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Statistical Analysis Plan

Product Name
Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) (NP-028), abbreviated as COVID-HIG

Protocol EBS-CVH-006
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

Protocol Version	**Date**
Original Protocol	12/OCT/2021
Amendment 2.0	23/NOV/2021
Amendment 3.0	18/FEB/2022

SAP Version	**Date**
1.0 (Final)	11 May 2022

SAP Signature Page

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

	Director, Biostatistics	*See Veeva*	*See Veeva*
Name	Position	Signature	DD/MMM/YYYY
	Senior Director, Biostatistics and Data Science	*See Veeva*	*See Veeva*
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Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) (NP-028), abbreviated as COVID-HIG
EBS-CVH-006 Statistical Analysis Plan

Change History Table

Version	Summary of Major Change(s) and Impact	Revision Date
Version 1.0	First approved version of SAP.	*See title page*

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List of Abbreviations and Definitions

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AU	Alliance Units
AUC	Area Under the Curve
AUC_{0-t}	AUC from time of dosing to time t (AUCT1T2)
AUC_{0-last}	AUC from time of dosing to last measurable concentration (AUCLAST)
$AUC_{0-\infty}$	AUC extrapolated to infinity from time of dosing, based on the last observed concentration (AUCINFO)
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
Cl^-	Chloride
C_{last}	Last measurable concentration (above the LLOQ) (CLAST)
C_{max}	Maximum Concentration (CMAX)
COVID-19	Coronavirus Disease 2019
COVID-HIG	Anti-SARS-CoV-2 Immunoglobulin Injection (Human)
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
%CV	Coefficient of Variation, Percentage
DAIDS	Division of Acquired Immunodeficiency Syndrome (AIDS)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
h	Hour(s)
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCO_3	Bicarbonate
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G (gamma globulin)

IgM	Immunoglobulin M
IM	Intramuscular
IP	Investigational Product
ITT	Intent-to-Treat
IV	Intravenous
K^+	Potassium
λ_z	The first order terminal elimination rate constant (LAMZ), also referred to as λ, K_e or K_{el}
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantitation
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
Na^+	Sodium
NCA	Non-compartmental Analysis
NP	Nasopharyngeal
PI	Principal Investigator
PD	Protocol Deviation
PDMP	Protocol Deviations Management Plan
PK	Pharmacokinetics
PT	Preferred Term
RT-PCR	Reverse Transciptase Polymerase Chain Reaction
RTSM	Randomization and Trial Supply Management
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	System Organ Class
SpO_2	Oxygen Saturation (Pulse Oximetry)
$t_{1/2}$	Terminal elimination half-life (LAMZHL)
TFL	Tables, Figures, and Listings
T_{max}	Time of maximum observed concentration during a dosing interval (TMAX)
V_z	Volume of distribution (VZ)
ULOQ	Upper Limit of Quantitation
US	United States
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
WV	Withdrawal Visit

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol EBS-CVH-006 "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" (Version 3.0, 18/FEB/2022). 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, figures, and listings (TFL shells). Some further details on the calculation of derived variables are provided as programmer's notes in the TFL shells. The TFL shells serve only as a guide for programming the final TFLs. They are working documents and can be updated as needed.

2 PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objectives

The following primary objectives are evaluated:

- To evaluate safety of COVID-HIG administered intramuscularly (IM) or subcutaneously (SC) as a single dose
- To evaluate pharmacokinetics (PK) of COVID-HIG administered IM or SC as a single dose

2.1.2 Secondary Objectives

The following secondary objectives are evaluated:

- To compare PK of COVID-HIG IM to COVID-HIG intravenously (IV)
- To compare PK of COVID-HIG SC to COVID-HIG IV
- To compare PK of COVID-HIG SC to COVID-HIG IM

2.1.3 Exploratory Objective

The following exploratory objective are evaluated:

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

2.2 Study Design and Conduct

This was 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. Subjects that provided written informed consent and meet eligibility criteria were stratified based on their SARS-CoV-2 detectable antibody status (≥lower limit of quantitation [LLOQ], but ≤80 Alliance

units (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. Cohort 1 consisted of 12 subjects; Cohort 2 comprised up to 24 subjects. Approximately thirty-six participants were to be enrolled and assigned equally to one of three study arms to receive a single IM, SC, or IV dose of COVID-HIG, respectively (Table 1). However, the study was truncated at 23 total randomized subjects in Protocol Amendment 3.0 due to the impact of high circulating SARS-CoV-2 omicron cases.

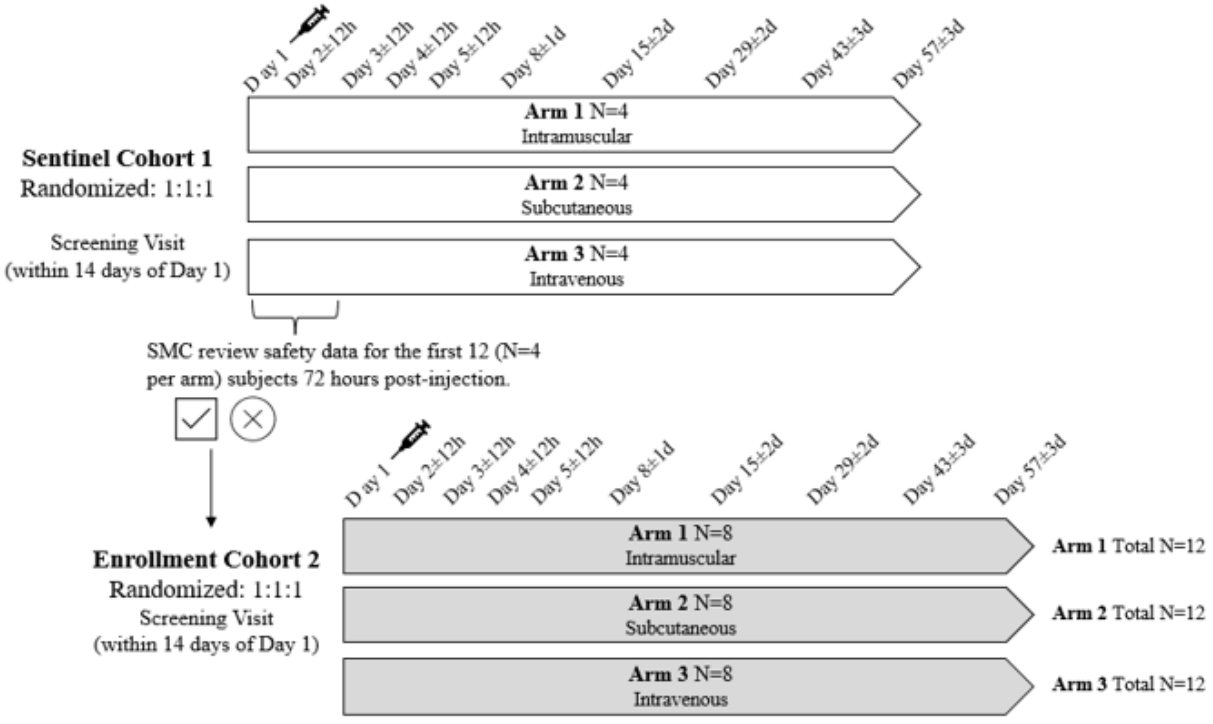
Table 1 Study Design

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 volume 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).

Enrollment into the study was staggered in Cohort 1, with no more than 5 participants dosed per day. Safety data were reviewed by a Safety Monitoring Committee (SMC; consisting of at least three independent external members) after all 12 participants in Cohort 1 completed at least 72 hours of safety follow-up. An overall decision by the SMC was made whether to proceed with full randomization (1:1:1) and dosing of the remaining study participants (Cohort 2, n=24).

Figure 1 Schematic of Study Design and Visits



Participants were admitted to the inpatient unit one day prior to dosing (Day -1), and following dosing on Day 1, each participant stayed overnight in the inpatient unit for close observation and PK sample collection. Each dosed participant was discharged from the inpatient unit once all assessments at 24 hours post-dosing timepoint (i.e., Day 2) were completed. Participants were to be followed for safety and PK up to 84 days post-dosing (Day 85) via in-clinic or at-home visits; however, the length of the study was shortened to 56 days (Day 57) in Protocol Amendment 3.0.

Study enrollment and administration of study treatments was to have been paused by the Principal Investigator (PI) or medical monitor for safety review if any of the following occurred after study product administration and during the enrollment period:

- One or more serious adverse events (SAE)
- Three or more of the same adverse event (AE) classified as Grade 3 severity
- Three or more hypersensitivity AEs classified as Grade 2

AE severity is graded according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) Severity Grading Scale per protocol Appendix I I (DAIDS, 2017).

If any participants became positive for SARS-CoV-2 during the study follow-up period, they were to be assessed using an Ordinal Outcome Scale (see protocol Appendix II) until they completed their last follow-up visit via telemedicine. Participants who tested positive for SARS-CoV-2 were excluded from PK analysis time points occurring after their positive test. For details of Schedule of Events, refer to Table 2.

2.3 Randomization and Blinding

The study was randomized, but it was open label upon individual subject treatment group assignment.

2.3.1 Methods of Randomization

Cohorts 1 and 2 (n=12 and n=24 but truncated to n=11, respectively) were randomized separately to receive a single dose of COVID-HIG via IM, SC, or IV. Randomization was stratified by SARS-CoV-2 detectable antibody status (≥15, but ≤80 AU/mL on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay) and undetectable antibody (<15 AU/mL) at screening; subjects with antibody >80 AU/mL were excluded from the study as screen failures. The randomization was blocked in groups of 3 subjects assigned one each to the 3 treatment groups, so while the overall numbers of antibody-positive and antibody-negative subjects were not prespecified for Cohort 1, the site was instructed to complete all four blocks of three subjects. After enrollment of Cohort 1 was finished, enrollment caps were to be set for Cohort 2 to control the overall numbers of antibody-positive and antibody-negative subjects enrolled to be approximately equal; 18 or 21 antibody-positive subjects of 36 total subjects was permissible. Once randomized, subjects were not replaced even if not dosed.

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).

Separate blinded randomization lists were created for antibody-positive and antibody-negative subjects, and randomization assignment was performed by the Randomization and Trial Supply Management (RTSM) system vendor in the order the subjects were randomized in the applicable stratum. When the treatment group was assigned to a subject, then that subject's assignment was unblinded to the Sponsor and all study staff for dosing. The blinded randomization schedules were not available to the site prospectively.

2.3.2 Randomization Errors

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

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

Both misrandomizations and stratification errors are reported as protocol deviations (PD).

2.3.3 Blinding and Unblinding

The RTSM system vendor created the blinded randomization lists and administered the randomization assignments. All study staff were blinded to the randomization schedule until each subject was assigned a treatment group in the order randomized, then that subject's assignment was unblinded to the study staff for dosing. The study proceeded as an open-label study after randomization.

3 STUDY ENDPOINTS

3.1 Pharmacokinetic Endpoints

3.1.1 Primary Pharmacokinetic Endpoints

The following primary PK endpoints, based on PK sample test results of an immunobinding IgG assay and a pseudovirus neutralization assay, were to be evaluated in healthy adults. However, Protocol Amendment 3.0 removed the pseudovirus neutralization assay PK analysis due to low sensitivity of this assay, so only the immunobinding IgG assay PK endpoints were analyzed:

- $AUC_{0\text{-}inf}$: $AUC_{0\text{-}last}$ 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 Day 29 (28 days after dosing)

3.1.2 Secondary Pharmacokinetic Endpoints

The following additional COVID-HIG PK endpoints, based on PK sample test results by an immunobinding IgG assay and a pseudovirus neutralization assay, were to be calculated when data permit. However, Protocol Amendment 3.0 removed the pseudovirus neutralization assay PK analysis due to low sensitivity of this assay, so only the immunobinding IgG assay PK secondary endpoints were analyzed when data permitted:

- $AUC_{0\text{-}inf}$ 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
- λ_z: terminal elimination rate constant after dosing
- $T_{1/2}$: apparent terminal elimination half-life after dosing
- CL: systemic clearance after dosing
- V_Z: volume of distribution after dosing

3.2 Exploratory Efficacy Endpoint

Descriptive analyses of COVID-19 disease severity were assessed by an Ordinal Outcome Scale (see protocol Appendix II).

3.3 Safety Endpoints

The following safety endpoints were 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 (changed from to 84 days post-administration in Protocol Amendment 3.0)

4 POWER AND 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 in Phase 1 clinical studies with healthy adults, Emergent deemed the number of participants planned to receive study treatments in the study (N=36; n=12 per each treatment arm planned and N=23; n=7-8 per each treatment arm after study truncation in Protocol Amendment 3.0) sufficient to descriptively assess COVID-HIG safety and PK of a single dose in healthy adults.

5 DATA CONSIDERATIONS

5.1 Protocol Deviations

PDs were identified through monitoring and through programmatic and data checks. All identified subject-level PDs were entered in the sponsor's Clinical Trial Management System (CTMS) and classified by category, subcategory, and type (important/not important) per the Protocol Deviations Management Plan (PDMP) by the Sponsor study team. Important PDs (ICH E3, 1996) were defined as those that may significantly affect a subject's rights, safety, or well-being or impact the completeness, accuracy, and/or reliability of the study data.

PD categories for this study included: subject eligibility, investigational product administration, study visits, study procedures, laboratory assessments, safety monitoring, and noncompliance.

5.1.1 Important Protocol Deviations

Examples of important PDs include:

- Subjects who did not sign informed consent prior to study-specific procedures, including reconsent
- Subjects who were randomized but did not meet study eligibility criteria
- Subjects who received no investigational product, received the wrong treatment route or dose level, or had investigational product (IP) administered via an incorrect method
- Subjects who received a prohibited concomitant medication, such as but not limited to COVID-19 vaccination
- Subjects who missed visits or assessments pertaining to key study endpoints (i.e., PK sample collection)
- Other deviations from key study procedures such as incomplete safety follow-up for an SAE or pregnancy, etc.

Subjects who contracted COVID-19, making subsequent PK samples ineligible for analysis, were recorded as AEs and not PDs.

5.1.2 Reporting of Protocol Deviations

The number of subjects with important PDs is summarized by PD category and treatment group. PD listings by subject are provided in the clinical study report (CSR).

5.2 Analysis Populations

Analysis is based on the following study populations:

Intent-to-Treat (ITT) Population: All randomized participants. Subjects are analyzed according to the treatment arm to which they were randomized.

Safety Population: All participants who were randomized and received any amount of COVID-HIG IM, COVID-HIG SC, or COVID-HIG IV. Subjects are analyzed according to the treatment arm received. This population is used for all safety analysis.

PK Population: All participants who were randomized and received COVID-HIG IM, COVID-HIG SC, or COVID-HIG IV according to the protocol, have adequate data for calculation of PK parameters, and have no important PDs that would affect PK assessment (i.e., COVID-19 vaccination or COVID-19 infection, either of which result in all PK time points post-vaccination date or post-test date excluded from PK analysis). Subjects are analyzed according to the treatment arm received. This population is used for all PK analysis.

SARS-CoV-2 Positive Population: Any randomized participant (whether or not dosed with COVID-HIG) who tested positive for SARS-CoV-2 during the study period. Subjects are analyzed according to the treatment arm to which they were randomized. This population is used for the COVID-19 symptom severity exploratory endpoint.

5.3 Analysis Groups

Tables are displayed by treatment arm (IM, SC, IV) columns and overall, for selected tables only. Data for subjects in Cohorts 1 and 2 are combined for all analyses.

5.4 Analysis Time Points

For PK analyses, SARS-CoV-2 antibody levels were assessed at screening, Day 1 (baseline) predose and postdose (from end of infusion/injection) at 1 hr ±10 min, 2 hr ±15 min, 4 hr ±15 min, 8 hr ±30 min, and 12 hr ±30 min, Day 2 ±0.5 day, Day 3 ±0.5 day (excluding IV arm), Day 4 ±0.5 day, Day 6 ±0.5 day (excluding IV arm), Day 8 ±1 day, Day 15 ±2 day, Day 29 ±2 day, Day 43 ±3 day, and Day 57 ±3 day. Since PK analyses use actual and not nominal day and time, out of window data entered as study visit data (i.e., not an unscheduled visit) are included in the analysis. In general, all available data are included in the summaries according to the analysis set defined for a subject's inclusion.

Data collected at unscheduled visits are not presented in the by-visit summary analyses but are 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 IP dosing.

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 is chosen in the by-visit summary analyses based on the following rules:

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

5.7 Coding Dictionaries

Medical history and adverse events were coded to system organ class (SOC) and preferred term (PT), based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 23.1.

Prior and concomitant medications and procedures were coded according to the World Health Organization's (WHO) WHO-Drug Global Dictionary version Sep2021 to Anatomical Therapeutic Chemical (ATC) classification and preferred drug name.

5.8 Toxicity and Severity Grading

AE severity (Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Potentially Life-threatening) was graded according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) Severity Grading Scale per protocol Appendix I I (DAIDS, 2017). Note that AEs that result in death are classified as Grade 5.

Severity of abnormal vital signs was assessed by the Investigator or designee using the criteria in 11Appendix I. Clinical laboratory results were graded by the Investigator or designee. For symptoms not appearing on the grading scale, the grading for generic "illness or clinical AE" were used (see protocol Table 5). Grade 0 was used to represent "normal" or "symptom not present." Values within the normal range as well as out of range laboratory values not meeting criteria for severity of at least Grade 1 are considered Grade 0.

6 STATISTICAL CONSIDERATIONS

6.1 General Considerations

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

Continuous endpoints are summarized by descriptive statistics including number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables are summarized by frequency counts (n) and percentages of subjects (%) in each category, including missing or unknown when appropriate. Unless otherwise specified, confidence intervals (CIs) are two-sided with 95% confidence.

All derivations, statistical analyses, summaries, and listings are 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 are reported using standard international units. Measures with non-standard units include:

- Anti-SARS-CoV-2 immunobinding IgG assay titer: AU, binding antibody titer normalized to reference standard.

Safety variables (i.e., clinical laboratory values, vital signs) including derivations thereof are reported to the same precision as the source data. Anti-SARS-CoV-2 immunobinding IgG assay titers are reported with one decimal place or two significant digits (e.g., 0.032, 18.0).

All PK concentrations are reported in listings and analyzed with the same precision as the source data provided by the bioanalytical laboratory. For derived PK parameters, the following conventions are used:

- Elapsed time from dosing is expressed as hours in the calculations and rounded to two decimal places.
- Parameters derived directly from source data (e.g., C_{max}, t_{max}, minimum, maximum) or first-order statistics (e.g., mean) are reported and analyzed with the same precision as the source data.
- Second-order statistics (e.g., SD) are reported with one more significant digit than the source data.
- Percentages are reported to one decimal place.
- Ratios of means for PK parameters are presented with two decimal places.

6.3 Derived Variables

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

AE, causing discontinuation of study treatment, is defined as one with action taken of "Drug Withdrawn" on the AE eCRF.

AE, causing study discontinuation, is defined as a Yes response to the corresponding question on the AE eCRF.

AE, medically attended (MAAE), is defined as a Yes response to the corresponding question on the AE eCRF.

AE, related, is defined as one that is "possibly," "probably," or "definitely" related to IP per Investigator assessment on the eCRF. If the relationship is missing for one or more occurrences of an AE for a given subject, the closest relationship of the remaining occurrences of the AE for that subject is used; if the relationship is missing for the only occurrence of an AE for a given subject, then that event is excluded from summaries by relationship.

AE, resulting in death, is defined as a Fatal outcome response on the AE eCRF.

AE, serious, is defined as a Yes response to the corresponding question on the AE eCRF, based on the individual criteria that make an AE qualify as serious (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, or any event that may require medical or surgical intervention to prevent one of these outcomes).

AE, severity, was graded Grade 1 (mild) to Grade 5 (death) as described in Section 5.8. If the severity is missing for one or more occurrences of an AE for a given subject, the maximum severity of the remaining occurrences of the AE for that subject is used; if the severity is missing for the only occurrence of an AE for a given subject, then that event is excluded from summaries by severity.

AE, special interest. There were no AEs of special interest in this study.

AE, treatment emergent. AE collection began after screening. AEs occurring after a subject has given informed consent, but before dosing, are excluded from summaries unless the condition worsened during or after dosing. Only treatment-emergent AEs are summarized.

Age at screening visit is automatically calculated by EDC based on date of birth versus date of informed consent.

Age group is defined in this study as ages 18 to 35 and 36 to 59 years.

Analysis visits are defined in Section 5.4.

Analysis populations are defined in Section 5.2.

Baseline is defined in Section 5.5. Change from baseline is defined as (value at post-baseline assessment – value at baseline).

Baseline seronegative stratum is defined as subjects with undetectable SARS-CoV-2 antibody (<LLOQ) at screening on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay.

Baseline seropositive stratum is defined as subjects with detectable SARS-CoV-2 antibody (≥LLOQ, but ≤80 AU/mL) on the Diasorin LIAISON SARS-CoV-2 S1/S2 IgG antibody assay.

Note that, if a subject is randomized into a stratum and their antibody status is later corrected such that s/he should have been placed into the other stratum, the subject is analyzed according to the corrected stratum for PK analyses but as randomized for baseline and efficacy analyses.

Body mass index at screening visit is automatically calculated by EDC as a subject's weight in kg divided by height in m^2.

Cohort is defined as the cohort specified for the subject on the corresponding eCRF.

Completion of study for an individual subject is defined as completion of the Day 57 visit and any required safety follow-up (i.e., a disposition status of completed).

Completion of study medication treatment is defined by the answer to the eCRF question, "Did the infusion/injection progress as planned?"

Early withdrawal for an individual subject is defined as completion of the Withdrawal Visit (i.e., a disposition status other than completed).

Enrolled/randomized is defined as receipt of a randomization number assignment within the EDC system.

Medical history items entered on the medical history eCRF will be considered to predate the study regardless of onset date.

Medication, concomitant, is defined as one taken after start of IP administration on Day 1 (baseline) through the end of study. For analysis purposes, any medication which is ongoing or with a stop date that is on or after the start date of the dosing is categorized as a concomitant medication. Partial or missing concomitant medication start and/or end date are imputed according to Section 6.5.1.

Medication, prior, is defined as one with a stop date within 30 days prior to the screening visit (60 days for COVID-19 vaccination) through the start of IP administration on Day 1 (baseline).

Protocol deviations are defined by inclusion in the EDC protocol deviation module (subject-level only, not site-level), including monitor-identified deviations as well as EDC system-identified programmatic deviations. Protocol deviations are classified by category and type (important/not important).

Rounding of values is described in Section 6.2.

Study Day 1 is defined as the day of IP administration on Day 1 (baseline). The day prior to Day 1 is Day -1. There is no Day 0. If the subject was not treated, then the Day 1 (baseline) is defined as the day of randomization.

Study day relative to Day 1 is calculated as:

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

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

Summary statistics are described in Section 6.1.

Time duration (in days) between event A and event B is (date of event B – date of event A + 1). For conversion of durations, 1 year = 365.25 days and 1 month = 365.25/12 = 30.4375 days.

Treatment, actual, is defined as the treatment administered to the subject by the site (i.e., corresponding to the kit number used).

Treatment arm or group is defined as IM, SC, or IV administration route.

Treatment, randomized, is defined as the treatment assigned to the subject by the EDC (i.e., corresponding to the kit number assigned).

6.4 Statistical Hypotheses

No formal statistical hypotheses are tested in this Phase 1 study; all analyses are descriptive.

6.5 Handling of Missing Data and Other Data Issues

This section describes the handling of missing data, and other data issues. Please see Section 6.3 for assumptions for AEs with missing relatedness and/or severity. Note that the handling of data issues for PK data is described in Section 8.4.4.

Unless otherwise specified, no imputation is performed for missing data and complete data analyses are used whenever possible.

6.5.1 Missing or Partial Dates

For missing or partial dates for AEs, medical history (or prior diagnosis), and prior and concomitant medications, the following conventions are used for the purpose of determining whether the AE is treatment-emergent, duration since prior diagnosis of the disease, and whether the medication/therapy is concomitant or not. Original values are 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.

6.5.2 Missing Outcome and Covariates

Subjects are included in the analyses to the extent of their available data; missing PK and efficacy data are not imputed. See Section 5.4.

Subjects with missing categorical data are counted in missing or unknown categories when appropriate. Subjects with missing numeric data are treated as missing completely at random when calculating summary statistics. For likelihood-based analyses (e.g., regression), missing at random is assumed.

6.5.3 Non-quantifiable Laboratory Data

For laboratory data, unless otherwise specified in laboratory manuals or assay protocols, values below LLOQ are substituted with LLOQ/2 and values above the upper limit of quantitation (ULOQ) are substituted with ULOQ in the calculation of summary statistics. When values are reported as ">xx" or "<xx", xx is considered as ULOQ or LLOQ, respectively. Original values as collected are provided in the listings.

6.5.4 Implausible Patient Reported Outcomes

Not applicable.

6.6 Adjustment for Covariates

No covariate adjustment, including adjustment for baseline SARS-CoV-2 antibody status, is performed since all analyses are descriptive in nature.

6.7 Multicenter Study

This study enrolled 23 subjects at two sites in the United States; data for subjects from both sites are pooled for all analyses. Data for subjects in Cohorts 1 and 2 are combined for all analyses.

6.8 Subgroup Analysis

No formal subgroup analyses are planned for this Phase 1 study.

6.9 Multiplicity Adjustment

Because all analyses are descriptive, multiplicity adjustment is not applicable in this study.

7 STUDY POPULATION CHARACTERISTICS

7.1 Subject Disposition

Subject disposition over the course of the study is summarized by treatment arm for all ITT population (randomized) subjects. Tabulations include the number of subjects randomized, treated, completed study medication treatment (see definition in Section 6.3), completed study, or withdrawn/terminated from the study. The reasons for stud medication noncompletion and/or study withdrawal/termination are summarized. Reasons for screen failure are listed, if available.

7.2 Protocol Deviations

Important PDs defined in Section 5.1 are summarized by category, subcategory, and treatment arm for all ITT population (randomized) subjects. All protocol deviations are listed by subject.

8 PHARMACOKINETICS ANALYSIS

8.1 Data Sets Analyzed

The number and percentage of participants in each analysis population is summarized by treatment arm and overall for all randomized subjects. Reasons for exclusion from analysis populations are summarized and listed by subject.

8.2 Demographics and Baseline Characteristics

8.2.1 Demographics

The following demographic characteristics are summarized as continuous variables using descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment arm for the Safety and PK populations:

- Age (years)
- Screening weight, height, BMI

The following demographic characteristics are summarized as categorical variables by treatment arm for the Safety and PK populations:

- Study site
- Age group (see definition in Section 6.3)
- Sex, and for women, childbearing potential
- Race
- Ethnicity

A subject listing of demographics is provided.

8.2.2 Medical History

Medical history is coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). A summary table by treatment arm and a listing of medical history is provided for the Safety population.

8.2.3 Prior and Concomitant Medications

Prior medications and concomitant medications are defined in Section 6.3. Prior and concomitant data are tabulated together by ATC classification, preferred drug name, and treatment arm for the Safety population. In the tabulation, ATC levels and standardized drug names within each ATC level are sorted in descending order of percentage in the Total column. A subject data listing of all medications is provided.

8.3 Treatment Compliance

Treatment compliance is not applicable, as the study treatment is administered to the subjects in clinic.

8.4 Pharmacokinetic Analysis

8.4.1 Serum Concentration Data

Serum concentration of SARS-CoV-2 binding antibody was measured by the anti-SARS-CoV-2 immunobinding IgG assay by Emergent laboratories. The assay has been validated for PK assessment, with an LLOQ value of 1 AU/mL and an ULOQ value of 48 AU/mL.

Subjects with incomplete data are 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 is provided, with flags to indicate sampling time deviations.

8.4.2 Pre-dose Concentration Values and Endogenous Compounds

The study drug SARS-CoV-2 binding IgG antibody is not expected to exist in the serum prior to receiving any dose, because a negative rapid SARS-CoV-2 IgG/IgM antibody and antigen test results were 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 are identified and are set to 0 (zero) for the calculation of PK parameters. The original concentration values are used in statistical summaries. If the pre-dose value is greater than 5% of C_{max}, the affected PK profile is excluded from statistical summaries and analysis. Similarly, PK concentrations for the affected profile are excluded from statistical summaries. If necessary, background subtraction may be applied for PK analysis.

8.4.3 Exclusion of Outliers

Individual serum concentrations may be excluded from the analysis because they are erroneous or abnormal at the discretion of the study statistician 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 statistician. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Any excluded data is flagged in the individual data listings.

8.4.4 Non-quantifiable and Missing Concentrations

When calculating summary statistics, including geometric mean and 90% CIs and PK parameters, PK (SARS-CoV-2 antibody) concentrations below the assay's LLOQ are 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.

If a concentration value is below the LLOQ:

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

For the purpose of calculating PK parameters:

- Missing pre-dose concentrations and concentrations prior to the first quantifiable concentration that are <LLOQ are set to 0 (zero).
- A value of <LLOQ after C_{max} that is between two quantifiable data points is treated as missing.
- Values of <LLOQ after the last quantifiable concentration value at the end of the collection interval are set to 0 (zero).
- For calculation of λ_z and parameters that depend on λ_z, trailing zero values are treated as missing.
- If there are more than two consecutive values <LLOQ after C_{max}, all subsequent values may be treated as missing, or the <LLOQ values themselves may be treated as missing, after review of available documentation (e.g., bioanalytical report, validation report).
- Missing concentration values are ignored in the calculations.

8.4.5 Pharmacokinetic Parameters

PK parameters in Table 3 will be derived from the concentration-time data by non-compartmental analysis (NCA; i.e., log-linear trapezoidal) methods using actual sampling times; concentrations at nominal time points may be imputed using linear interpolation. 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. Additional partial AUCs may be added as needed. 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 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% 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.

NCA PK parameter calculations and graphics are performed using SAS version 9.4 or higher.

Table 3 Pharmacokinetic Parameters for SARS-CoV-2 Binding IgG Antibody

Parameter	Definition and Calculation
Primary	
$AUC_{0-\infty}$	Area under the serum concentration-time curve extrapolated to infinity. It is calculated as AUC_{0-t} plus the additional area extrapolated to infinity using the linear regression line for the calculate of λ_z. If λ_z cannot be estimated $AUC_{0-\infty}$ will not be calculated. If the percentage of extrapolated area exceeds 40% of the estimated $AUC_{0-\infty}$, the $AUC_{0-\infty}$ value will not be included in statistical analyses.
AUC_{0-last}	Area under the serum concentration-time curve from time 0 to the last quantifiable concentration. A minimum of 3 non-LLOQ concentration values is required.
C_{max}	Maximum observed serum concentration. If there are missing data near the expected C_{max}, it may be set to missing after statistician review.
t_{max}	Time of maximum observed serum concentration, if C_{max} exists.
C_{28d}	Observed or estimated concentration at Day 29 (28 days after dosing).
Secondary	
AUC_{0-inf} ratios	Bioavailablity will be compared between routes for comparable dose levels (COVID-HIG SC to IV; IM to IV; and SC to IM).
AUC_{0-14d} after dosing	Area under the serum concentration-time curve from time 0 to 14 days after dosing. It is calculated using linear-up log-down trapezoidal summation. A minimum of 3 non-LLOQ concentration values is required. If the Day 29 sample is missing or collected outside of the protocol specified window, AUC_{0-28d} will be determined to a nominal time point of 28 days using two-point linear interpolation, or extrapolation if λ_z can be estimated.
AUC_{0-28d} after dosing	Area under the serum concentration-time curve from time 0 to 14 days after dosing. It is calculated using linear-up log-down trapezoidal summation. A minimum of 3 non-LLOQ concentration values is required. If the Day 15 sample is missing or collected outside of the protocol specified window, AUC_{0-14d} will be determined to a nominal time point of 14 days using two-point linear interpolation, or extrapolation if λ_z can be estimated.
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 including C_{max}) that maximizes the adjusted r^2. A minimum of 3 data points is required for determination. If the maximum adjusted r^2 is <0.700, it is considered not estimable and the λ_z will not be included in statistical analyses.
$t_{1/2}$	Terminal elimination half-life, or just referred to as half-life. It is calculated as ((ln 2)/λ_z), when λ_z can be estimated.
CL	Apparent systemic clearance. It is calculated as (dose / $AUC_{0-\infty}$). 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).

8.4.6 Pharmacokinetic Analysis

All PK analyses are conducted based the PK population. All PK data listings are presented based on the PK population. A detailed listing for the excluded subjects is provided with reasons for exclusion.

PK concentration data are summarized by study day/nominal time point and treatment arm. The summary statistics for concentration data include n, arithmetic mean, SD, median, minimum, maximum, geometric mean and 95% CI, and percentage coefficient of variation (%CV).

PK parameters in Table 3 are summarized by treatment arm overall and by baseline seronegative or seropositive SARS-CoV-2 antibody stratum. Summary of t_{max} includes n, median, minimum, and maximum only. For the other PK parameters, summary statistics include n, arithmetic mean, SD, median, minimum, maximum, geometric mean and 95% CI, and geometric percentage coefficient of variation (%CV). The geometric %CV is calculated as,

$$\%GCV(x) = 100 \times \sqrt{\exp(Var(\ln x)) - 1}$$

Scatterplots for individual PK concentration-time profiles are presented on linear and semi-logarithmic scales for the PK population. Mean and 95% CI concentration-time plots on linear and semi-logarithmic scales are presented by treatment arm overall and by baseline seronegative or seropositive SARS-CoV-2 antibody stratum.

8.5 Exploratory Efficacy Endpoint

For subjects that become SARS-CoV-2 positive during the study period (at any time post-dosing on Day 1 and up to last follow-up visit/contact) an Ordinal Outcome Scale is collected to assess COVID-19 symptom severity. Maximum score on the Ordinal Outcome Scale is summarized by treatment arm and overall and presented in a subject listing for the SARS-CoV-2 Positive population with data available.

9 SAFETY ANALYSIS

All safety data are presented in the form of tabulations and listings, based on the Safety population.

9.1 Extent of Exposure

The frequencies and percentages of subjects treated and completing study medication treatment are summarized in the disposition Section 7.1.

Extent of exposure is summarized overall and by baseline seronegative or seropositive SARS-CoV-2 antibody stratum and treatment arm for the Safety population. Route of administration (actual and not randomized), volume administered (mL), potency (AU), and total protein (g) are tabulated.

A subject listing of treatment exposure is provided.

9.2 Adverse Events

AEs are coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs, related AEs, SAEs, and AEs causing death or treatment/ study discontinuation are defined in Section 6.3. Only treatment-emergent AEs are included in the summary tables described below and "AE" refers to treatment-emergent AE, unless otherwise specified. AE severity is assessed on the scale of Grade 1 (mild) to Grade 4 (potentially life-threatening) as described in Section 5.8. Subjects having the same AE more than once are counted once for each PT and once within each SOC at the maximum severity or closest relationship.

A subject data listing of all AEs sorted by treatment arm, subject ID, and AE start date/time is provided for the Safety population with a "non-treatment-emergent" flag.

9.2.1 Overall Summary of Adverse Events

An overall summary of AEs is provided by SOC, PT, and treatment arm for the Safety population. The events are sorted in descending frequency of subjects in the 'Total" column for SOC, then PT, unless otherwise specified. Each of the line items below on the AE summary is a separate tabulation as well.

- Any AE
- Related AEs
- AEs occurring within 72 hours post-dosing
- Related AEs occurring within 72 hours post-dosing
- Grade 3 or higher AEs
- Grade 3 or higher related AEs
- MAAEs
- Related MAAEs
- SAEs
- Related SAEs
- COVID-19 AE and COVID-19 SAE
- AEs leading to death
- AEs leading to discontinuation of study treatment
- AEs leading to study withdrawal

9.2.2 Adverse Events of Special Interest

There were no AEs of special interest in this study.

9.2.3 Medically Attended Adverse Events

MAAEs are tabulated using the MedDRA coded terms of SOC, PT, and treatment arm for all MAAEs and related MAAEs.

9.2.4 COVID-19

Cases of COVID-19 as an AE and as an SAE are summarized separately by SOC, PT, and study arm.

9.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

9.3.1 Deaths

Deaths are not expected in this study with healthy participants. A tabulation and subject data listing of deaths is provided as appropriate, including the primary cause of death.

9.3.2 Serious Adverse Events

SAEs are tabulated using the MedDRA coded terms of SOC, PT, and treatment arm for all SAEs and related SAEs. A subject data listing of SAEs is provided.

9.3.3 Adverse Events Leading to Discontinuation of Study Treatment and/or Study Withdrawal

Separate tabulations are displayed for AEs leading to discontinuation of study treatment and withdrawal from the study by SOC, PT, and treatment arm.

9.4 Clinical Laboratory Tests

9.4.1 Safety Laboratory Tests

Clinical laboratory analytes included Na+, K+, Cl-, HCO3-, BUN, creatinine, glucose, total and direct bilirubin, ALT, AST, LDH, and CBC with differential. Urinalysis parameters included appearance, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, and urobilogen. Clinical laboratory tests were required at Day 2 and 4; at other visits, tests were done as clinically indicated only. Clinical laboratory test results were assigned a toxicity grade by the investigator as described in Section 5.8.

Safety laboratory measurements are summarized as follows for the Safety population:

- Observed values and changes from baseline of continuous laboratory variables (hematology and serum chemistry) are summarized using descriptive statistics by study visit and treatment arm.
- Shifts from baseline in hematology and serum chemistry analyte values according to normal reference ranges (reported as ‘Low,’ ‘Normal,’ and ‘High’) or toxicity grades (Grade 0, 1-4) are summarized (number and percentages) by study visit and treatment arm.

- Frequency and percentage of subjects with the highest toxicity grade of abnormal hematology and serum chemistry laboratory values at any time on study are summarized by study visit and treatment arm. In this analysis, analytes with toxicity criteria for both increases and decreases are presented separately for each direction (e.g., sodium increased and sodium decreased).
- Urinalysis data are listed only.

All laboratory records (including local laboratory measurements if applicable) are provided in the subject data listings, with applicable toxicity grades or abnormal flags displayed.

9.4.2 Pregnancy Testing

Subject listings of FSH and pregnancy test results (serum and urine) are provided.

9.4.3 Urine Drug Testing, Viral Serology Testing, and COVID-19 Testing at Screening or Baseline

Urine drug screening, alcohol breath test, and viral serology testing results are provided in the subject listings. COVID-19 testing results at screening and baseline are also provided for those tests that occur only at screening and/or baseline.

9.4.4 Nasopharyngeal Swab Results

Nasopharyngeal swabs at Days 8, 15, 29, 43, and 57 are analyzed for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) and results are reported by time point and administration route for the Safety population.

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

9.5.1 Vital Signs

Vital signs parameters included blood pressure, heart rate, SpO_2 (pulse oximetry), respiratory rate, and temperature. Vital signs were assessed at screening, on Day 1 (baseline) at pre-dose and 30 min and 1 hour after the end of dosing, and on Days 2, 3 (except IV arm), 4, 6 (except IV arm), 8, 15, 29, 43, and 57. Vital sign test results were assigned a toxicity grade by the investigator using the criteria in 11Appendix I as described in Section 5.8.

Vital sign data are summarized as follows for the Safety population:

- Shift from baseline in toxicity grade (Grade 0-4) are summarized (number and percentages) by study visit and treatment arm.

All vital sign records are provided in the subject data listings.

9.5.2 Physical Examinations

Complete physical examination occurred at screening and symptom-directed or targeted physical examination occurred at Days -1, 1, 2, 3 (except IV arm), 4, 6 (except IV arm), 8, 15, 29, 43, and 57.

Normal/abnormal physical examination findings are provided in data listings by subject and body system.

10 DATA MONITORING AND INTERIM ANALYSIS

10.1 Study Monitoring Committee or Data Monitoring Committee

An independent SMC provided safety oversight. The SMC reviewed aggregated, blinded safety data after the first 50 subjects completed at least seven days of safety follow-up. The remaining subjects were enrolled following the safety review by the SMC and based on the Sponsor's consideration of the SMC's recommendation. Any further safety reviews are at the discretion of the SMC and per the SMC Charter.

10.2 Interim Analysis

No interim analysis is planned for this study.

11 REFERENCES

1. DAIDS (2017). Division of AIDS (DAIDS) *Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1.* U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.
2. ICH E3 (1996) Guidance for Industry: Structure and Content of Clinical Study Reports.

APPENDIX I VITAL SIGNS GRADING SCALE

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

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

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