[COVID-HIGIV]
[EBS-CVH-003]

Statistical Analysis Plan

Product Name
Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV)

Protocol EBS-CVH-003
A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) in Adults with and without SARS-CoV-2 Infection

Protocol Version	**Date**
4.0	21/Apr/2021

SAP Version	**Date**
1.0 (Fina1)	28/May2021
1.1 (Amendment)	08 Dec 2021

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SAP Signature Page

Signatures below indicate that the final version of the SAP or amended SAP is released for execution.

Study Statistician

Name	Position	*(See electronic signature attached)* Signature	DD/MMM/YYYY

Statistical Reviewer

Name	Position	*(See electronic signature attached)* Signature	DD/MMM/YYYY

Clinical Study Scientist

Name	Position	*(See electronic signature attached)* Signature	DD/MMM/YYYY

Medical Monitor

Name	Position	*(See electronic signature attached)* Signature	DD/MMM/YYYY

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Change History Table

Version	Summary of Major Change(s) and Impact	Revision Date
Version 1.0	First approved version of SAP	28/May/2021
Version 1.1	Amendment for change of ULOQ of binding immunoassay in SAP Section 8.5.1, due to update in PK Analytical Testing Plan	01/Dec/2021

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List of Abbreviations and Definition of Terms

Table 1: List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the Curve
AU	Alliance unit(s)
BMI	Body Mass Index
CI	Confidence Interval
cm	Centimeter(s)
COVID-19	Coronavirus disease 2019
COVID-HIGIV	Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human)
CSR	Clinical Study Report
CV	Coefficient of Variation
d	Day(s)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EWV	Early Withdrawal Visit
g	Gram(s)
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GMR	Geometric Mean Ratio
h	Hour(s)
ICF	Informed Consent Form
ID	Identification, as in Subject Identification (number)
IgG	Immunoglobulin G (gamma globulin)
IgM	Immunoglobulin M
IP	Investigational Product
IV	Intravenous
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre(s)
NP	Nasopharyngeal
PE	Physical Examination

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PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
TLF	Tables, Listings and Figures
ULOQ	Upper Limit of Quantification
US	United States
WHO	World Health Organization

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol EBS.CVH.003 "A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) Administered as a Single Dose or a Repeat Dose Regimen to Healthy Adults" (Version 4.0, 21Apr2021). This document specifies details of the definitions of the derived variables, analysis methods, assumptions and data handling conventions. The document is accompanied by mock-up tables, listings, and figures (TLF Specification). Some further details on the calculation of derived variables will be provided as programmer's notes in the TLF shells. The TLF shells serve only as a guide for programming the final TLF. They are working documents and can be updated as needed.

2 PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objectives

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

2.2 Study Design and Conduct

This study is a Phase 1, single-center, double-blind, randomized, placebo-controlled design to evaluate three dose levels of COVID-HIGIV for safety and PK in healthy adults.

Subjects will be enrolled into the study consisting of healthy adult non-pregnant females and males (SARS-CoV-2 negative). In total, 28 subjects are planned for the study (Table 1 below).

Table 1

Study Arm	No. of Subjects	Treatment*	Study Arm Label
1	8	COVID-HIGIV Dosage 1	COVID-HIGIV 100 mg/kg
2	8	COVID-HIGIV Dosage 2	COVID-HIGIV 200 mg/kg
3	8	COVID-HIGIV Dosage 3	COVID-HIGIV 400 mg/kg
4	4	Placebo (saline)	Placebo

* Note: COVID-HIGIV Dosage 1-3 are prepared by IP volume (mL) based on subject body weight (kg). COVID-HIGIV protein concentration ≈ 100 mg/mL, the dosages in study arm label are in the unit of mg.kg.
Dosage 1: prepared by COVID-HIGIV volume (≈1 mL/kg), with a maximum of 100 mL, labeled as 100 mg/kg,
Dosage 2: prepared by COVID-HIGIV volume (≈2 mL/kg), with a maximum of 200 mL, labeled as 200 mg/kg.
Dosage 3: prepared by COVID-HIGIV volume (≈4 mL/kg), with a maximum of 400 mL, labeled as 400 mg/kg.

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

The enrollment/dosing of the first seven subjects in the study will be staggered wherein no more than three subjects will be dosed on the same day (to be dosed at least one hour apart). Principal Investigator (PI) and the Sponsor's Medical Monitor (MM) will review blinded data (up to 24 hours after end of IV infusion) before proceeding with dosing subsequent set of remaining subjects for the stagger. Available safety (blinded) data will be reviewed by Study Monitoring Committee (SMC) (consisting of at least three independent external members) after seven subjects from Cohort A have completed at least 72 hours of safety follow-up. If unblinding of the safety data is required, closed session by the SMC will be held. An overall decision by the SMC will be made whether to proceed with full randomization and dosing of the remaining study subjects.

Following dosing, each subject will stay overnight in the inpatient unit for close observation; each dosed subject will be discharged from the inpatient unit once all assessments at 24 hours post-dosing timepoint (i.e., Day 2) are completed.

The SMC will perform overall ongoing review of safety data during the study. Study enrollment and administration of study treatments may be temporarily paused by the SMC for safety review if any of the following occur after study product administration and during the study's follow-up period:

- One or more serious adverse event(s) [SAE(s)]
- Three or more of the same adverse events (AEs) classified as grade 3 severity.
- Five or more of the same AEs classified as grade 2 severity.

Subjects will be followed for safety and PK assessments up to 84 days post-dosing. If any subject tests positive for SARS-CoV-2 via a point-of-care RT-PCR test of nasopharyngeal (NP) samples during the study follow-up period, they may be withdrawn from the study, but allow for telemedicine follow-up plus home healthcare visits. They will be assessed for COVID-19 symptoms using modified WHO ordinal score (Appendix V) in the Early Withdrawal visit (EW).

The final statistical analyses will be conducted after all subjects complete the study.

2.3 Randomization and Blinding

This is a double-blinded, placebo-controlled, single site study.

2.3.1 Methods of Randomization

Subjects will be randomized into four treatment arms, with a randomization ratio of 2:2:2:1, and a block size of seven (two subjects at COVID-HIGIV dosage level 1, two subjects at COVID-HIGIV dosage level 2, two subjects at COVID-HIGIV dosage level 3, and one placebo subject).

The first seven subjects will be randomized and dosed in a staggered manner, with dosing at least one hour apart, and not exceeding three subjects on the same day.

2.3.2 Randomization Errors

A *mis-randomization* is defined as a subject receiving a study treatment other than the one assigned by randomization.

Stratification error happens when a subject is randomized based on incorrect stratification information at baseline or if a subject is mistakenly put into a wrong block. In either case, the subject uses up one position in the assigned block and randomization can continue.

Both mis-randomization and stratification error are reported as protocol deviations.

2.3.3 Blinding and Unblinding

Randomization list is generated by a third-party statistician (Axiom RTSM team) and not provided to the sponsor until unblinding.

At the site, the designated unblinded pharmacist will receive the treatment and dosage assignment from the Randomization and Trial Supply (RTSM) module and prepare the infusion bags accordingly, all infusion bags are of 400 mL volume and masked for blinding. Details on the randomization procedures are provided in the Pharmacy Manual (*Version 1.0, 03Dec2020*).

In addition, designated personnel at the bioanalytical laboratory assigned to perform PK sample testing will be unblinded due to nature of test; however, the personnel at the bioanalytical laboratory will not have access to clinical data and will not disseminate the link between bioanalytical laboratory results and the actual subject ID until database lock. PK statistician will analyze PK result by dummy subject ID and nominal timepoints of PK sampling during the study. Other personnel involved in the conduct of the clinical study will remain blinded until database lock and final unblinding. Details on the blind maintenance will be provided in the Blind Maintenance Plan (*Version 1.0, 15Jan2021*).

The final study unblinding is planned after all subjects complete the Day 85 visit (i.e., 84 days post-dosing).

Per current CDC guidelines, subjects who received immunoglobulin products should avoid vaccination for up to 90 days afterwards. The local standard of care in COVID-19 pandemic changed during the trial such that all adults >16 years of age because eligible to receive the COVID-19 vaccine in New York State. As a result, subjects who received placebo will be informed of their treatment assignment after all subjects have completed the Day 29 so that they may follow current COVID-19 vaccine recommendations. Immediate unblinding of treatment assignment to receive COVID-19 vaccination is also allowed after the Day 29 visit on a case-by-case basis based on PI judgement and will be considered as medical emergency unblinding. Unblinded Placebo recipients will be kept in the study for safety follow-up, but no PK samples will be drawn. Unblinded COVID-HIGIV recipients will continue follow up as per the protocol.

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3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

COVID-HIGIV is indicated for the treatment and prevention of COVID-19. This study is conducted in healthy adult volunteers to evaluate the safety and pharmacokinetics of COVID-HIGIV. Efficacy is not evaluated in this study.

3.2 Safety Endpoints

The following primary safety endpoints will be evaluated:

- Adverse Events (AEs) within 72 hours post-dosing.
- AEs leading to discontinuation or temporary suspension of infusion.
- AEs and Serious Adverse Events (SAEs) up to 84 days post-administration of a single COVID-HIGIV dose.

3.3 Pharmacodynamics Endpoints

Primary PK Endpoints: The following PK parameters will be estimated after a single dose of COVID-HIGIV infusion:

- $AUC_{0\text{-last}}$: area under the concentration-time curve from time 0 to the last quantifiable concentration after a single dose. Time 0 is defined as the end of infusion; time t is defined as time of the last quantifiable concentration.
- $AUC_{0\text{-inf}}$: $AUC_{0\text{-last}}$ plus the additional area extrapolated to infinity.
- $AUC_{0\text{-14d}}$: AUC from time 0 to 14 days post-dosing.
- $AUC_{0\text{-28d}}$: AUC from time 0 to 28 days post-dosing.
- C_{max}: maximum observed post-dosing concentration.
- T_{max}: time at which C_{max} occurs.
- C_{min28d}: observed or estimated concentration (by interpolation/extrapolation) at 28 days post-dosing.
- λ_z: terminal elimination rate constant after a single dose.
- $T_{1/2}$: apparent terminal elimination half-life after a single dose.
- CL: systemic clearance after a single dose.
- V_Z: volume of distribution after a single dose.

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

- C_{max}BWN: Body weight normalized C_{max}
- C_{min28d}BWN: Body weight normalized C_{min28d}

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

3.4 Exploratory Endpoints

There are no exploratory endpoints in this study.

4 POWER AND SAMPLE SIZE CONSIDERATIONS

There was no formal sample size calculation for this Phase 1 study. However, the number of subjects planned to receive COVID-HIGIV is deemed sufficient to descriptively assess safety and PK of three COVID-HIGIV dose levels with healthy adults.

In total, 28 subjects are planned for the study. Eight subjects for each of the three COVID-HIGIV dose levels, and four subjects for placebo arm.

5 DATA CONSIDERATIONS

5.1 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. The occurrence of protocol deviations will be routinely monitored for evaluation of Investigator compliance with the protocol, GCP, and regulatory requirements.

Upon identification, protocol deviations will be classified by category, sub-category and type (important/not important) per the Protocol Deviation Management Plan (PDMP *version 2.0 19May2021*). All protocol deviations will be reviewed, finalized and documented prior to final database lock and study unblinding.

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

5.1.1 Important Deviations

Emergent will review all protocol deviations on an ongoing basis and will determine if the deviation should be categorized as an Important Protocol Deviation, which are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints.

Examples of major protocol deviations may include:

- Subjects who were enrolled/randomized but did not meet study eligibility criteria.

- Subjects who met criteria for study termination but remained in the study.
- Subjects who received the wrong treatment (IP or dosage level).
- Other deviations from key study procedures such as accidental unblinding, subject noncompliance with treatment schedule, subject noncompliance with assessment of primary outcome measures.

The importance of a protocol deviation will be assessed and determined case by case by study team review.

5.1.2 Reporting of Protocol Deviations

The important protocol deviations will be summarized by category and treatment arms. Listings of important and non-important protocol deviations with be provided respectively.

5.2 Analysis Sets

- Safety Set (SS): all randomized subjects who receive any amount of COVID-HIGIV or placebo. Analyses based on SS will be analyzed according to the study treatment arm (dispensed IP and dosage level) recorded in Drug Accountability form.
- PK Set (PKS): all subjects who are randomized and received COVID-HIGIV according to the protocol, had adequate data for calculation of PK parameters, and had no protocol deviations that would affect PK assessment.

5.3 Analysis Groups

Safety evaluations will be based on Safety Set, subjects will be grouped by the study treatment they received (dispensed IP and dose level). PK evaluation will be based on PK Set; subjects who receive placebo only will be excluded.

5.4 Analysis Time Points

Study visits occur on protocol-specified days are associated with visit windows (see details in Appendix I: Schedules of Events). For purposes of data analysis, if the study day of assessment falls within the visit window, the corresponding analysis visit will be assigned as specified as following:

- Screening: 7 days prior to randomization.
- Day 1 - Randomization (the randomization day is defined as Day 1 of the study)
- Day 1 - Dosing (dosing is scheduled on the same day as randomization):
    - PK sampling nominal timepoints on Day 1:

      Pre-dose: 0-4 hours

      Post-dose: 1, 2, 4, 8, 12 hours
    - Vital Signs nominal timepoints on Day 1:

Pre-dose: 0-2 hours

Post-dosing: 30 and 60 minutes.

- Day 2 (discharge): 24 hr after end of IV infusion on Day 1
- Day 4 (3 days post-dose), Day 8 (7 days post-dose), Day 15 (14 days post-dose), Day 22 (21 days post-dose), Day 29 (28 days post-dose), 43 (42 days post-dose), and 57 (56 days post-dose)
- Day 85 (84 days post-dose, end of study) / Early Withdrawal

For all analyses, pre-dose is defined as prior to the start of infusion. Post-dose timepoints in unit of hour are defined as post the infusion stop time; unless otherwise specified; the post-dose timepoints in unit of day are defined as post the day of infusion, which starts and ends on the same day in this study.

Data at unscheduled visits/timepoints that do not fall into a scheduled visit or nominal timepoint window will not be presented in the summary analyses by visit/timepoint but will be included in the summary tables by maximum toxicity grade or abnormality when applicable, and in data listings.

5.5 Definition of Baseline

For all analyses, the baseline value for each measure is defined as the last non-missing value prior to the dosing of any study treatment (COVID-HIGIV or placebo).

5.6 Multiple Records in an Analysis Window

For clinical laboratory data, vital signs, and physical examinations, if multiple valid non-missing observations exist in an analysis window for a specific visit, a single value will be chosen in the by-visit summary analyses based on the following rules:

- if the analysis values are pre-dosing, the latest pre-dose value will be selected as baseline;
- if the analysis values are numeric and the toxicity grades are available, the record with the highest toxicity grade will be selected;
- if the analysis values are numeric and the toxicity grades are identical or not available, the last (newest) value will be used;
- if the analysis values are categorical, the most conservative value will be selected (e.g., abnormal will be selected over normal).

5.7 Coding Dictionaries

Medical history (including procedure history) and adverse events will be coded to system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 23.0.

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Prior and concomitant medications will be coded to up to ATC Level 4 using WHO-DD version 2020-09-01.

5.8 Toxicity and Severity Grading

The toxicity and severity grading scales used for adverse events and clinical laboratory assessment in this study are provided in Appendix II. Severity grading scales used for vital signs in this study are provided in Appendix III.

Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Potentially life-threatening. Event causes death will be assigned as Grade 5. Grade 0 is used to represent "normal" or "symptom not present".

The severity of AEs, vital signs will be assessed by the principal investigator (PI) or the designee. For symptoms not appearing on the grading scale, the grading for generic "illness or clinical AE" will be used. Clinical laboratory results will be graded by the laboratory for analytes appearing in Section 9.4, reviewed by the PI or the designee.

COVID-19 symptoms will be graded by Severity (Appendix IV) and Modified WHO Ordinal Scale (Appendix V).

6 STATISTICAL CONSIDERATIONS

6.1 General Considerations

Data summaries will be tabulated by appropriate grouping for each analysis population as specified in Section 5.3.

Continuous endpoints will be summarized by descriptive statistics including number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum. When log-normal distribution is appropriate, logarithm transformation will be used and geometric mean (Geo. Mean) and geometric coefficient of variation as a percentage (Geo. CV%) will be reported. Categorical variables will be summarized by counts (n) and percentages of subjects (%) in each category, including missing or unknown when appropriate.

Unless otherwise specified, confidence intervals (CIs) are two-sided at 95% confidence level.

All derivations, statistical analyses, summaries, and listings will be generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, United States).

6.2 Units and Precision

All clinical laboratory data and vital sign data will be reported using US convention units. Measures with non-standard units include:

- Anti-SARS-COV-2 IgG Binding Titer: AU/mL, binding antibody titers normalized to reference standard (Appendix VI).

- Anti-SARS-COV-2 Pseudo-virus Neutralizing Antibody Titer: AU/mL, neutralizing antibody titers normalized to reference standard (Appendix VI).
- All PK concentrations will be reported in listings and analyzed with the same precision (with 1 decimal place) as the source data provided by the bio-analytical laboratory, unless otherwise specified. For derived PK parameters, the following convention will be used:
- Elapsed time from dosing will be expressed as hours or days in the calculations and rounded to two decimal places.
- Parameters derived directly from source data (e.g., Cmax, Tmax, minimum, maximum) or first-order statistics (e.g., mean) will be reported and analyzed with the same precision as the source data.
- Second-order statistics (e.g., SD) will be reported with one more significant digit than the source data.
- Percentages (including Geo. CV%) will be reported to one decimal place.
- Ratios of means for PK parameters will be presented with two decimal places.

6.3 Derived Variables

This section provides definitions of the derived variables. In some cases, the definitions are provided in the relevant sections.

Study Day 1 (SD1) is defined as the day of randomization. The day prior to Study Day 1 is Day -1. There is no Day 0.

Study day relative to SD1 will be calculated as:

Study Day = (assessment date – date of SD1 + 1) if the assessment is on or after SD1.

Study Day = (assessment date – date of SD1) if the assessment is before SD1.

Duration between event A and event B = (date/time of event B – date/time of event A).

For conversion of duration, 1 year = 365.25 days, 1 month = 365.25/12 = 30.4375 days.

6.4 Statistical Hypotheses

Not applicable because no formal hypothesis is tested in this study.

6.5 Handling of Missing Data and Other Data Issues

This section describes the handling of missing data, and other data issues. Note that the handling of data issues for PK data is described in Section 8.5.4.

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6.5.1 Missing Dates

For missing or partial dates for AE, medical history (or prior diagnosis), prior and concomitant medications and procedures, the following conventions will be used for the purpose of determining whether the AE is treatment emergent AE (TEAE), whether the medication/procedure is concomitant or not. Original values will be provided in the listings as is, without imputation.

- For start date missing completely or missing the year, impute the date to the date of first exposure to any study treatment.
- For start date missing both the month and the day, if the year is the same as the date of first exposure to any study treatment, impute the date to the date of first exposure to any study treatment, otherwise, impute the date to January 1st.
- For start date missing the day only, if the year and the month are the same as the date of first exposure to any study treatment, impute the date to the date of first exposure to any study treatment, otherwise, impute the date to the first of the month.
- For end date missing completely or missing the year, impute the date to the date of last contact.
- For end date missing both the month and the day, if the year is the same as the date of last contact, impute the date to the date of last contact, otherwise, impute the date to December 31st.
- For end date missing the day only, if the year and the month are the same as the date of last contact, impute the date to the date of last contact, otherwise, impute the date to the last day of the month.

Note that when the dates are parts of an outcome measure (e.g., the date of death, date of hospital discharge), the imputation rules in this section do not apply. Instead, imputation rules if any, should be described in the next section.

6.5.2 Missing Outcomes and Covariates

Subjects with missing numeric data are treated as missing completely at random (MCAR) when calculating summary statistics.

6.5.3 Non-Quantifiable Laboratory Data

For laboratory data, unless otherwise specified in laboratory manuals or assay protocols, values below LLOQ (Lower Limit of Quantification) will be substituted with LLOQ/2; and values above the upper limit of quantification (ULOQ) will be substituted with ULOQ in the calculation of summary statistics; When values reported as “>xx” or “<xx”, xx will be considered as ULOQ or LLOQ, respectively. Original values as collected will be provided in the listings, unless otherwise specified.

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6.6 Adjustment for Covariates

Not applicable because no formal hypothesis is tested in this study.

6.7 Multicenter Study

This study is planned to be conducted at one site - Mount Sinai Hospital at New York of the United States.

6.8 Subgroup Analysis

No subgroup analyses are planned.

6.9 Multiplicity Adjustment

Not applicable because no formal hypothesis is tested in this study.

7 STUDY POPULATION CHARACTERISTICS

7.1 Subject Disposition

Subject disposition over the course of the study will be summarized for all subjects who signed and dated the informed consent form (ICF). Tabulations will include the number of subjects screened, randomized, treated, completed or discontinued study treatment, completed or withdrawn/terminated from protocol-specified follow-up period.

The number and percentage of participants will be summarized by study arms and overall for all randomized subjects. The reasons for study treatment discontinuation or study withdrawal/termination will be summarized by analysis group based on Safety Set.

Disposition data will be listed by subject, incomplete study treatment and/or incomplete study due to COVID-19 pandemic will be indicated. A CONSORT flow diagram will be provided in CSR.

7.2 Protocol Deviations

Important protocol deviations will be summarized by category/sub-category. A listing of all protocol deviations will be provided for all subjects who signed the informed consent form. Protocol deviation due to COVID-19 pandemic will be assessed and indicated in the listing.

8 EFFICACY ANALYSIS

8.1 Data Sets Analyzed

A summary of subjects included in each analysis set will be provided. Detailed listings will be provided for each subject that was excluded from each analysis set, including the reasons for exclusion.

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8.2 Demographics and Baseline Characteristics

8.2.1 Demographics

The following demographics and baseline characteristics will be summarized as continuous variables using descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment group for all subjects in the Safety set:

- Age (years)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI

The following demographics and baseline characteristics will be summarized as categorical variables with counts and percentages by treatment group and overall for Safety set:

- Sex (Female, Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiracial, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

Subject demographics and baseline characteristics data listing will be provided.

8.2.2 Medical History

Medical history will be coded to system organ class (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs reported from the signing of the ICF until immediately before the first dose of IP on Day 1, will be in generally recorded as Medical History, unless it is study procedure associated, which may be considered as non-treatment-emergent AE. A listing of medical history will be provided.

8.2.3 Prior Medications

Prior medication, concomitant medications will be coded using WHO-Drug. The number and percentages of subjects taking each drug, by ATC level 4 and preferred terms will be summarized by treatment group.

8.3 Treatment Compliance

Subjects with incomplete study treatment (i.e., partial infusion) or infusion interruption will be summarized by reason for incompletion and by analysis group for Safety set.

Study drug administration data, such as infusion volume (saline for placebo arm, COVID-HIGIV for other arms), and overall infusion duration will be summarized by analysis group as well.

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A subject listing of study drug administration will be provided including infusion start/end date and time, pharmacist prepared, and subject received infusion volume, infusion duration, and if any infusion interruption the reason(s).

8.4 Efficacy Analysis

There are no efficacy endpoints and efficacy analyses in this study.

8.5 Pharmacokinetic Evaluation

8.5.1 Serum Concentration Data

Serum concentration of SARS-CoV-2 antibody is measured by two assays:

- Binding IgG Immunoassay
- Pseudovirus Neutralization Assay

The assays have been validated for PK assessments, with a lower limit of quantitation (LLOQ) value of and the upper limit of quantitation (ULOQ) value of for the binding immunoassay; and LLOQ of and ULOQ of for pseudovirus neutralization assay.

Subjects with incomplete data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

A listing of PK sample collection times will be provided, with flags to indicate sampling time deviations.

8.5.2 Pre-Dose Concentration Values and Endogenous Compounds

The anti-SARS-CoV-2 IgG is not expected in study participants because a negative rapid anti-SARS-CoV-2 IgG/IgM antibody test result is required for inclusion. A pre-dose serum sample for SARS-CoV-2 antibody was drawn on Day 1. Any anomalous concentration values observed prior to the first dose will be identified and may be excluded from PK analysis or statistical summaries. If necessary (e.g., anomalous pre-dose concentration detected in multiple subjects), background subtraction will be applied before the concentration values are used in PK analysis or statistical summaries.

8.5.3 Exclusion of Outliers

Individual serum concentrations may be excluded from the analysis because they are erroneous or abnormal at the discretion of the study team following a review of available documentation (e.g., bioanalytical report, validation report). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire serum concentration-time profiles for a participant may be excluded following review of available documentation (e.g., bioanalytical report, validation report, and protocol

deviation log) as determined by the study team. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Any excluded data will be flagged in the individual data listings.

8.5.4 Non-Quantifiable and Missing Concentrations

If a concentration value is below the LLOQ,

- Individual concentration listings in the CSR should list these concentrations as "<LLOQ".
- For the calculation of concentration summaries and plotting mean and individual concentration-time profiles, concentration values <LLOQ are imputed with LLOQ/2.

For the purpose of calculating PK parameters,

- Missing pre-dose values, pre-dose concentrations and concentrations prior to the first quantifiable concentration that are <LLOQ are set to 0 (zero) and included in the analysis.
- A value of <LLOQ after C_{max} that is between two quantifiable data points or after the last quantifiable concentration value at the end of the collection interval will be treated as missing and excluded from the analysis.

If a concentration value is ">ULOQ", the ULOQ threshold will be imputed for PK parameter estimate and descriptive statistics calculation. Individual concentration listings in CSR will report the concentration as ">ULOQ".

Missing concentration values are left as missing and excluded from the analysis.

8.5.5 PK Parameters

PK parameters in Table 2 will be derived from the concentration-time data by non-compartmental methods using actual sampling times. If the actual sampling time is missing, but a valid concentration value has been measured, the nominal time as specified in the protocol may be used.

Non-compartmental PK parameter calculations and graphics will be implemented using SAS version 9.4 or higher.

Table 2: PK Parameters for COVID-HIGIV

Parameter	Definition and Calculation
C_{max}	Maximum observed serum concentration after a single dose (. If there are missing data near the expected C_{max}, it may be set to missing after team review.
C_{max}BWN	Body weight normalized C_{max}

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T_{max}	Time of maximum observed serum concentration, if C_{max} exists.
C_{min28d}	Minimum observed or estimated serum concentration on the day of 28 days post-dose after a single dose.
C_{min28d}BWN	Body weight normalized Cmin28d
λ_z	Apparent first order terminal elimination rate constant. It is calculated by linear regression analysis of log concentration values that include consecutive data points in the terminal phase (i.e., including the last quantifiable value, preferably not include C_{max}) that maximizes the adjusted r^2. A minimal of 3 data points is required for determination. If the maximum adjusted r^2 is < 0.700, it is considered as not estimable and the λ_z will be listed but not included in statistical analyses.
$T_{1/2}$	Terminal elimination half-life, or just referred to as half-life. It is calculated as $((\ln 2)/\lambda_z)$, when λ_z can be estimated.
$AUC_{0\text{-}14d}$	Area under the serum concentration-time curve (AUC) from time 0 to 14 days. Time 0 is defined as the end time of IP administration of a single dose. AUC is calculated using linear-up log-down trapezoidal summation. A minimal of 3 non-LLOQ concentration values is required.
$AUC_{0\text{-}14d}$BWN	Body weight normalized $AUC_{0\text{-}14d}$
$AUC_{0\text{-}28d}$	AUC from time 0 to 28 days.
$AUC_{0\text{-}28d}$BWN	Body weight normalized $AUC_{0\text{-}28d}$
$AUC_{0\text{-}last}$	AUC from time 0 to the last quantifiable concentration after a single dose. A minimal of 3 non-LLOQ concentration values is required.
$AUC_{0\text{-}last}$BWN	Body weight normalized $AUC_{0\text{-}last}$
$AUC_{0\text{-}inf}$	AUC extrapolated to infinity after a single dose. It is calculated as $AUC_{0\text{-}last}$ plus the additional area extrapolated to infinity using the linear regression line for the calculate of λ_z. If λ_z cannot be estimated $AUC_{0\text{-}\infty}$ will not be calculated. If the percentage of extrapolated area exceeds 40% of the estimated $AUC_{0\text{-}\infty}$, the $AUC_{0\text{-}\infty}$ value will be listed but not included in statistical analyses.
$AUC_{0\text{-}inf}$BWN	Body weight normalized $AUC_{0\text{-}inf}$
CL	Apparent systemic clearance. It is calculated as (Dose / $AUC_{0\text{-}inf}$). Note that the dose needs be measured by the same PK assay and expressed in the same unit.
V_z	Apparent volume of distribution (during the terminal phase). It is calculated as (CL / λ_z).

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8.5.6 Pharmacokinetic Analysis

All PK summary analyses will be conducted based on the PKS. Listings of PK concentration will be presented based on the COVID-HIGIV treated subjects with a flag indicating data points excluded from the PK analyses. Listings of PK parameters will be based on COVID-HIGIV treated subjects, with an indicator for parameter(s) considered as unreliable and being excluded from the summary analysis. A listing for the excluded subjects will be provided with reasons for exclusion.

PK concentration data will be summarized by nominal time points. The summary statistics for concentration data include n, arithmetic mean (Mean), standard deviation (SD), median, minimum (Min), maximum (Max), geometric means (Geo. Mean), and geometric percentage coefficient of variation (Geo. CV%).

PK parameters in Table 2 will also be summarized with the descriptive statistics list above. Summary of T_{max} will include n, median, minimum, and maximum only. The Geo. CV% is calculated as,

Geo. CV%(x) = 100*(sqrt (exp (variance of log(x)) - 1)), x = PK concentrations

Scatterplots for individual PK concentration-time profiles will be presented.

To investigate the dose proportionality of body weight normalized $AUC_{0\text{-}14d}$ and Cmax (if data permit), the power model will be used which fits a linear regression model with the log PK parameter against the log dose (COVID-HIGIV dose in mg/kg unit), i.e.,

$$\log(\text{PK parameter}) = \text{intercept} + \text{slope}*\log(\text{COVID-HIGIV dose})$$

Estimates of the intercepts and slopes along with 90% CIs will be reported. If the assumption of linearity is considered acceptable (i.e., adjusted $r^2 > 0.8$) and if the 90% CI for the slope is entirely with (0.9, 1.1), the relationship between dose and the PK parameter will be concluded to be dose proportional for the dose range studied.

8.6 Other Exploratory Analysis

There is no exploratory endpoint in this study.

9 SAFETY ANALYSIS

9.1 Extent of Exposure

Treatment exposure measured by COVID-HIGIV volume (mL), body weight normalized volume (mL/kg) and dose (mg/kg), potency (AU) and body weight normalized potency (AU/kg) will be summarized for all subjects treated with COVID-HIGIV by analysis group.

Subject listings of treatment exposure and drug administration will be provided.

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9.2 Adverse Events

AEs will be coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA).

AEs reported from the signing of the ICF until immediately before the first dose of IP on Day 1, will be in generally recorded as Medical History, unless it is study procedure associated, which may be considered as non-treatment-emergent AE. A treatment emergent adverse event (TEAE) is defined as an AE that was not present prior to administration of the first dose of study medication and any study procedures and present after the first dose or procedure, or if it represents the exacerbation of an event that was present prior to the first dose or procedure.

Only TEAEs will be included in the summaries described below and 'AE' will refer to TEAE, unless otherwise specified. For AE summaries, an AE occurs on the first dosing date but without onset time will be counted as treatment emergent. AEs with missing start dates, but with stop dates overlapping into the treatment period will also be counted as treatment emergent.

A subject data listing of all AEs (including treatment-emergent AEs (TEAEs) and non-TEAEs) sorted by analysis group, subject ID and AE start date/time will be provided.

9.2.1 Overall Summary of AEs

The following list of AEs summaries will be provided by SOC and PT in tabulate format. The events will be sorted in descending frequency of subjects in the 'Total" column for SOC, then PT, unless otherwise specified.

- All AEs
- All AEs occur within 72 hours post-dosing (from the start of infusion to 72 hours post the end of infusion)
- All AEs by maximum severity
- AEs related to study treatment (COVID-HIGIV or placebo)
- AEs of Grade 3 and higher severity
- AEs of Grade 3 and higher severity and related to study treatment
- AEs by analysis group sorted by PT in descending frequency among all COVID-HIGIV treated subjects AE Severity

The Investigator is responsible for the assessment of the severity of an AE using the following criteria:

- Mild (Grade 1): awareness of a sign or symptom but subject can tolerate.
- Moderate (Grade 2): discomfort enough to cause interference with normal daily activity.
- Severe (Grade 3): resulting in an inability to do work or do usual daily activity.

- Potentially Life-Threatening (Grade 4): emergency room visit or hospitalization.
- Death (Grade 5)

Subjects having the same AE more than once will be counted once for each PT and once within each SOC at the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used.

9.2.2 AEs Related to Study Treatment

Relationship of AEs to the study treatment will be assessed by the PI or designee, and reviewed by the Sponsor, using terms and scales "Unrelated", "Possibly related", "Probably related", and "Definitely related". If the relationship between the AE and the study treatment is determined to be "Possibly" or "Probably" or "Definitely" related, the event will be considered as related to the study treatment.

9.3 Deaths, Other Serious Adverse Events and Significant Adverse Events

9.3.1 Deaths

Deaths is not expected in this study with healthy participants. A subject listing of deaths (if any) will be provided as appropriate, including the primary causes of death.

9.3.2 Serious Adverse Events (SAEs)

An SAE is an AE that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

- All SAEs will be tabulated by SOC and PT.
- All SAEs related to study treatment will be summarized by SOC, PT, and severity.

A subject data listing of all SAEs will be provided.

9.3.3 TEAEs Leading to Study Treatment Discontinuation and/or Study Withdrawal

AEs leading to discontinuation or infusion interruption will be summarized by study arm and listed by subject.

9.4 Clinical Laboratory Tests

9.4.1 Safety Laboratory Tests

Clinical safety laboratory assessment includes the following –

- Chemistry panel: sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate ($HCO3^-$), blood urea nitrogen (BUN), creatinine, glucose, total and direct bilirubin, alanine

aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH),

- Hematology panel: complete blood count (CBC); i.e., red blood cells, white blood cells, platelets, hemoglobin, and hematocrit, with differential (neutrophils, eosinophils, basophils, monocytes and lymphocytes).
- Urinalysis: PH, specific gravity, urobilinogen, blood, bilirubin, color, glucose, ketone, leukocyte esterase, nitrite, protein.

Numeric laboratory results and change from baseline will be summarized by analysis group at scheduled visits only.

The abnormality of the laboratory results (Low, Normal, High) will be assessed according to normal ranges. The clinical significance of abnormality will be assessed by PI. 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 II).

Values not meeting criteria for toxicity of at least grade 1 will be considered as grade 0. If laboratory tests with toxicity criteria for both increased and decreased directions exist (e.g., Sodium), toxicity grades for each direction will be presented separately (e.g., Sodium Increased versus Sodium Decreased).

For selected laboratory parameters, shift of abnormality (Low, Normal, High) and toxicity grade from baseline to the maximum/minimum post-dosing results will be tabulated with counts and percentages by analysis group and timepoint.

The qualitative results of urinalyses will be summarized by analysis group at scheduled visits. Count and percentage of subjects of each result category will be presented.

All laboratory records will be provided in the subject data listings, with applicable toxicity grades or abnormal flags displayed. A separate listing will be provided for post-baseline laboratory results at Grade 1 or higher.

9.5 Vital signs, Physical Findings and Other Variables Related to Safety

9.5.1 Vital Signs

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

Vital sign results will be assessed and assigned a severity grade 1 to 4 (see Appendix III). Grade 0 includes all values not meeting criteria for severity of at least Grade 1. If vital signs with toxicity criteria for both increased and decreased directions exist (e.g., Blood pressure), analyses for each direction will be presented separately (e.g., Hypertension versus Hypotension).

Shift of abnormality (Normal, Abnormal) and severity grade from baseline to 30 minutes and 1 hour post-dosing (post the end of infusion) results will be summarized by treatment group.

All vital sign records will be provided in the subject data listings.

9.5.2 Physical Examinations

Complete and targeted PE findings will be tabulated by body system, and analysis group. Listings will be provided.

9.5.3 Concomitant Medication

Concomitant medications will be coded using the WHO Drug Dictionary ATC level 4 and displayed by treatment group for the safety population. Concomitant medications for COVID-19 treatment will be summarized separately.

9.6 COVID-19 Symptoms (if applicable)

For subjects that become SARS-CoV-2 RT-PCT positive during the study period (at any time post-dosing on Day 1 and up to last visit/contact), a list of pre-specified COVID-19 symptoms will be assessed, which include fever, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea/vomiting, and diarrhea.

The frequencies and percentages of subjects reporting COVID-19 symptoms will be presented by analysis group for the Safety population. The following summaries of COVID-19 symptoms will be performed:

- COVID-19 symptoms any time during study, for each symptom and for any symptoms.
- COVID-19 symptoms by maximum severity (Appendix IV), for each symptom and for any symptoms.

9.7 Clinical Status based on Modified WHO Ordinal Scale (if applicable)

For subjects that become SARS-CoV-2 RT-PCT positive during the study period (at any time post-dosing on Day 1 and up to last follow-up visit/contact) Modified WHO Ordinal Scale will be collected. Maximum score on the modified WHO ordinal scale (Appendix V) will be summarized and presented in a subject listing.

10 DATA MONITORING AND INTERIM ANALYSIS

10.1 Safety Monitoring Committee

An independent Safety Monitoring Committee (SMC) (also referred to as Data Safety and Monitoring Board, DSMB) will perform review of the safety data after the first seven subjects have completed at least 72 hours of follow-up. The SMC will also provide on-going

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review of safety data during the study as specified in the DSMB Charter (*Version 1.0, 20Jan2021*).

10.2 Interim Analysis

No interim analysis is planned for this study.

Final analysis for clinical study report (CSR) will be conducted after all subjects finishing the study and the database being locked and unblinded.

11 REFERENCES

1. Agresti, A. (1992), A Survey of Exact Inference for Contingency Tables, Statistical Science, 7:131–177.
2. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, and Bottomley A on behalf of the EORTC Quality of Life Group. (2001) The EORTC QLQ-C30 Scoring Manual (3rd Edition). European Organisation for Research and Treatment of Cancer, Brussels.
3. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Intern Med 2001;134:657-62.
4. Emergent SOP003107: Production and Control of Statistical Analysis Plan (SAP) and SAP Amendments. Version 5.0, effective on 15 May 2020.
5. Emergent SOP041684: Statistical Oversight of Clinical Studies. Version 4.0, effective on 15 May 2020.
6. Emergent SOP002988: Database Lock. Version 5.0, effective on 18 Jun 2020.
7. Blank Case Report Form (CRF v1.0, 22Dec2020)
8. DSMB Charter (v1.0, 20Jan2021)
9. Data Management Plan (DMP v1.0, 30Nov2020)
10. Pharmacy Manual (v1.0, 03Dec2020)
11. Lab Manual (v1.0, 15Dec2020)
12. Blind Maintenance Plan (BMP v1.0, 15Jan2021)
13. Protocol Deviation Management Plan (PDMP v2.0, 19May2021)
14. Analytical Testing Plan EBCIGCLP-2101 (PLN041045 v3.0, 13Sep2021)

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APPENDIX I SCHEDULE OF EVENTS

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

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

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APPENDIX II GRADING OF ADVERSE EVENTS/LABORATORY TESTS

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

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APPENDIX III GRADING OF VITAL SIGNS

Grading Scale*	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (potentially life-threatening)**
Temperature (C°) (F°)	 38.0-38.4 100.4-101.1	 38.5-38.9 101.2-102.0	 39.0-40.0 102.1-104	 >40.0 >104
Tachycardia (beats/min)	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia (beats/min)	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Hypertension systolic (mmHg)	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension diastolic (mmHg)	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension systolic (mmHg)	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths/min)	17-20	21-25	>25	Intubation
SPO_2 (%)	92 - <95	90 - <92	85 - <90	<85 or ER visit or hospitalization for hypoxia
* Taken from Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials {CBER, 2007}, except SPO_2.				

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APPENDIX IV GRADING OF COVID-19 SYMPTOMS

COVID-19 Related Symptom	Response Options (Scoring/Grade)
For items 1-9, what was the severity of your symptom at its worst over the last 24 hours?	
Stuffy or runny nose	None (0) Mild = defined as no interference with daily activity (1) Moderate = Interference with activity (2) Severe= prevents daily activity (3) Serious = life threatening or requires hospitalization (4)
Sore throat	
Shortness of breath (difficulty breathing)	
Cough	
Low energy or tiredness	
Muscle or body aches	
Headache	
Chills or shivering	
Nausea (feeling like you wanted to throw up)	
Fever	None= (0) Mild =100.4-102°F (1) Moderate 102.1 -104°F (2) Severe >104°F (3)
How many times did you vomit (throw up) in the last 24 hours	I did not vomit at all (0) 1- 2 times (1) 3-4 times (2) 5 or more times (3) Life threatening/requires hospitalization (4)
How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	I did not have diarrhea at all (0) 1=2 times (1) 3-4 times (2) 5 or more times (3) Life threatening/requires hospitalization (4)
Rate your sense of smell in the last 24 hours	My sense of smell is the SAME as usual (0) My sense of smell is LESS than usual (1) I have NO sense of smell (2)
Rate your sense of taste in the last 24 hours	My sense of taste is the SAME as usual (0) My sense of taste is LESS than usual (1) I have NO sense of taste (2)

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APPENDIX V MODIFIED WHO ORDINAL SCALES FOR COVID-19

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

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APPENDIX VI INVESTIGATIONAL PRODUCT (IP) INFORMATION

The active IP for this study is COVID-HIGIV, a sterile liquid preparation of purified human immunoglobulin (IgG) fraction containing SARS-CoV-2 antibodies, with total protein of 104 mg/mL. The Lot Number is . The anti-SARS-CoV-2 potency of COVID-HIGIV was tested by two assays, the corresponding potencies are:

- by Binding IgG Immunoassay
- by Pseudovirus Neutralization Assay

COVID-HIG was used as reference standard in the assays.

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APPENDIX VII SAP REVISION SUMMARY OF CHANGE

SAP Section	Prior Wording (Version x.x)	Amended Wording (Version x.x)	Rationale for Change
8.5.1	"The assays have been validated for PK assessments, with a lower limit of quantitation (LLOQ) value of and the upper limit of quantitation (ULOQ) value of for the binding immunoassay," (Version 1.0)	"The assays have been validated for PK assessments, with a lower limit of quantitation (LLOQ) value of and the upper limit of quantitation (ULOQ) value of for the binding immunoassay," (Version 1.1)	Per Analytical Testing Plan EBCIGCLP-2101 (PLN041045 v3.0, 13Sep2021), Section 10.2 Testing by the PK Binding IgG Method - *"The PK COVID-HIG Binding IgG test method (EBCIGCLP-2101.01) will be used to test select specimens.* ***The method was validated to quantify COVID-HIG IgG antibodies over the range of*** *Although, the method demonstrated acceptable accuracy and precision over the range of the specificity samples prepared in individual human serum at a concentration of did not meet the validation criteria, as only were within the %RE limit of (4). The specificity assessment passed at This observation is not critical to the PK testing in this plan, as the predicted Cmax value for the high dose level (400 mg/mL) with maximum dose volume (400 mL) is expected to be approximately Results achieved above and less than or equal to will be reported as a number but with the comment "For Information Only" (FIO) and that it is greater than the ULOQ for the method. Results greater than will be reported as >ULOQ. The Clinical Scientist may exclude FIO data during their analysis."*
References		Added the reference No. 14 in SAP	Analytical Testing Plan EBCIGCLP-2101 (PLN041045 v3.0, 13Sep2021) was added as the 14th reference for the change of ULOQ of binding immunoassay mentioned above.

Document Approvals
Approved Date: 08 Dec 2021

Approval Task Verdict: Approve	07-Dec-2021 19:55:05 GMT+0000

Approval Task Verdict: Approve	07-Dec-2021 19:58:56 GMT+0000

Approval Task Verdict: Approve	07-Dec-2021 22:56:20 GMT+0000

Approval Task Verdict: Approve	08-Dec-2021 15:29:00 GMT+0000