI 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.

## 12.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB)

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

The PI (or designee) is responsible for informing, and obtaining appropriate approval from, the IRB/IEC/REB of any amendment to the protocol or ICF in accordance with local requirements.

The PI (or designee) is also responsible for providing the IRB/IEC/REB with reports of any reportable serious adverse drug reactions from any other study conducted with the IP, if required by the IRB/IEC/REB. Emergent will provide this information to the PI.

Initial IRB/IEC/REB approval, and all materials approved by the IRB/IEC/REB for the study including the ICF and recruitment materials, must be maintained by the PI and made available for inspection.

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

### 12.3 Compensation for Injury

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

### 12.4 Documentation Required Prior to Study Initiation

The PI (or designee) is responsible for forwarding the following documents to the Sponsor for review prior to study initiation:

- Signed protocol signature page, form FDA 1572 (or equivalent, depending on applicable local and federal regulations), financial disclosure form (principal and sub-investigators), Clinical Study Agreement, and any other required regulatory documents.
- Copy of IRB/IEC/REB-approved informed consent form and assent form (as applicable).
- Copy of the written IRB/IEC/REB approval for the following documents: protocol, Investigator's Brochure, informed consent and assent form(s), participant compensation (if any), any study materials and advertising, and any other written information or tools (including diaries and/or memory aids) to be provided to the participant.
- Current signed and dated Curriculum Vitae and a copy of medical license (if applicable) of the principal and sub-investigator, and other investigational site personnel as required by the Sponsor.
- 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.

### 12.5 Subject Confidentiality

The PI must ensure the anonymity of each participant is maintained at all times. Participants should only be identified by their Subject Study ID number on the CRF or on any other study documents provided to the Sponsor (or designee(s)). Biospecimens should only be identified by sample numbers/codes as specified in the Laboratory Manual. Any documents that identify the participant should be kept in strict confidence by the investigational site.

Based on ICH GCP Guidelines and regulatory requirements, the PI is required to allow authorized personnel of Emergent (or its designee), the IRB/IEC/REB, and members of the appropriate regulatory authority(ies) to review participant's files that are related to EBS-CVH-006. Participants must be informed that their records may be reviewed by the Sponsor, its designee(s), the IRB/IEC/REB and the appropriate regulatory authority(ies) through direct access to the participant's original medical records.

Redacted copies of participant medical records that are related to EBS-CVH-006 may be collected by Emergent for the purposes of adverse event follow up and reporting, and/or monitoring. Redacted copies of medical records may be transferred via encrypted email (AES or triple DES); via secure fax line; or uploaded to a secure, encrypted password-protected environment hosted by a third-party service provider to which only assigned site personnel and monitors have access, with a list of users maintained for the duration of the study and audit trails available on all activities.

Copies of redacted medical records related to monitoring will be permanently destroyed at study closure.

### 12.6 Future Use of Stored Samples

Stored specimens (e.g., PK samples) will be identified by subject ID/sample numbers/codes for future testing. Participants 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 two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two years have elapsed since the formal discontinuation of clinical development.

## 13 ADMINISTRATIVE AND LEGAL REQUIREMENTS

### 13.1 Sponsorship

This clinical study is sponsored by Emergent BioSolutions Canada Inc., 155 Innovation Drive, Winnipeg, Manitoba, Canada, who is the manufacturer of COVID-HIG.

### 13.2 Protocol Amendments

Protocol amendments will only be made by the Sponsor. 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 PI, the Sponsor, and the IRB/IEC/REB prior to implementation. The PI 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 the Sponsor.

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

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

### 13.3 Clinical Study Registration

The Sponsor is responsible for clinical trial registration and reporting to Clinicaltrials.gov and other registries in accordance with applicable regulations.

### 13.4 Publication Policy

Following the completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and may work with the PI to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues. The Sponsor has final approval authority over all such issues.

Any proposed publication will be participant to review conditions and timelines agreed between the Sponsor and the investigational site PI and detailed in the agreements with these parties prior to the start of the study. The Sponsor will also post the results of the clinical study on ClinicalTrials.gov (or other applicable registries) in a period no greater than 12 months from the completion of the study (if applicable as per FDAAA 801 requirements), defined as the time the final participant was examined or received an intervention for purposes of final collection of data for the primary outcome.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

All publication rights are delineated in the Clinical Trial Agreement.

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# 15 APPENDICES

## APPENDIX I 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 II ORDINAL OUTCOME CATEGORIES AND CRITERIA

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

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

## APPENDIX III GRADING OF VITAL SIGNS

Use the following criteria to grade vital signs. Vital signs can be repeated twice if grade 3 or higher to verify the severity.

| **Grading Scale*** | **Grade 1 (mild)** | **Grade 2 (moderate)** | **Grade 3 (severe)** | **Grade 4 (potentially life-threatening)** |
|---|---|---|---|---|
| Temperature<br>(C°)<br>(F°) | <br>38.0-38.4<br>100.4-101.1 | <br>38.5-38.9<br>101.2-102.0 | <br>39.0-40.0<br>102.1-104.0 | <br>>40.0<br>>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<br>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 $SPO_2$.

Document Approvals
Approved Date: 17 Feb 2022

| | |
|---|---|
| Approval Task<br>Verdict: Approve | 17:07:12 GMT+0000 |
| Approval Task<br>Verdict: Approve | 17:15:05 GMT+0000 |
| Approval Task<br>Verdict: Approve | 20:31:30 GMT+0000 |