Official Title: A Multi-center, Single-Sequence, Open-label Study to Evaluate IGSC 20% Biweekly Dosing in Treatment-Experienced Subjects and Loading/Maintenance Dosing in Treatment-Naïve Subjects with Primary Immunodeficiency

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STATISTICAL ANALYSIS PLAN (SAP)

IGSC 20% / GC1906

Title: A Multi-center, Single-Sequence, Open-label Study to Evaluate IGSC 20% Biweekly Dosing in Treatment-Experienced Subjects and Loading/Maintenance Dosing in Treatment-Naïve Subjects with Primary Immunodeficiency

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Approvals

Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AR	Adverse reaction
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0\text{-}7\ days}$	Area under the concentration-time curve from 0 to 7 days
$AUC_{0\text{-}14\ days}$	Area under the concentration-time curve from 0 to 14 days
$AUC_{0\text{-}\tau}$	Area under the concentration-time curve at steady state over the dosing interval (from time 0 to τ)
BLQ	Below the limit of quantification
BUN	Blood urea nitrogen
CI	Confidence interval
C_{max}	Maximum concentration
CSR	Clinical Study Report
CV	Coefficient of variation
DAF	Dose adjustment factor
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
dL	Deciliter
eCRF	Electronic Case Report Form
HR	Heart rate
HYQVIA	Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IGSC 20%	Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (Grifols)
IP	Investigational product
IV	Intravenous
IVIG	Intravenous Immune Globulin (generic terminology)
IWRS	Interactive web response system
kg	Kilogram
LDH	Lactate dehydrogenase
LQI	Life Quality Index
LLN	Lower limit of normal
LSM	Least-squares mean

MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NAT	Nucleic acid amplification technology
PCS	Physical component summary
pH	Potential of hydrogen; acidity/alkalinity measure
PI	Primary immunodeficiency
PK	Pharmacokinetic(s)
PT	Preferred term
QOL	Quality of Life
RBC	Red blood cell
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBI	Serious bacterial infection
SBP	Systolic blood pressure
SC	Subcutaneous
SC#1	First subcutaneous infusion
SCIG	Subcutaneously delivered immune globulin or subcutaneous immunoglobulin (generic terminology)
SD	Standard deviation
SOC	System Organ Class
SF-10	10-item short form health survey (for pediatric subjects)
SF-12	12-item short form health survey
SF-36	36-item short form health survey
T	Temperature
TB	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TSQM-9	Treatment Satisfaction Questionnaire for Medication
t_{max}	Time to reach C_{max}
ULN	Upper limit of normal range
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
%CV	Percent coefficient of variation

TABLE OF CONTENTS

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol GC1906 Version 1.0, dated 17 Mar 2020.

The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables and figures which will be produced, are appropriate and complete to support valid conclusions regarding the study objectives and the completion of Clinical Study Report (CSR). Additional post-hoc or unplanned analyses, which are not defined in this SAP, may be performed to support the clinical development program. Such analyses will be documented in the CSR.

2 STUDY DESIGN AND OBJECTIVES

2.1 Study Design

This is a multi-center, single-sequence, open-label study with 2 cohorts of subjects: (a) a treatment experienced cohort (approximately 25 subjects) and (b) a treatment naïve cohort (approximately 6 subjects).

2.1.1 Treatment-Experienced Cohort

The Screening Period is up to 5 weeks to accommodate treatment-experienced subjects who may enter the study on commercial intravenous immune globulin (IVIG) or immune globulin infusion 10% (Human) with recombinant human hyaluronidase (HYQVIA) solution, for subcutaneous administration with a monthly dosing schedule. The treatment-experienced cohort will enroll subjects with primary immunodeficiency (PI) already maintained on Immunoglobulin G (IgG) replacement therapy for at least 3 months who will receive immune globulin subcutaneous (IGSC) 20% at 2 different dosing frequencies using a subcutaneous (SC) infusion pump during 2 treatment periods (16 weeks per treatment period).

Treatment Period 1:

In Treatment Period 1, treatment-experienced subjects will receive 16 weekly IGSC 20% doses from Week 0 to Week 15:

- For subjects entering study on IVIG, IGSC 20% will be dosed at 1.37 times the equivalent weekly dose
- Subjects entering on subcutaneous immune globulin (SCIG) will receive the same mg/kg equivalent weekly dose as given prior to entry, without using a dose adjustment factor (DAF)

For treatment-experienced subjects, a 16-week treatment period duration has been shown to be adequate to achieve steady state based on a predecessor study of IGSC 20% (GTI1502) that demonstrated bioequivalence using PK profiling at SC Weeks #13 to 14 (please see Protocol Section 2.2 for further details).

Once on-study, dose adjustments may be made for safety reasons in Treatment Period 1 before Week 9 in the event the IgG trough level is less than or equal to 500 mg/dL or at the investigator's discretion. Any dose adjustments beyond a 20% increase from the dose producing the low IgG trough will require consultation with the Grifols Medical Monitor. No dose adjustments should occur at or after Week 9 except in extenuating circumstances after discussion with the Grifols Medical Monitor.

Treatment Period 2:

In Treatment Period 2, treatment-experienced subjects will receive biweekly IGSC 20% dosing (i.e., IGSC 20% every 2 weeks) for a total of 9 doses, with the first IGSC 20% dose administered at Week 16 and the last IGSC 20% dose given at Week 32. The dose in Treatment Period 2 is calculated by multiplying the calculated weekly dose of IGSC 20% in Treatment Period 1 by 2.

Final follow-up Visit:

The final Follow-up Visit will take place at Week 33.

The overall study schema for the treatment-experienced subjects is shown in Figure 2-1.

2.1.2 Treatment-Naïve Cohort

For treatment-naïve subjects, the Screening Period should be as short as possible in order to facilitate rapid commencement of IGSC 20% as IgG replacement treatment.

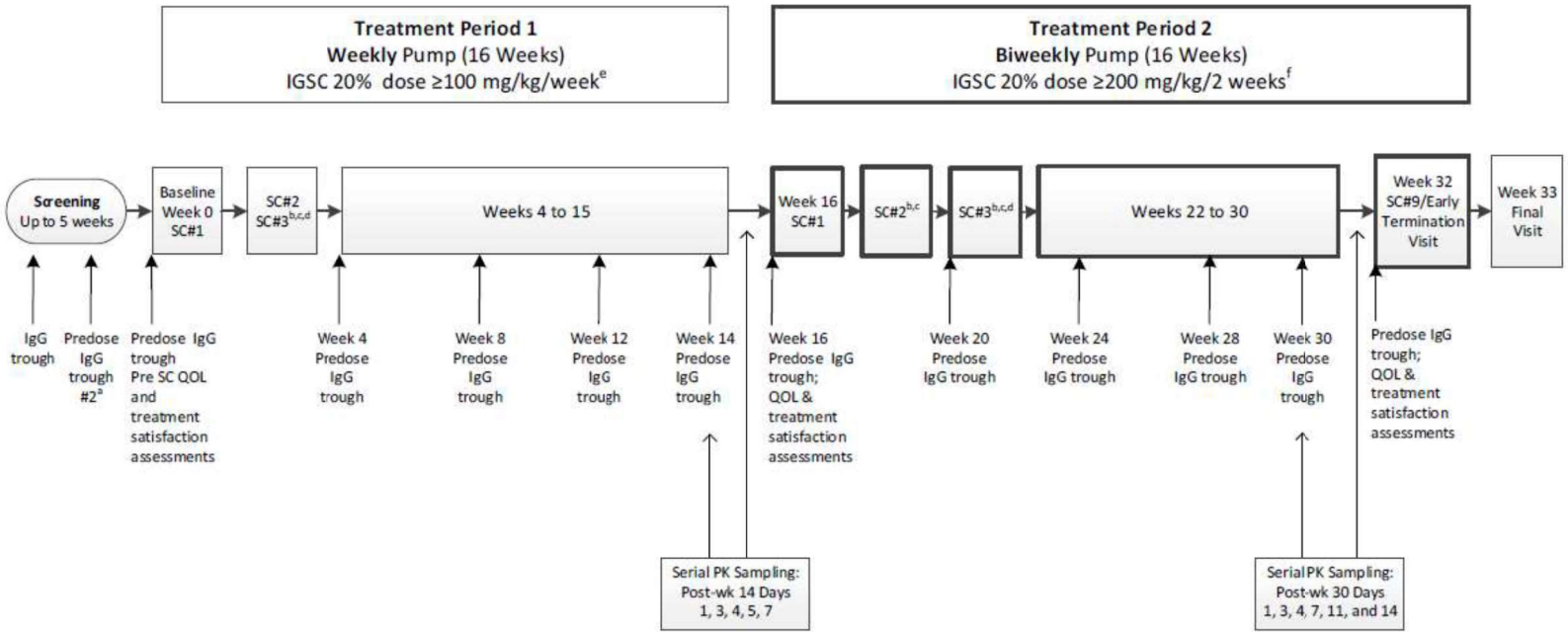
Treatment-naïve subjects will be enrolled one at a time based on the previous subject achieving a minimum IgG trough level target defined per the algorithm for sequential enrollment of treatment-naïve subjects in Protocol Section 4.1.2.1. Recruitment of treatment-naïve subjects will be controlled by the Interactive Web Response System (IWRS), which will only allow one-at-a-time enrollment of treatment-naïve subjects and will allow subsequent enrollment of treatment-naïve subjects only after the sponsor or designee has reviewed IgG trough values and reinstated treatment-naïve enrollment in the IWRS. Stopping rules are described in Protocol Section 4.5.3.

Subjects in the treatment-naïve cohort will receive a loading dose of IGSC 20% consisting of 5 consecutive daily doses of 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly maintenance infusions of IGSC 20% 150 mg/kg starting Week 1 (Day 8) through Week 32. During the treatment phase, individual treatment-naïve subject's IGSC 20% dose will be adjusted to achieve an optimal target IgG trough value of ≥700 mg/d (Protocol Section 4.1.2.2).

There will be a Final Follow-up visit at Week 33.

The study schema for treatment-naïve subjects is shown in Figure 2-2.

Figure 2-1 Overall Study Schema – Treatment-Experienced Subjects



[a] Applicable to subjects entering on commercial IVIG or HYQVIA only.

[b] Subjects demonstrating proficiency with the administration method at the first clinic visit as per the investigator's judgment may administer SC#2 and SC#3 of each treatment period at home under the supervision of a healthcare provider (home health aide). Healthcare provider monitoring of SC#2 and SC#3 of each treatment period is required for subjects who were receiving IVIG treatment prior to study entry (naïve to SCIG administration), and is also recommended for subjects receiving SCIG treatment prior to study entry if the method or frequency of administration is different from that of this study.

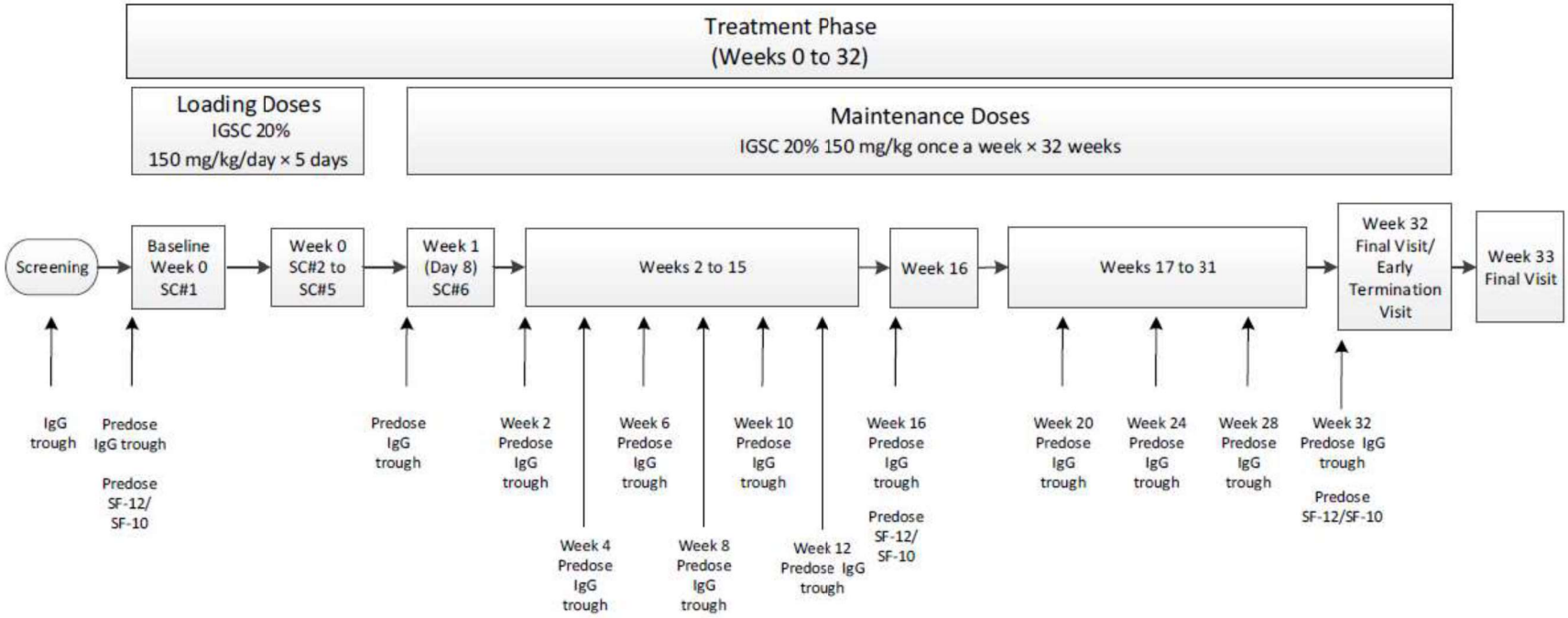
[c] SC#2 and SC#3 are the second and third observed doses at the new assigned frequency for each treatment period.

[d] For weekly pump administration, SC#3 will coincide with Week 2, and for every 2 weeks (biweekly) pump administration, SC#3 will coincide with Week 20.

[e] IGSC 20% dose (mg/kg) is 1:1 with previous SCIG dose and 1:1.37 with prior IVIG dose with a minimum IGSC 20% dose of 100 mg/kg/week in Treatment Period 1.

[f] First dose of biweekly IGSC 20% will be administered after Week 16 pre-dose assessments are complete at Week 16 visit in Treatment Period 2.

Figure 2-2 Overall Study Schema – Treatment-Naïve Subjects



2.1.3 Expected Duration of Subject Participation in the Study

For treatment-experienced subjects, the study consists of a Screening Visit (up to 5 weeks), Baseline Visit, Treatment Period 1 (16 weeks), Treatment Period 2 (16 weeks) inclusive of Week 32 Visit/Early Termination Visit, and Final Follow-up Visit (Week 33).

For treatment-naïve subjects, the study consists of a Screening Visit, Baseline Visit, Treatment Phase (32 weeks) inclusive of Week 32 Visit/Early Termination Visit, and Final Follow-up Visit (Week 33). For treatment-naïve subjects, the screening period will be as short as possible to allow instigation of IgG replacement treatment with IGSC 20% as soon as eligibility is confirmed.

The expected duration of a study subject's participation will be up to 38 weeks.

2.2 Study Objectives

2.2.1 Primary Pharmacokinetic Objective

- The primary PK objective of this Phase 4 study is to determine whether biweekly (every 2 weeks) administration of IGSC 20% produces a steady-state AUC of total IgG that is noninferior to that produced by weekly administration of IGSC 20% in treatment-experienced subjects with PI.

2.2.2 Secondary Objectives

- To determine if IGSC 20% replacement therapy maintains steady-state mean trough total IgG levels when administered biweekly (every 2 weeks) that are comparable to steady state mean trough total IgG levels obtained when IGSC 20% is administered weekly in treatment-experienced subjects with PI.
- To evaluate maximum concentration (C_{max}) and time to reach C_{max} (t_{max}) of total IgG at steady state in given IGSC 20% weekly and biweekly (every 2 weeks) in treatment experienced subjects.
- To evaluate if a loading dose of IGSC 20% consisting of 5 consecutive daily doses of 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly infusions of IGSC 20% 150 mg/kg starting Week 1 (Day 8) through Week 32 achieves and maintains total IgG trough >500 mg/dL in treatment-naïve subjects with PI.
- To evaluate the rate of serious bacterial infection (SBIs) as defined in Protocol Appendix 4 in all subjects.
- To evaluate all infections of any kind as determined by the investigator in all subjects.
- To evaluate validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (e.g., rapid streptococcal antigen detection test) in all subjects.
- To evaluate the number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic) in all subjects.

- To evaluate the number of hospitalizations due to infection in all subjects.

2.2.3 Exploratory Objectives

- To compare treatment burden and treatment satisfaction related to immune globulin therapy using the Life Quality Index (LQI) questionnaire and the Treatment Satisfaction Questionnaire for Medication (TSQM-9) for IGSC 20% administered weekly or biweekly (every 2 weeks) in treatment-experienced subjects with PI. (Protocol Appendix 3)
- To survey Quality of Life (QOL) in subjects with PI using the Short Form Health Survey (12-Item Short Form Health Survey [SF-12] for subjects ≥18 years [observer: subject] in both treatment experienced and treatment-naïve subjects with PI. (Protocol Appendix 3). In addition, 10-Item Short Form Health Survey [SF-10] for treatment-naïve subjects aged 6 to 17 years [observer: parent or legal guardian]) will also be used.

2.2.4 Safety Objectives

- To assess the safety and tolerability of biweekly and weekly dosing regimens of IGSC 20% as an IgG replacement therapy in treatment-experienced subjects with PI.
- To assess the safety and tolerability of the loading/maintenance dosing regimen of IGSC 20% in treatment-naïve subjects with PI.

3 STUDY VARIABLES

3.1 Primary Pharmacokinetic Variables

- AUC of IGSC 20% administered weekly: Steady-state AUC of total IgG over a regular dosing interval (τ), every week (i.e., $AUC_{0-\tau}$, weekly or AUC_{0-7} days) in treatment-experienced PI subjects
- AUC of IGSC 20% administered biweekly: Steady-state AUC of total IgG over a biweekly dosing interval (τ) (i.e., $AUC_{0-\tau}$, biweekly or AUC_{0-14} days) in treatment-experienced PI subjects

3.2 Secondary Variables

- Steady-state mean trough (predose) concentration of total IgG following SC administration of IGSC 20% given IGSC 20% weekly and biweekly (every 2 weeks) in treatment experienced subjects.
- C_{max} and t_{max} of total IgG at steady state given IGSC 20% weekly and biweekly in treatment-experienced subjects.
- In the treatment-naïve cohort, ability of a loading dose of IGSC 20% 150 mg/kg/day and maintenance infusion of IGSC 20% 150 mg/kg to achieve and maintain total IgG trough >500 mg/dL through Week 32 (End of Treatment).

Additional secondary variables include the following evaluations of infections in all subjects:

- Total number of SBIs, proportion of subjects who experience SBIs, and rate of SBI as defined in Protocol Appendix 4.
- All infections of any kind (serious/non-serious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the investigator.
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms e.g., bacterial, viral, fungal, or protozoal pathogens (e.g., rapid streptococcal antigen detection test).
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection.
- Number of hospitalizations due to infection.

3.3 Exploratory Variables

- LQI score in treatment-experienced subjects.
  The LQI covers 3 domains: treatment interference, therapy-related problems, and therapy settings. Change in LQI from Pre-SC#1 Week 0 to Week 16 , and from Week 16 to Week 32 will be analyzed (Protocol Appendix 3).
- TSQM-9 score in treatment-experienced subjects.
  This questionnaire is a measure of treatment satisfaction in 3 categories of effectiveness, convenience, and global satisfaction. Change in TSQM-9 from Pre-SC#1 Week 0 to Week 16, and from Week 16 to Week 32 will be analyzed (Protocol Appendix 3).
- SF-12 survey (subjects ≥18 years [observer: subject]) which measures dimensions of health analogous to the 36-item short form health survey (SF-36) in both treatment-experienced subjects and treatment-naïve subjects. In addition, 10-Item Short Form Health Survey [SF-10] for treatment-naïve subjects aged 6 to 17 years [observer:parent]) will also be used.
  In treatment-experienced subjects, change in SF-12 from Pre-SC#1 Week 0 to Week 16 (end of Treatment Period 1), and from Week 16 to Week 32 (end of Treatment Period 2) will be analyzed (Protocol Appendix 3). In the treatment-naïve cohort, the time points for comparison SF-12/SF-10 will be change from Pre-SC#1 Week 0 (before first loading dose) to Week 16 and to Week 32 (End of Treatment).

In all questionnaires, higher scores indicate higher satisfaction.

3.4 Safety Variables

Safety of IGSC 20% will be evaluated in this study. Safety variables will include:

- Adverse events (AEs) including serious AEs (SAEs), suspected adverse drug reactions (suspected ADRs, potentially related AEs), and adverse reactions (ARs, definitely related AEs). All infusion site reactions will be recorded in the subject's source documents and

eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.

- Vital signs during clinic visits – systolic blood pressure and diastolic blood pressure, heart rate, temperature, respiratory rate (SBP and DBP, HR, T, RR)
- Physical assessments: physical examinations will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded
- Laboratory assessments including chemistry, hematology, urinalysis, haptoglobin, serum/plasma free hemoglobin (central laboratory), and DAT (central laboratory) (see Table 3-1)

Table 3-1 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel	Description	Location
Hematology[a]	Hemoglobin, hematocrit, platelets, RBC count, WBC count with differential, ARC	Central
Additional Special Tests[a]	Haptoglobin	Central
	Serum/plasma free hemoglobin	Central
	DAT	Central
Chemistry[a]	Sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, TB, indirect bilirubin	Central
IgG levels[a] (trough)	Total IgG levels will consist of trough (predose) measurements for all subjects	Central
Serial total IgG concentrations[a]	Serial total IgG concentrations post Week 14 and Week 30 dosing for PK profiling in treatment-experienced subjects	Central
Serum pregnancy test[a]	Qualitative serum β-HCG for females of child-bearing potential will be performed at Screening	Central
Urine pregnancy test	Qualitative Baseline urine β-HCG test for females of child-bearing potential	Local
Urinalysis[a]	Microscopic evaluation is done only with cause. pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of the urine if abnormal)	Central

[a] Samples collected for laboratory analyses that are non-analyzable due to any factor (ie, lost, quantity not sufficient, laboratory error) need to be recollected by contacting the subject and arranging for re-sampling.

4 GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses and data presentations will be generated using SAS version 9.4 or higher.

Unless otherwise specified, for the continuous/quantitative data, descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum. For categorical/qualitative data, descriptive statistics will include absolute and relative frequency counts and percentages. The hypothesis testing for the primary PK analysis of AUC non-inferiority will be tested at 1-sided with α=0.05. When applicable, formal statistical comparisons of other PK parameters will be tested at 2-sided with α=0.10. All other statistical tests will be 2-sided at a significance level of 0.05.

In general, data will be analyzed separately for treatment-experienced and treatment-naïve subjects. Furthermore, for treatment-experienced subjects, when applicable summaries will be provided by treatment group as defined by the two different IGSC 20% dosing frequencies investigated in this study (weekly and biweekly). For data analysis purpose, treatment groups of interest in this study include weekly dosing regimen of IGSC 20% in treatment-experienced subjects, biweekly dosing regimen of IGSC 20% in treatment-experienced subjects and loading/maintenance dosing regimen of IGSC 20% in treatment-naïve subjects.

For table summaries, the data will be presented at the scheduled visits according to protocol. Any data collected at the unscheduled visits will be listed.

4.1 Data Handling

4.1.1 Missing Data Imputation

Unless otherwise noted, if an observation is missing at a specific scheduled visit/time point, the value at that visit will not be imputed and will be set to missing.

4.1.2 Baseline Definition

For treatment-experienced cohort, Baseline will be defined as the last measurement taken prior to the start of the study drug infusion (IGSC 20%) at the Baseline visit (Week 0, Day 1) during the pre-SC#1 infusion for Treatment Period 1 or pre-Week 16 infusion for Treatment Period 2.

For treatment-naïve cohort, Baseline will be defined as the last measurement taken prior to the start of the study drug infusion (IGSC 20%) at the Baseline visit (Week 0, Day 1) pre-SC#1 infusion.

4.1.3 PK Data Handling

4.1.3.1 Time Window for Pharmacokinetic Analysis

The time window allowed for serial PK blood sample draws for treatment-experienced subjects is specified in the study protocol Section 7.2.1.2.8 (see Table 4-1). However, if samples are drawn outside the protocol specified (nominal) time or the allowable window, the samples will still be included in the PK analysis as long as the actual sample collection date and clock time for each sample is recorded and the actual elapsed time from the start of infusion can be calculated.

The scheduled time points specified in the protocol will be used in the tables for presenting the summary data of IgG concentrations. The nominal time (hours) will be used in figures for presenting the mean or median concentration vs. time curve. Due to the variable infusion duration in individual subjects, the nominal time may be adjusted by using the average infusion duration among all subjects in the PK population when plotting the mean or median concentration vs. time curve.

Table 4-1 Blood sample Time Points for Serial PK assessments

Pharmacokinetics Week	Scheduled Time
PK Sampling Week 14 (Treatment Period 1)	Prior to the Week 14 infusion (within 0.5 hour of infusion start [predose])
	1 day ± 4 hours post end of Week 14 infusion
	3 days ± 4 hours post end of Week 14 infusion
	4 days ± 4 hours post end of Week 14 infusion
	5 days ± 8 hours post end of Week 14 infusion
	7 days (+1 day) post end of Week 14 infusion
PK Sampling Week 30 (Treatment Period 2)	Prior to the Week 30 infusion (within 0.5 hour of infusion start [predose])
	1 day ± 4 hours post end of Week 30 infusion
	3 days ± 4 hours post end of Week 30 infusion
	4 days ± 4 hours post end of Week 30 infusion
	7 days ±1 day post end of Week 30 infusion
	11 days ± 1 day post end of Week 30 infusion
	14 days (+1 day) post end of Week 30 infusion

The actual elapsed time between the start of the infusion (for pre-dose sample) or the end of the infusion (for post-dose samples) and each PK blood sample draw will be calculated. The PK parameter calculation for each subject will be based on the actual elapsed time instead of the scheduled time or nominal time.

An example of actual elapsed time calculated from the time of the start/end of the Week 14 IGSC 20% infusion is shown below (assuming the duration of the infusion is 2 hours).

Scheduled Time	Nominal Time (Hours)	Example Actual Elapsed Time (Hours)
Pre-infusion	0	-0.25
1 day post end of infusion	26	26.50
3 days post end of infusion	74	73.86
4 days post end of infusion	98	98.30
5 days post end of infusion	122	123.20
7 days post end of infusion	170	169.75

In addition, the actual duration of the infusion for IGSC 20% will be calculated.

4.1.3.2 IgG Concentration Missing Values

For PK and IgG concentration analysis, any invalid IgG concentration values will be treated as missing, e.g., if the sample was hemolyzed or if a planned trough sample was drawn post-infusion. If necessary, invalid or missing values will be interpolated or extrapolated using PK principles, as appropriate, and such interpolations or extrapolations will be documented in the CSR.

4.1.3.3 Samples below the Limit of Quantification (BLQ)

PK samples with concentrations values below the limit of quantification (BLQ) will be imputed as follows:

- BLQ values will be treated as missing.

4.2 Analysis Populations

4.2.1 Safety Population

The safety population will include all subjects (including both treatment

-experienced and treatment-naïve subjects) who received any amount of IGSC 20% and will be used for safety analysis.

4.2.2 Efficacy Evaluable Population

The efficacy evaluable population will include all subjects (including both treatment-experienced and treatment-naïve subjects) who received at least one dose of IGSC 20%. The efficacy evaluable population is the same as the safety population in this study and will be used for all efficacy analyses except for the primary PK analysis of $AUC_{0-\tau}$ and secondary PK analysis of the trough concentrations of total IgG, which will be based on the PK population and IgG population, respectively (defined below).

4.2.3 PK Population

The PK population will consist of all treatment-experienced subjects who received IGSC 20% and had sufficient and valid total IgG concentration vs. time data to allow the calculation of $AUC_{0-\tau}$, weekly or $AUC_{0-\tau}$, biweekly (the primary PK endpoint). The primary PK analysis will be based on this population.

Adequate treatment compliance will be considered when determining valid concentration-time data for inclusion in the PK analyses. The values or profiles deemed not reliable due to treatment non-compliance or other reasons (e.g., blood sampling/collection or testing issues) will be excluded from the PK analyses and flagged in the listing. Any subject who has at least one major protocol deviation which might have an impact on the PK analyses (to be defined in a data review meeting prior to database lock) will be excluded from the PK population. PK parameters (i.e., AUC values) will only be calculated for PK profiles with at least 3 quantifiable samples following data imputations (if applicable).

4.2.4 IgG Population

The IgG population will consist of all treatment-experienced and treatment-naïve subjects who received any amount of IGSC 20% and had any trough total IgG concentration data. The analyses of the trough total IgG concentration data will be based on this population.

4.3 Sample Size Considerations

The planned number of treatment-experienced subjects is 25 subjects dosed with IGSC 20% to ensure at least 20 subjects provide the primary PK endpoint (AUC0-τ) estimates in both treatment periods, assuming a drop-out rate of 20%. This sample size will provide at least 90% power to demonstrate non-inferiority at a 1-sided alpha level of 0.05, assuming the %CV of AUC is no greater than 20% and the true ratio between the 2 treatment groups is 1.0. In addition, this sample size will provide clinical experience with up to 400 weekly infusions (16 infusions × 25 subjects) and 225 biweekly infusions (9 infusions × 25 subjects).

The planned number of treatment-naïve subjects is 6 subjects; this should provide sufficient safety information for the 5 consecutive days of IGSC 20% loading dose of 150 mg/kg/day and subsequent weekly IGSC 20% infusions at 150 mg/kg/week through the end of the 32-week Treatment Phase. This would amount to up to 222 infusions (37 infusions × 6 subjects) of 150 mg/kg in the treatment-naïve subjects.

4.4 Interim Analysis

No interim analysis is planned in this study.

5 SUBJECT DISPOSITION

Subject disposition will include the number of subjects screened, subjects rescreened, number of subjects treated, number and percentage of subjects in each analysis population, and number and percentage of subjects completing the study by treatment group and overall.

The number and percentage of subjects discontinuing early from the study will be summarized for primary reasons of discontinuation by treatment group and overall. The number and percentage of subjects discontinuing the study due to COVID-19 will be summarized. Also, the number and percentage of screening failures will be summarized for primary reasons of ineligibility.

Disposition status will be listed for all subjects.

6 PROTOCOL DEVIATIONS

Protocol deviations will be identified during the study and evaluated before the database lock. The type/category of protocol deviations and severity (i.e., minor, major, or critical) will be summarized and listed. In addition, protocol deviations designated as related to COVID-19 will be summarized.

7 DEMOGRAPHY AND MEDICAL HISTORY

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including age, sex, race, ethnicity, age categories (≥6 - <18, ≥18 - ≤65, >65 - ≤75 years), height, weight, baseline total IgG level, and subject

entry status will be summarized for the Safety Population. The primary immunodeficiency and IgG treatment history will also be summarized. The summaries will be provided by treatment group and overall.

All demographic and baseline characteristics data will be listed.

7.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized/listed. The summaries will be provided by System Organ Class (SOC) and Preferred Term (PT).

8 CONCOMITANT MEDICATION AND TREATMENT

8.1 Prior and Concomitant Medication

All medications as documented by the investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug classification Dictionary (WHO-DD). All medications will be summarized and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 2 or 4 term is missing, the higher ATC level term will be used in the medication summary table and data listing.

Prior medications and concomitant medications will be summarized separately either overall (prior medications) or by treatment group (concomitant medications). Prior medications are defined as any medication ended prior to the start of study treatment. Concomitant medications are defined as any medication started on or after the start of study treatment or any medication taken prior to the start of study treatment and continued after the start of study treatment during the study.

The following conservative imputation rules will be used for missing or partial end date/time information in order to determine whether a medication is prior or concomitant (i.e., the unknown portions of a medication end date/time will be assumed to be as late as possible):

- Note: year is required on the eCRF, except for ongoing medication
- If the entire end year, date and time values are missing (i.e., ongoing medication), then no imputation is performed and the medication will be assigned to the “concomitant” category
- If the month is missing, impute “December”
- If the day is missing, impute the last day of the month (i.e., “28/29/30/31” depending on the year and month)
- If the hours are missing, impute “23”
- If the minutes are missing, impute “59”

The start/end dates/times reported on the eCRFs will be presented in the listings.

8.2 Extent of Study Treatment Exposure

8.2.1 Extent of Study Treatment Exposure

Duration of exposure will be determined for each treatment group.

Duration of exposure in days

Treatment-Experienced Cohort

For Treatment Period 1, the duration of exposure will include not only the total time between the first and last IGSC 20% infusion, but also include an additional 7 days to take into account total exposure time to the study drug since each IGSC 20% infusion is administrated weekly. It is calculated in days as:

(Last infusion date during Treatment Period 1 – Infusion date of Baseline Week 0 SC#1) + 7

For Treatment Period 2, subjects on every 2 weeks (biweekly) dosing schedule, the duration of exposure in days will be calculated as:

(Last infusion date during Treatment Period 2 – Infusion date of SC#1 in Week 16) + 14

Treatment-Naïve Cohort

For subjects who receive daily loading doses, the duration of exposure in days will be calculated as:

Last infusion date during loading doses – Infusion date of Baseline Week 0 SC#1

For subjects who receive maintenance doses, the duration of exposure will include not only the total time between the first and last IGSC 20% infusion, but also include an additional 7 days to take into account total exposure time to the study drug since each IGSC 20% infusion is administrated weekly. It is calculated in days as:

(Last infusion date during maintenance doses – Infusion date of Week 1 SC#6) + 7

Since patients in the Treatment-Naïve cohort receive *both* the initial daily loading doses (planned for 5 consecutive days) plus weekly maintenance infusions commencing on Week 1 (Day 8), the Total duration of exposure in days will be calculated as:

(Last infusion date during maintenance doses – Infusion date of Baseline Week 0 SC#1) + 7

Duration of exposure expressed in other units

Duration of exposure in weeks will be calculated as:

Duration of exposure in days / 7

Duration of exposure in years will be calculated as:

Duration of exposure in days / 365.25

Duration of infusion

Duration of infusion in minutes will be calculated for each infusion as:

Stop time of infusion – Start time of infusion

For each treatment group, the duration of exposure (weeks), the number of infusions received, the total volume infused (mL), and the duration of infusion (minutes) will be summarized. Further, infusions temporarily interrupted and permanently stopped will be summarized. The distribution and number of IGSC 20% infusion sites will be separately summarized. The summaries will also be provided by treatment group and overall.

The initial and revised (if applicable) dose adjustment factor(s) (see Protocol Appendix 6) for all subjects will be listed.

8.2.2 Compliance

Infusion compliance, treatment compliance, and overall compliance will be calculated separately for each treatment period and treatment group. Prescribed IGSC 20% dose information are collected via the IRT system Endpoint. The Endpoint data will be used to determine expected dose. The Actual dose patients received by week is recorded in the EDC Weekly Pump Dosing Log for Treatment Period 1, and in the Biweekly Pump Dosing Log for Treatment Period 2.

Infusion Compliance

Infusion compliance (%) will be calculated as:

(Number of infusions received / Number of infusions expected) x 100%

For subjects who prematurely discontinued from the study, the number of infusions expected is the total number of infusions which should have been taken based on the date of the last infusion, and it is the visit or week number of the last infusion of the treatment period in which the discontinuation occurred.

Treatment Compliance

Treatment compliance (%) will be calculated as:

(Total volume infused [mL] / Total volume expected [mL]) x 100%.

The total volume infused will be calculated as the sum of the volume infused at each visit; actual volume will be based on visits collected on eCRF, and expected volume will be based on visits captured in IRT system Endpoint.

The total volume expected will be derived as follows:

First, at each visit, the volume expected (mL) at that visit will be calculated as:

Dose expected (mg/kg) x Weight (kg) / Concentration of 200 (mg/mL)

If at any visit the dose expected and/or weight is not collected, the latest available values among the prior visits will be used. Treatment on 'end of study' visit will not be considered for treatment compliance, since it is not considered as scheduled dose.

The total volume expected will then be calculated as the sum of the volumes expected from the first planned visit of the Treatment Period to the last planned visit of the Treatment Period if a subject completed the Treatment Period, or to the visit of the last infusion if the subject did not complete the Treatment Period.

Overall Compliance

The overall compliance (%) will be calculated as:

(Infusion compliance x Treatment compliance) / 100

Infusion compliance, treatment compliance, and overall compliance will be listed and summarized by treatment period. The number and percentage of subjects with compliance between 80% and 120% will also be summarized. The summaries will also be provided by treatment group and overall.

Additional consideration regarding compliance will be given when determining legitimacy for inclusion of total IgG concentration data for the calculation of the PK parameters. Reasons for excluding total IgG concentration data or a subject from the analysis of PK parameters will be documented in the CSR.

9 PK ANALYSIS

9.1 Calculation of PK Parameters

The steady-state PK parameters of serial total IgG following the Week 14 or Week 30 infusion will be determined by noncompartmental PK methods, as appropriate and as data permits. The PK parameters include: $AUC_{0-\tau}$, C_{max}, and t_{max}. The PK parameters will be determined for weekly dosing following the Week 14 infusion and for biweekly dosing following the Week 30 infusion.

Pharmacokinetic parameters will be calculated by Nuventra LLC. using Phoenix® WinNonlin® software, version 8.1 or later (Certara USA, Inc. [Princeton, NJ]).

The PK parameters of interest are determined as follows:

$AUC_{0-\tau}$	area under the concentration vs. time curve at steady state over the dosing interval (from time 0 to τ), calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration × time (e.g., mg × hour/dL). The linear trapezoidal method will be used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations. The dose interval τ is 7 days for subjects on weekly IGSC 20% dosing interval in the Treatment Period 1 or 14 days for subjects on a biweekly IGSC 20% dosing interval in the Treatment Period 2.
C_{max}	the observed maximum total IgG concentration following drug infusion obtained directly from the experimental data without interpolation, expressed in concentration units (e.g., mg/dL).
t_{max}	the observed time to reach maximum total IgG concentration obtained directly from the experimental data without interpolation, expressed in time units (hour). If there is more than one maximum observed concentration, the t_{max} is the time to the first observed maximum concentration.

9.2 Descriptive Statistics of PK Parameters

The analyses of all PK parameters will be based on the PK population.

PK parameters will be listed and summarized using descriptive statistics including n, mean, SD, %CV, median, minimum, and maximum will be calculated for all PK parameters. Geometric mean and 90% confidence interval (CI) for the geometric mean will also be calculated for all PK parameters (except t_{max}).

Depending on the number of subjects being dosed on IGSC 20% at weekly and biweekly dosing schedules, subgroup analyses may be identified and performed in an exploratory fashion to summarize the PK parameters by treatment period.

9.3 Statistical Analysis of Primary PK Parameter (Treatment-Experienced Subjects)

This study is designed to determine if IGSC 20% replacement therapy given biweekly (every 2 weeks) provides non-inferior systemic exposure in terms of steady state AUC to weekly IGSC 20% administration in treatment-experienced PI subjects.

9.3.1 Serial Total IgG Data

Serial total IgG concentrations for weekly dosing following the Week 14 infusion and for biweekly dosing following the Week 30 infusion in treatment-experienced subjects will be presented in a listing by subject, treatment period, visit, date, and scheduled/nominal sampling time point. The data listing will provide details of all planned total IgG collection time points relative to the start of the Week 14 or the Week 30 infusion (scheduled and nominal times as shown in Protocol Appendix 1), actual collection dates and clock times and

actual elapsed times from the start of the infusion, as well as total IgG concentrations. If any concentration values are excluded from the PK analyses, they will be flagged in the listing.

The clock time for the start and completion of the infusion, the actual duration (time interval) for the infusion, and the actual volume infused will be presented in a separate listing.

Serial total IgG concentrations will be summarized by treatment period and the scheduled/nominal time point. The summaries will include n, mean, SD, coefficient of variation (%CV), median, minimum, maximum, and geometric mean.

Total IgG concentration vs. time curves for individual subjects will be presented with the actual elapsed time from the start of the Week 14 or Week 30 infusion plotted on the x-axis. Individual concentration vs. time plots will also be presented for all subjects on the same figure (spaghetti plot), separately for each treatment period. For all subjects combined, mean or median total IgG concentration vs. time curves will be presented in one figure with the nominal time plotted on the x-axis. All total IgG concentration vs. time curves will be plotted on both the linear and the semi-log scale.

9.3.2 Primary PK Parameter (treatment-experienced subjects)

The primary PK endpoint is the steady-state AUC of total IgG over the regular dosing interval (τ):

- $AUC_{0\text{-}\tau}$, weekly, the steady-state AUC over the regular dosing interval (τ) following weekly infusion, i.e., $AUC_{0\text{-}7}$ days.
- $AUC_{0\text{-}\tau}$, biweekly, the steady-state AUC over the regular dosing interval (τ) following biweekly infusion, i.e., $AUC_{0\text{-}14}$ days.

Because the dosing intervals are different between the weekly and biweekly dosing frequencies, prior to the statistical comparison, the $AUC_{0\text{-}14}$ days for the biweekly dosing will be divided by 2 for comparison with $AUC_{0\text{-}7}$ days for the weekly dosing.

Formal non-inferiority testing will be performed for $AUC_{0\text{-}7}$ days based on established regulatory guidelines for bioequivalence testing.

The null hypothesis for the non-inferiority testing is:

$$H_0: \frac{\mu_T}{\mu_R} \leq 0.8$$

The alternative hypothesis is:

$$H_1: \frac{\mu_T}{\mu_R} > 0.8$$

Where μ_T is $AUC_{0\text{-}7}$ days for the biweekly dosing (derived as $AUC_{0\text{-}14}$ days divided by 2) and μ_R is $AUC_{0\text{-}7}$ days for the weekly dosing. The hypothesis testing will be performed at a one-sided alpha level of 0.05.

Natural log-transformed $AUC_{0\text{-}7}$ days values will be analyzed by analysis of variance with a mixed-effect model. The model will include treatment period (weekly or biweekly dosing) as a fixed effect, and subject as a random effect. From this model, the geometric least-squares mean ratio between biweekly and weekly dosing and the corresponding 90% CI will be calculated. Non-inferiority will be demonstrated if the lower limit of the 90% CI is above 0.8.

This analysis can be implemented by the following sample SAS code:

```
PROC MIXED;
    Class  trtperiod subjid;
    Model log(AUC) = trtperiod;
    Random subjid;
    Lsmeans trtperiod / pdiff cl alpha = 0.1;
    Estimate 'biweekly vs weekly' trtperiod -1 1 / cl alpha = 0.1;
Run;
```

where trtperiod, log(AUC), and subjid represent treatment period (biweekly or weekly), natural logarithm of the primary PK parameter ($AUC_{0\text{-}7\ days}$), and subject number, respectively. Only those subjects or values in the PK population determined to be legitimate for inclusion in the statistical analysis during the data review will be included in the mixed-effect model.

The weekly dosing will be considered as the Reference treatment group, and the biweekly dosing will be treated as the Test treatment group. The ANOVA will include calculation of LSMs, differences between LSMs, and the standard error associated with these differences. The administration effect between biweekly and weekly will be assessed by exponentiation of the difference in LSMs for $AUC_{0\text{-}7\ days}$ between treatment groups (Test-Reference) and the corresponding 90% CI for the geometric LSM ratio between treatment periods (Test/Reference) and the corresponding 90% CI for the ratio. The Test (biweekly) is considered non-inferior to Reference (weekly) if the lower bound of the 90% CI for the geometric LSM ratio of $AUC_{0\text{-}7\ days}$ between the Test and Reference is above 0.80 (80%).

As sensitivity analyses, the ANOVA above will be repeated for subjects who had serial PK profile in both the weekly and biweekly dosing schedules. The analysis will be implemented if applicable (i.e., Some subjects discontinue early before entering biweekly dose).

9.4 Secondary PK Parameters (treatment-experienced subjects)

The PK population will be used for the analyses of additional steady-state PK parameters of total IgG, C_{max} and t_{max}. Descriptive statistics as noted in section 9.2 above will be used to summarize these parameters for treatment-experienced subjects. No inferential statistical analyses will be performed.

10 SECONDARY ANALYSES

10.1 Steady-State Mean Trough Concentration of Total IgG

The IgG population will be used for the analyses of mean trough total IgG concentrations. All data will be listed.

The secondary variable of steady-state mean trough concentration of total IgG in treatment-experienced subjects will be analyzed as follows. For each treatment period, all pre-infusion total IgG concentrations obtained prior to and at the 12th week of IGSC 20% dosing will be evaluated to determine if an approximate steady-state condition has been achieved by the 12th week of the treatment period. In Treatment Period 1, the steady-state mean trough concentration of total IgG following SC administrated IGSC 20% will be determined as the average value of IgG trough measurements obtained at Weeks 12, 14, and 16 during weekly dosing. In Treatment Period 2, the steady-state mean trough concentration of total IgG following SC administrated IGSC 20% will be determined as the average value of the IgG trough measurements obtained at Weeks 28, 30, and 32 during biweekly dosing. Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG by treatment period. The steady-state mean trough will also be analyzed by a mixed-effect model similar to that for the primary PK analysis (see SAP Section 9.4).

Descriptive statistics will be used to summarize mean trough concentrations of total IgG for treatment-naïve subjects. No inferential statistical analyses will be performed.

10.2 Trough Concentration of Total IgG at Individual Time Points

The IgG population will be used for the analyses of trough total IgG concentrations. All data will be listed.

Descriptive statistics will be used to summarize trough concentrations of total IgG at individual time points for treatment-experienced subjects and for treatment-naïve subjects. No inferential statistical analyses will be performed.

10.3 Secondary Endpoints Related to Infection

Secondary endpoints related to infection include the following:

- Total number of SBIs, proportion of subjects who experience SBIS, and rate of SBIs as defined in Protocol Appendix 4 in all subjects
- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infection diarrhea, etc.) as determined by the Investigator
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)

- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection.
- Number of hospitalizations due to infection

The Efficacy Evaluable population will be used for the analyses of all secondary endpoints related to infection.

These variables will be summarized descriptively for all subjects (treatment-experienced and treatment-naïve subjects will be analyzed separately). The number and percentage of subjects with the events, the total number of events or days, the annualized rate of events or days for individual subjects, and the rate of events or days per person per year will be summarized descriptively for each study phase. The rate of events or days per person per year will be analyzed using the generalized linear model procedure for Poisson regression. All data will be listed as well.

The annualized rate of events or days for individual subjects will be calculated as:

$$annualized\ rate\ of\ events\ or\ days\ for\ the\ individual\ subject$$

$$= \frac{number\ of\ events\ or\ days\ for\ the\ individual\ subject}{duration\ of\ exposure\ in\ years\ for\ the\ individual\ subject}$$

The rate per person per year of SBIs, all infections, validated infections, days on antibiotics, and hospitalizations will be calculated and the two-sided 95% CI will be provided, using the generalized linear model procedure for Poisson regression with log link (assuming occurrence of the events or days follows the Poisson distribution).

Person-year during each study phase will be calculated for each subject as (duration of exposure in days/365.25), and the natural log-transformed person-year will be used in the generalized linear model as an offset variable. No covariates but the intercept term are included in the model. The estimated intercept term and its two-sided 95% CI will be transformed by using the natural exponential function, to provide the point estimate of the rate per person per year and its two-sided 95% CI.

Note the point estimate obtained from the generalized linear model above is the same as the rate of events/days per person per year directly calculated as follows:

$$rate\ of\ events\ or\ days\ per\ person\ per\ year$$

$$= \frac{total\ number\ of\ events\ or\ days\ for\ all\ subjects}{total\ duration\ of\ exposure\ in\ years\ for\ all\ subjects}$$

In addition, a summary of total number and percentage of weekly or biweekly infusions by season will be generated to explore potential seasonal effect on these secondary variables.

11 EXPLORATORY ANALYSIS

Exploratory analyses will be based on the Efficacy Evaluable population.

For treatment–experienced subjects, analysis of surveys and questionnaires pertaining to treatment satisfaction and QOL including LQI, TSQM-9, and SF-12 (subjects ≥18 years) will be performed to evaluate change from Baseline to end of Treatment Period 1 (weekly IGSC 20% dosing), and from end of Treatment Period 1 to end of Treatment Period 2 (biweekly IGSC 20% dosing). This will allow a comparison of weekly versus biweekly dosing frequencies via infusion pump. Change from period-specific baseline (pre-SC#1 infusion for Treatment Period 1 and pre-Week 16 infusion for Treatment Period 2) to end of the period (Week 16 for Treatment Period 1 and Week 32 for Treatment Period 2) will be analyzed by a mixed-effect model. The model will include period-specific baseline as a covariate, treatment period (weekly or biweekly) as a fixed effect, and subject as a random effect. From this model, the LSMs for each treatment period, the between-treatment differences in LSMs, and the associated 95% CIs will be calculated for the treatment comparison between biweekly and weekly IGSC 20% dosing. For treatment-naïve subjects, analysis of SF-12/SF-10 will compare the subject's perception of state of health from study entry (pre-SC#1 infusion) to Week 16 and to Week 32.

11.1 LQI

The LQI comprised 15 items with assessments to be made on a 7-point Likert scale ranging from extremely good (=7) to extremely bad (=1). The LQI was psychometrically evaluated and comprised four scales:

- I treatment interference (items 4, 7, 9, 12, 14, 15)
- II therapy related problems (items 1, 2, 3, 10)
- III therapy setting (items 5, 6, 8)
- IV treatment costs (items 11, 13)

LQI scale scores are computed by summing up item values within a factor, and transforming them into scores ranging from 0 to 100 using the following formula:

Normalized score = (Sum – Min) / (Max – Min) * 100, where:

- Sum = sum of non-missing scores in the scale
- Min = (Number of non-missing items in the scale) * 1

- Max = (Number of non-missing items in the scale) * 7

Higher scores indicated a higher treatment satisfaction or health-related quality of life.

11.2 TSQM-9

TSQM-9 is a measure of treatment satisfaction in 3 categories:

- Effectiveness Scale (questions 1 to 3)
- Convenience Scale (questions 4 to 6)
- Global Satisfaction Scale (questions 7 to 9)

TSQM-9 Scale scores are computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provides a transformed score between 0 and 1 that should be multiplied by 100. [Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent]

Effectiveness
- If no items are missing: (Sum(Items 1 to 3) – 3) / 18) * 100
- If one item is missing: (Sum(the 2 completed items) – 2) /12 * 100

Convenience
- If no items are missing: (Sum(Items 4 to 6) – 3) / 18) * 100
- If one item is missing: (Sum(the 2 completed items) – 2) / 12 * 100

Global Satisfaction
- If no items are missing: (Sum(Item 7 to 9) – 3) / 14) * 100
- If item 7 or 8 is missing: (Sum(the 2 completed items) – 2) / 10)* 100
- If item 9 is missing: (Sum(Item 7 and 8) – 2) / 8 * 100

The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

Change in TSQM-9 domain scores from Pre-SC#1 Week 0 to Week 16, and from Week 16 to Week 32 will be analyzed.

11.3 SF-12

The SF-12 is a health status survey with 12 questions. It is normed for use with adults. The SF-12 summary scales will be calculated using the SF-12 Health Survey Standard Scoring software. Summary scores will be computed for Physical Component Summary (PCS) and Mental Component Summary (MCS). Subscores will also be computed for the following 8 domains: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), Social Functioning (SF), Mental Health (MH), Role-Emotional (RE), Vitality (VT), General Health (GH).

Process for arriving at T scores for the SF-12 health domain scales and component summary measures are presented in detail below. Single-item scales (BP, GH, VT, SF) without responses are considered missing. All items, scales, and summary measures are scored so that a higher score indicates a better health state.

Step 1: Recode item response values.
Derives the final item response scores, to be used when calculating the raw scale score for each health domain.

Step 2: Determine health domain scale total raw scores.
The total raw score is the simple algebraic sum of the final response values for all items in a given scale. For example, the total raw score for the RP scale is the sum of the final response values (i.e., recoded response values or, when applicable, imputed values) for Items 3a and 3b.

Step 3: Transform health domain scale total raw scores to 0–100 scores.
The next step in scoring the health domain scales involves transforming each total raw scale score to a 0–100 scale score using the following formula:

$$\text{Transformed scale score} = \frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}} \times 100$$

Step 4: Transform health domain scale 0–100 scores to *T* scores using health domain *z* scores.
The first step in transforming the 0–100 scores to T scores is standardizing each SF-12 health domain scale using a z-score transformation. A linear z-score transformation is used so that each of the 8 health domain scales has a mean of 0 and a standard deviation of 1. A z score is computed by subtracting each health domain scale's population mean from the 0–100 score for that scale, and then dividing the difference by that scale's standard deviation.

The next step is transforming each obtained *z* score to a *T* score (mean = 50, SD = 10). To do so, each z score is multiplied by 10, and then 50 is added to the resulting product. Thus, the formula for computing T scores for the PF scale is:

$$\text{PF T score} = 50 + (\text{PF z} \times 10)$$

Step 5: Score Physical and Mental Component Summary measures using health domain *z* scores.
Aggregating scale scores. When computing PCS and MCS scores, the first step is computation of aggregate scores for the physical and mental components using the physical and mental factor score coefficients and the z scores previously computed for each of the eight health domain scales (see Step 4). Computing an aggregate physical component score consists of multiplying each SF-12 health domain scale z score by its respective physical factor score coefficient, and then summing the resulting eight products.

Transforming summary scores to T scores. The second step is transforming each standard or acute form aggregate component score to a *T* score. This is accomplished by multiplying each aggregate component scale score by 10, and then adding 50 to the resulting product. The formulas for computing the *T* score for each component summary measure are:

PCS *T* score = 50 + (Aggregate physical component score x 10)
MCS *T* score = 50 + (Aggregate mental component score x 10)

11.4 SF-10

The SF-10 Health Survey for Children is a brief, 10-item, parent- or guardian-completed assessment designed to measure the physical and psychosocial functioning of children aged 5 through 17 years.

Scoring the summary measures for the SF-10 requires three steps: assigning a value to each item response choice, calculating the Physical Health Summary (PHS-10) T score (mean = 50, SD = 10), and calculating the Psychosocial Summary (PSS-10) T score. The PHS-10 and PSS-10 are scored so that higher scores indicate more favorable physical and psychosocial functioning, respectively.

The PHS-10 score is computed by: (a) summing the final response values for the five PHS-10 items, arriving at an aggregated score; (b) standardizing the aggregated score to a z score using the associated mean and SD; and (c) converting the z score to a T score. The PSS-10 score is computed in the same manner, instead using the five PSS-10 items and the appropriate mean and SD. Valid responses for all five items in a given summary scale (i.e., PHS-10 or PSS-10) must be available to score that summary scale.

12 SAFETY ANALYSIS

Safety analyses will be based on the Safety population.

Safety analyses for all subjects will be addressed by listing and tabulation of AEs (including suspected ADRs), clinical laboratory tests, vital signs, and physical assessments. Data will be summarized using descriptive analyses, and treatment comparisons will be based on review of descriptive statistics.

Safety data will be analyzed separately for treatment-experienced and treatment-naïve subjects.

12.1 Adverse Events

All reported AEs will be coded and summarized by system organ class (SOC) and preferred term (PT) according to MedDRA.

When the causal relationship of an AE is classified by the investigator as definitely or possibly related, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of “definitely related” will be defined as an AR. The sponsor will

consider the investigator's causality assessment and also provide its own assessment. If there is any disagreement in the causality assessment between the investigator and the sponsor, a separate summary of suspected ADRs/ARs will be provided.

For summary purposes, AEs will be classified as TEAEs or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment. A TEAE will be defined as an AE which occurs between the start of study treatment and the final follow-up visit of the clinical study. A non-TEAE will be defined as an AE which occurs prior to the start of study treatment. Non-TEAEs and TEAEs will be summarized separately.

Adverse events will be considered treatment emergent (TEAE) if the start date is missing, or the start date is non-missing and same as first dose date but the time is partial/missing. Note: the eCRF does not permit entry of partial dates, only partial times are permitted.

In addition, TEAEs, suspected ADRs, and ARs will be summarized by treatment group, treatment regimen at the time of TEAE, system organ class, preferred term, causal-relationship, severity, and seriousness (serious vs non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe AE or the AE with the strongest causal relationship. Summaries will also be provided for the total number of events and the rate per infusion.

AEs temporally associated with the infusion of IGSC 20% (i.e., infusional AEs, including infusional suspected ADRs) will be summarized by presenting infusion/subject incidences and percentages, and listed. In addition, local infusion site reactions will be tabulated and summarized for the total duration of each treatment period (for treatment-experienced subjects) or the total duration of the treatment phase (for treatment-naïve subjects), and by IGSC 20% infusion week.

Summaries will also be provided for the total number of events, the rate per infusion, and the rate per exposure week.

The rate per infusion will be calculated as:

Total number of events / Total number of infusions received

The rate per exposure week will be calculated as:

Total number of events / Total duration of exposure in weeks

Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed.

Temporally associated AEs defined as those occurring during or within 72 hours following the end of study drug and investigational product infusion will be separately summarized. If an AE occurs after the dose on the end of study visit, it will be considered as TEAE, but will not be considered as temporally associated AE. For AEs that occur during study drug infusion, the infusion rate in effect at the time of onset of the AE, the time when the AE is

first reported and the time when the AE changes materially in intensity and/or resolves will be listed.

Local infusion site reactions during the IGSC 20% treatment period that do not meet the definition of an AE will be separately summarized by IGSC 20% infusion week and overall. The summaries will be presented by preferred term and infusion site and include the number and percentage of subjects with any event, the total number of events, and the rate per infusion. The percentage of subjects with any local infusion site reactions and the rate per infusion will also be plotted vs. IGSC 20% infusion week number.

All AEs and local infusion site reactions that meet the definition of an AE will be presented in a data listing. Local infusion site reactions that do not meet the definition of an AE will be listed separately.

12.2 Laboratory Assessments

The following tests will be collected for all subjects if applicable at the assigned visits according to the protocol:

- Hematology (hemoglobin, hematocrit, platelets, red blood cell count , white blood cell count with differential, absolute reticulocyte count [ARC]),
- Clinical chemistry (sodium, potassium, creatinine, chloride, calcium, blood urea nitrogen [BUN], lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, indirect bilirubin, special tests (direct antiglobulin test [DAT], serum/plasma free hemoglobin, haptoglobin),
- Urinalysis (pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase [with microscopic examination of the urine if abnormal])
- Pregnancy testing will be performed for child-bearing potential females only and will be analyzed by a local laboratory, serum at Screening visit and local urine testing at Baseline visit.
- Total IgG levels will consist of trough (predose) measurements for all subjects
- Serial total IgG concentrations post Week 14 and Week 30 dosing for PK profiling in treatment-experienced subjects

All laboratory panels (with the exception of pregnancy testing) will be stored and/or analyzed by a central laboratory.

The hematology, clinical chemistry, special tests, pregnancy tests, and urinalysis parameters will be summarized at each visit with number of subjects, mean, SD, median, minimum, and maximum values for continuous variables and counts and percentages per category for categorical variables. The original value and change from Screening, change from the pre-SC#1 infusion for Treatment Period 1 or pre-Week 16 infusion for Treatment Period 2 will

be descriptively summarized for continuous variables. Shift tables, based on the high/low flags, will also be summarized at each visit for each parameter with normal ranges. For selected analytes, tabular summaries and listings will be provided of treatment-emergent laboratory abnormalities utilizing the following thresholds of interest which are in some cases relative to the established reference range (multiples of lower limit of normal [LLN] or upper limit of normal [ULN]) and in others an absolute value threshold:

- Hemoglobin: treatment-emergent (TE) value 8.9 g/dL or less AND a decrease of 1 g/dL from Baseline
- Absolute Neutrophils: TE Neutrophils <750/mm^3, < 500/mm^3 (2 thresholds) (Note: 1/ mm^3 = 1/uL = 0.001 x10^3/uL)
- Creatinine: TE > 2.5 x ULN (reference range specific to gender/age)
- Alanine aminotransferase [ALT]: TE > 3 x ULN (reference range specific to gender/age)
- Total bilirubin: TE > 3 x ULN (reference range specific to gender/age)
- Haptoglobin: < LLN

A listing of patients with positive direct antiglobulin (DAT) test results (positive for at least one of IgG and C3) from Screening through end of study will be provided that includes all DAT results for any patient with at least one positive DAT value, and all hemoglobin, absolute reticulocyte count, serum free hemoglobin, haptoglobin, LDH, and total and indirect bilirubin values at corresponding time points.

The analysis of serial total IgG and trough IgG data are described in SAP sections 9 and 10.

All laboratory data will be presented in data listings.

12.3 Vital Signs

Vital sign data (SBP, DBP, HR, T, and RR) will be summarized with the number of subjects, mean, SD, median, minimum, and maximum values by treatment group and visit. Summaries will be presented for the original value and change from Screening, change from the pre-SC#1 infusion for Treatment Period 1 or pre-Week 16 infusion for Treatment Period 2. Body weight, height, and BMI will be similarly summarized.

All vital sign data will be listed.

12.4 Physical Assessments

Full physical assessment findings at the Screening Visit will be summarized with numbers and percentages by body system. Entries for 'Other' body systems will be grouped together; a subject with 2 or more 'Other' entries will be counted only once.

All physical assessment data will be listed.

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Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	2/1/2022 3:32:02 AM
Certified Delivered	Security Checked	2/1/2022 8:18:00 AM
Signing Complete	Security Checked	2/1/2022 8:18:33 AM
Completed	Security Checked	2/2/2022 10:05:56 AM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

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Parties agreed to: [redacted]

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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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