STATISTICAL ANALYSIS PLAN (SAP)

IGSC 20% / GTI1502

Title: An open-label, multi-center study to evaluate the safety and pharmacokinetics of IGSC 20% administered for 6 months in subjects with primary immunodeficiency

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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
$AUC_{0\text{-}21\ days}$	Area under the concentration-time curve from 0 to 21 days
$AUC_{0\text{-}28\ days}$	Area under the concentration-time curve from 0 to 28 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
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
DVT	Deep Vein Thrombosis
dL	Deciliter
eCRF	Electronic Case Report Form
HR	Heart rate
IgG	Immunoglobulin G
IGIV-C 10%	Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified (Grifols)
IGSC 20%	Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (Grifols)
IV	Intravenous
IVIG	Intravenous Immune Globulin (generic terminology)
kg	Kilogram
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LSM	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NAT	Nucleic acid amplification technology
PE	Pulmonary Embolism

PI	Primary immunodeficiency
PK	Pharmacokinetic(s)
PT	Preferred term
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBI	Serious bacterial infection
SBP	Systolic blood pressure
SC	Subcutaneous
SCIG	Subcutaneously delivered immune globulin or subcutaneous immunoglobulin (generic terminology)
SD	Standard deviation
SOC	System Organ Class
SSC	Specific Signs/Symptoms Check
T	Temperature
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to reach C_{max}
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol GTI1502 Version 3.0, dated 15 Mar 2016. 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 prospective, multi-center, open-label, single-sequence, 6-month, pharmacokinetic (PK) and safety and tolerability study of Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) in subjects with primary immunodeficiency (PI). Approximately 50 subjects will be enrolled in order to have approximately 30 adult subjects and 12 to 18 pediatric subjects (ages 2-16 years) completing treatment with subcutaneously administered IGSC 20%. Pediatric enrollment will be stratified by age category with a target of 4 to 6 children for each group: 2 to 5 years, >5 to 12 years, and >12 to 16 years of age. The PK profiles of total immunoglobulin G (IgG) following administration of both intravenous (IV) (Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified [IGIV-C 10%]) administration and subcutaneous (SC) (IGSC 20%) administration under approximate steady-state conditions will be determined and compared. The primary objective is to determine a weekly SC dose of IGSC 20% that achieves an area under the concentration-time curve (AUC) of total IgG that is non-inferior to that achieved by a subject's IV dose of immune globulin.

This study will include 3 treatment phases: Run-In Phase, IV Phase (IV administration of IGIV-C 10% treatment), and SC Phase (SC administration of IGSC 20%). Before a subject is to be enrolled (entering either the Run-In or IV Phase) into the study, the subject will be screened during the Screening Phase, which is up to 28 days. The specific inclusion and exclusion criteria for this study are described in Section 3.2 of the protocol.

Subjects, depending on their current IgG treatment regimen, may be required to enter the Run-In Phase to receive IV IGIV-C 10% treatment (Sponsor provided) to achieve an approximately steady-state condition prior to entering the IV Phase. They will then enter the IV Phase to determine the AUC profile of IV infusions of IGIV-C 10%.

Subjects with a qualifying IV IGIV-C 10% treatment regimen (on stable IGIV-C 10% doses of 300-800 mg/kg) can enter the IV Phase directly where they will receive IGIV-C 10% (Sponsor provided). In the IV Phase, steady-state IV PK assessments including AUC will be performed.

After completing the IV Phase, subjects will enter the SC Phase to receive weekly SC doses of IGSC 20% for at least 24 weeks. The IGSC 20% dose will be determined by using an

initial IV to SC dose adjustment factor of 1.37. After reaching an approximate steady-state condition, the SC PK profiles including AUC at SC Week#13 will be determined.

The interim serial PK samples (for both the IGIV-C 10% IV and the IGSC 20% SC dosing phases) may be obtained at an alternate location. If an outside agency is utilized for sample collection, the samples will be drawn and processed per protocol and laboratory manual instructions.

Comparison of the IV PK profiles and IGSC 20% PK profiles in the first 6 adult/adolescent subjects will be performed through an interim PK analysis. If the dose adjustment factor is deemed acceptable (SC dose of IGSC 20% is non-inferior to the subject's IV dose) (Section 3.1.5 of the protocol), all subjects will continue to complete treatment and assessments through Week#25 (no further monthly extension visits). Otherwise, a new dose adjustment factor will be employed for all subjects following the procedures described in Section 3.1.5 of the protocol, and subjects will receive 24 weeks of IGSC 20% treatment at the new IGSC 20% dose. In this study, the PK profiles will be assessed in all subjects. Subjects aged 2 to 5 years old will be assessed using an abbreviated sampling schedule for PK profiles.

The overall study diagram is depicted in Figure 2-1 and Figure 2-2. The study entry of subjects is described in Table 2-1. Further details on study design and the schedule of study procedures are provided in Section 3.1 and Appendix 1 of the protocol.

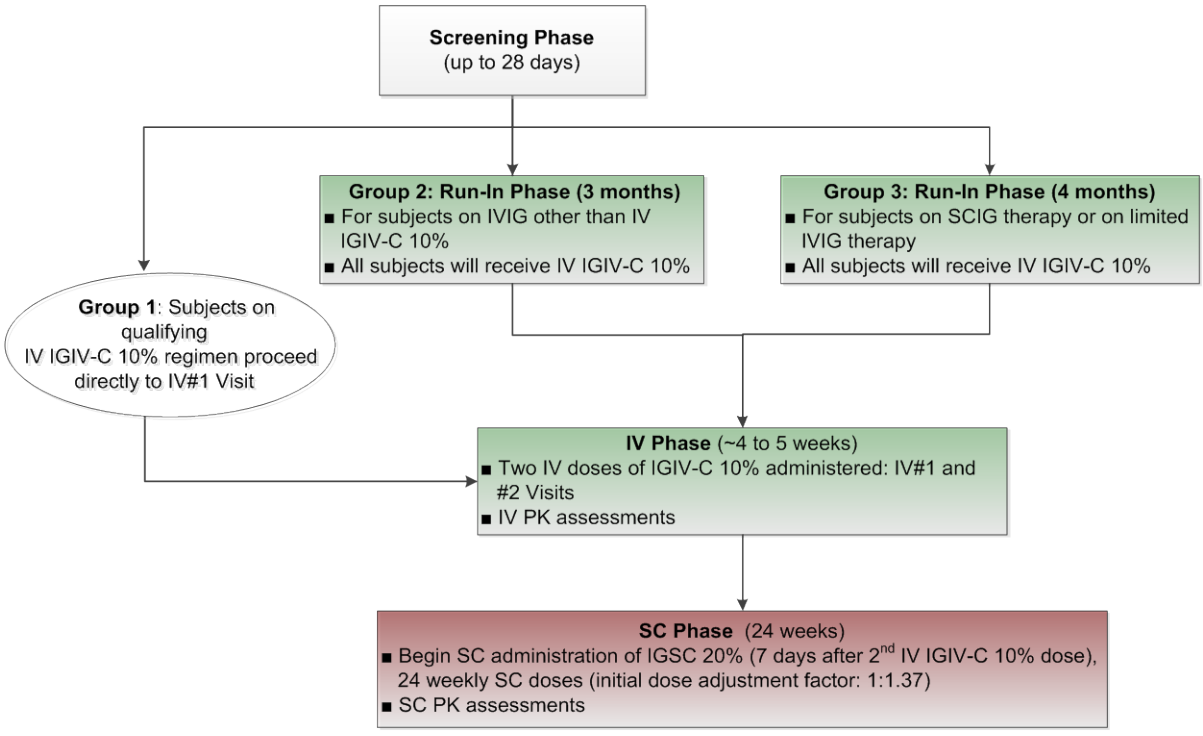
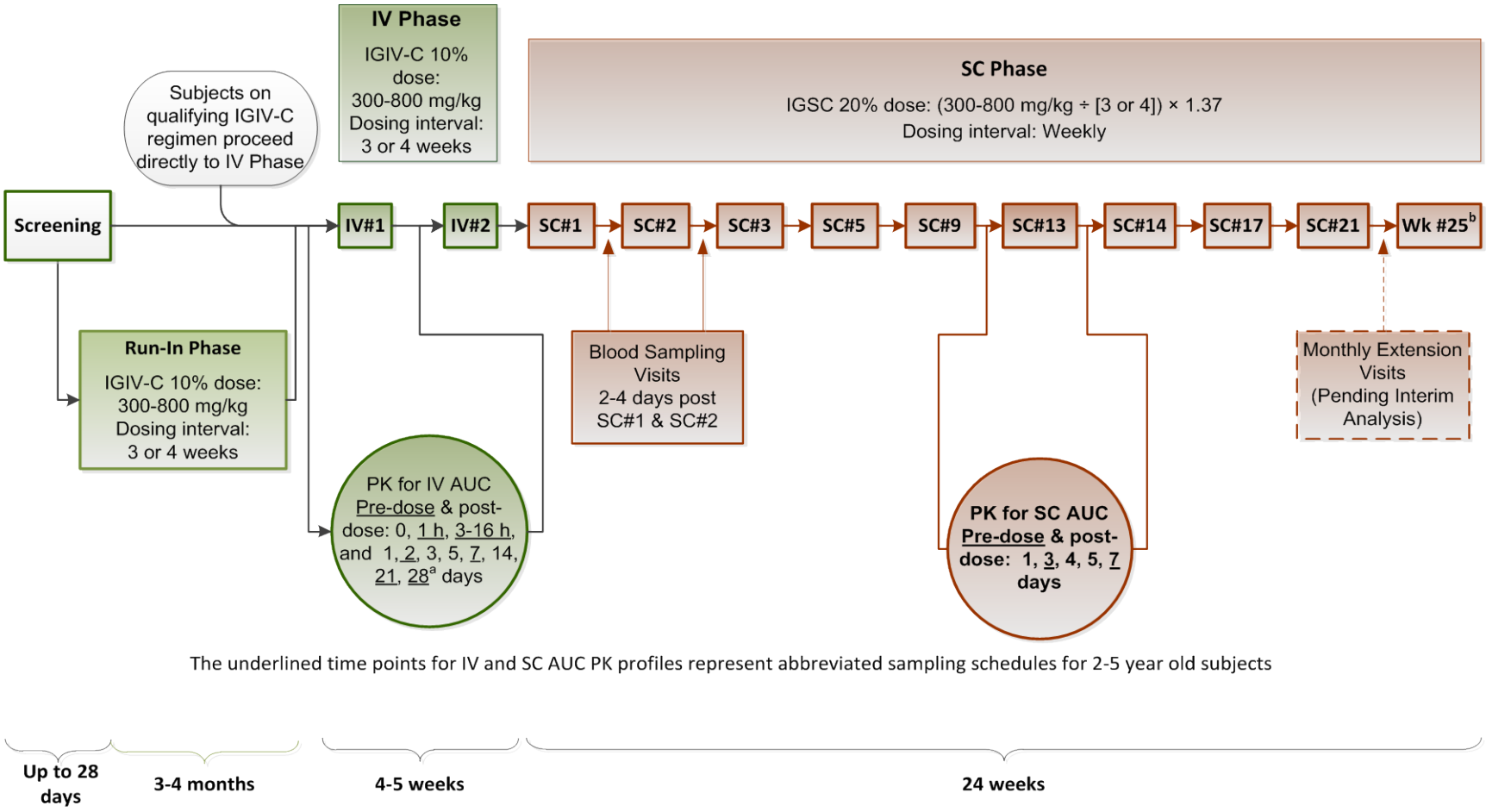


Figure 2-1 Overall study design



[a] Only applicable to subjects who are on a 4-week dosing interval

[b] Wk#25 = Final Visit (Week #25)/Early Termination Visit

Figure 2-2 IV dosing of IGIV-C 10% and SC dosing of IGSC 20% Clinic Visits and PK sampling schedules (Also see Sections 3.6.2.3 and 3.6.2.4 of the protocol)

Table 2-1 Study entry of subjects

	Subject Populations at Screening Based upon Most Recent IgG Treatment History (All must have confirmed diagnosis of PI)	Required Study Entry Point	IGIV-C 10% Dose and Interval during Study
1	Receiving stable (≥3 months) dose of IV IGIV-C 10% between 300 and 800 mg/kg, every 3 or 4 weeks	**IV Phase** (IV#1)	Same dose and interval as at screening.
2	Receiving IVIG other than IGIV-C 10% with doses between 300 and 800 mg/kg, every 3 or 4 weeks	**Run-In Phase** (3 month)	Same dose and interval as at screening.
3	Receiving IVIG other than IGIV-C 10%, but either not on stable dose (≥ 3 months) OR dose is not between 300 and 800 mg/kg OR interval is not every 3 or 4 weeks	**Run-In Phase** (4 month)	Dose (300-800 mg/kg) and interval (3 or 4 weeks) to be determined by Investigator.
	Receiving SCIG	**Run-In Phase** (4 month)	Dose (300-800 mg/kg) and interval (3 or 4 weeks) to be determined by Investigator.

2.2 Study Objectives

2.2.1 Primary Pharmacokinetic Objective

- To determine a dose of weekly subcutaneously administered IGSC 20% that produces steady-state AUC of total IgG that is non-inferior to that of the regularly administered IV dose of IGIV-C 10% in PI subjects

2.2.2 Secondary Objectives

- To determine if IGSC 20% replacement therapy maintains mean steady-state trough total IgG levels that are comparable to the mean trough total IgG levels with the IGIV-C 10% replacement therapy in PI subjects

2.2.3 Exploratory Objectives

- To evaluate t_{max} (time to reach C_{max}) and C_{max} (maximum concentration) in PI subjects at steady state
- To evaluate trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- To evaluate antibody levels for *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Clostridium tetani* (tetanus)
- To evaluate the rate of serious bacterial infections (SBIs)
- To evaluate all infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- To evaluate validated infections documented by positive radiograph, fever (> 38°C oral or > 39°C rectal), culture, or diagnostic testing for microorganisms, eg, bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)

- To evaluate 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.
- To evaluate number of hospitalizations due to infection
- To evaluate number of days of work/school/daily activities missed due to infections and their treatment
- Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes

2.2.4 Safety Objectives

- To assess the safety and tolerability of IGSC 20% as an IgG replacement therapy in subjects with PI

3 STUDY VARIABLES

3.1 Primary Pharmacokinetic Variables

- AUC in the IV Phase: Steady-state AUC of total IgG over a regular dosing interval (τ), either every 3 weeks or every 4 weeks (ie, $AUC_{0\text{-}\tau,\ IV}$ or $AUC_{0\text{-}21\ days,\ IV}$ or $AUC_{0\text{-}28\ days,\ IV}$, respectively) in PI subjects
- AUC in the SC Phase: Steady-state AUC of total IgG over a weekly SC dosing interval (τ) (ie, $AUC_{0\text{-}\tau,\ SC}$ or $AUC_{0\text{-}7\ days,\ SC}$) in PI subjects

3.2 Secondary Pharmacokinetic Variables

- Mean steady-state trough (pre-dose) concentration of total IgG following IV administration of IGIV-C 10% or SC administration of IGSC 20%

3.3 Exploratory Variables

- t_{max} (time to reach C_{max}) and C_{max} (maximum concentration) in PI subjects at steady state
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *S. pneumoniae*, *H.influenzae*, and *C. tetani* (tetanus)
- Rate of SBIs
- All infections of any kind (serious/nonserious 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, eg, 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
- Number of days of work/school/daily activities missed due to infections and their treatment
- Trough measles antibody titers (functional assay) for informational purposes

3.4 Safety Variables

The following safety variables will be assessed in this study:

- Adverse events (AEs), suspected adverse drug reactions (suspected ADRs), adverse reactions (ARs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
  Note: All infusion site reactions will be recorded in the electronic case report form (eCRF). For 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, they will be considered as AEs.
- Vital signs during clinic visits (systolic blood pressure [SBP] and diastolic blood pressure [DBP], heart rate [HR], temperature [T], respiratory rate [RR])
- Physical Assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Laboratory assessments including chemistry, hematology, and urinalysis.
- Total number of non-serious infections and proportion of subjects who experience non-serious infections of any kind (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator.

4 GENERAL STATISTICAL CONSIDERATIONS

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

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. The hypothesis testing for the primary PK analysis of non-inferiority will be tested at 1-sided with α=0.05. All other statistical inferences will be tested at 2-sided with α=0.05, if applicable.

Unless otherwise noted, all data collected in the eCRFs or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number) and grouped/sorted by age

group, followed by study phases (Run-In Phase, IV Phase, and SC Phase) and visit/time point.

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.

For table summaries that are presented by age group and overall, the following age groups will be used: ≥2 - ≤5, >5 - ≤12, >12 - ≤16, >16 years.

4.1 Data Handling

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.

Baseline in general will be defined as the last measurement taken prior to the start of the study drug infusion (commercial IV IGIV-C 10%) at the first infusion visit during the Run-In Phase for subjects who are enrolled into the Run-In Phase or at IV Visit #1 for subjects who are enrolled directly into the IV Phase. Where appropriate, additional analyses will be performed for treatment-emergent changes from Screening and from the start of investigational product (IP) which is subcutaneous IGSC 20% relative to predose parameters at the SC Week #1 visit.

4.1.1 PK Data Handling

4.1.1.1 Time Window for Pharmacokinetic Analysis

The time window allowed for serial PK blood sample draws during the IV Phase and the SC Phase is specified in the study protocol. 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.

The actual elapsed time between the start of the infusion 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 of the IGIV-C 10% IV#1 infusion is shown below.

Scheduled Time	Nominal Time (Hours)	Example Actual Elapsed Time (Hours)
Pre-infusion *	0	0
Start of infusion	0	0
Immediately at the completion of the infusion	5	5.15
1 hour post-infusion *	6	6.55
3 to 16 hours post-infusion *	21	18.20
1 day post-infusion	29	28.50
2 days post-infusion *	53	52.67
3 days post-infusion	77	76.86
5 days post-infusion	125	126.20
7 days post-infusion *	173	172.75
14 days post-infusion	341	347.67
21 days post-infusion *, †	509	511.50
28 days post-infusion *, §	677	677.30

* Abbreviated sampling schedule for subjects ≤5 years of age; † Last sample for subjects on an every-3-week IV dosing schedule and is also the pre-dose trough sample for IV#2; § Only for subjects on an every-4-week IV dosing schedule and is also the pre-dose trough sample for IV#2.

An example of actual elapsed time calculated from the time of the start of the IGSC 20% SC#13 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
Start of infusion	0	0
1 day post-infusion	26	26.50
3 days post-infusion *	74	73.86
4 days post-infusion	98	98.30
5 days post-infusion	122	123.20
7 days post-infusion *, †	170	169.75

* Abbreviated sampling schedule for subjects ≤5 years of age; † Within 0.5 hour prior to the IGSC 20% SC#14 infusion and is also the pre-dose trough sample for SC#14.

In addition, the actual duration of the infusion for the IV and SC doses will be calculated.

4.1.1.2 IgG Concentration Missing Values

For PK and IgG concentration analysis, any invalid IgG concentration values will be treated as missing, eg, 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.

4.1.1.3 Samples below the Limit of Quantification (BLQ)

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

Safety population

The Safety population will include all subjects who received any amount of study drug(s) (IGIV-C 10% and/or IGSC 20%) and will be used for safety analysis.

IgG population

The IgG population will consist of all subjects who receive study drug(s) and have any total IgG concentration data. The summary of total IgG concentration data will be based on the IgG population.

PK population

The PK population will consist of all subjects who receive study drugs and have sufficient and valid total IgG concentration vs. time data for either the IV or SC Phase to allow calculation of $AUC_{0\text{-}\tau,\,SC}$ or $AUC_{0\text{-}\tau,\,IV}$ (the primary PK endpoint).

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 (eg, 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).

4.3 Sample Size Considerations

The planned number of subjects is 50 enrolled to provide 30 completing adult subjects and 12 to 18 completing pediatric subjects. This sample size is primarily based on safety assessment consideration. Also, a sample size of 42 to 48 with at least 24 scheduled administrations of IGSC 20% would provide the clinical experience data on a total of more than 1008 to 1152 IGSC 20% dosing administrations for safety assessment.

The planned minimum enrollment of 42 completing subjects should be more than adequate to establish that the AUC for total IgG for IGSC 20% is non-inferior to that achieved by IGIV-C 10%.

4.4 Interim Analysis

An interim PK analysis will be conducted as described in Section 3.1.5 of the protocol. This analysis will be performed as soon as practical after the first 6 adult/adolescent subjects (aged ≥12-75 years) have completed the PK sampling schedule for both the IV (starting pre-infusion at IV#1 and ending pre-infusion at IV#2) and SC (starting pre-infusion at SC#13 and ending pre-infusion at SC#14) Phases of the trial. PK data from these 6 adult/adolescent subjects will be analyzed using the same PK and statistical methodology as that for the final PK analysis (see Section 9 for details), to evaluate and compare the $AUC_{0-\tau}$'s of total IgG from the IV administration of IGIV-C 10% and SC administration of IGSC 20%.

The outcome of this interim analysis will determine whether the dose adjustment factor will be modified. If the ratio of geometric least-squares means (LSM) for $AUC_{0\text{-}7\ days,\ SC}$ vs. adjusted $AUC_{0\text{-}7\ days,\ IV}$ falls below 10% of the desired 1.0 (ie, <0.9), and the mean trough concentrations for the SC administration of IGSC 20% falls below the target level of 500 mg/dL in more than 3 of the 6 adult/adolescent subjects, then a dose adjustment factor increase would be implemented to ensure that the subjects receive an optimal IGSC 20% dose and are not susceptible to potential bacterial infections.

If the ratio of geometric LSM for $AUC_{0\text{-}7\ days,\ SC}$ vs. adjusted $AUC_{0\text{-}7\ days,\ IV}$ achieves ≥0.9, there will be no change in the dose adjustment factor.

Subjects enrolled early in the trial may complete their regularly scheduled 24 weeks of SC therapy on the initial IGSC 20% dose before a decision from the interim analysis is available. In this event, these subjects will continue to receive weekly SC infusions of IGSC 20% until the interim PK analysis deems whether or not a new dose adjustment factor would be required. Subjects will return to the study center every 4 weeks for evaluation and have the same study procedures performed as those at SC Week#21 with (at less frequent intervals) safety laboratory assessments, IgG subclass levels, and specific antibody titers for *S. pneumoniae*, *H. influenzae*, and *C. tetani* (tetanus) every 8 weeks as detailed in Section 3.6.2.5 of the protocol. This will continue until the interim analysis is completed. If the results of the interim analysis do not indicate a need for a dose adjustment factor change, subjects will be brought into the clinic and end of study procedures will be performed.

If the need for changing the dose adjustment factor arises, the revised dose adjustment factor will be calculated based on the ratio of the geometric LSM for $AUC_{0\text{-}7\ days,\ SC}$ vs. adjusted $AUC_{0\text{-}7\ days,\ IV}$ with consideration of mean trough levels obtained from the SC administration of IGSC 20%.

The revised dose adjustment factor will be communicated to sites and the revised dose adjustment factor would be applied to the subjects' next SC infusion of IGSC 20% in the clinic, which should be scheduled as soon as possible, upon receiving formal notification from the Sponsor. These subjects will re-commence at SC#1 with the new dose adjustment factor. All subjects will be required to have a minimum of 24 weekly SC infusions of IGSC 20% with the new dose adjustment factor. For subjects currently in the SC Phase or who have completed the 24 weeks of the SC Phase and are continuing on treatment until the results of the interim PK analysis are available, subjects will be required to continue in the

SC Phase with the revised dose adjustment factor for 24 weekly SC infusions. In both of the above situations, all subjects will have a complete IGSC 20% PK profile (repeat, if necessary) after 12 weeks on the new dose adjustment factor (same assessment as initial SC Week #13). The time points for PK blood sample collection will be those outlined in Figure 2-2 and Section 3.6.2.4 of the protocol.

Final PK and statistical analysis will be based on the PK data in all subjects obtained with the final dose adjustment factor. If a revised dose adjustment factor is used, all available PK data obtained with the original dose adjustment factor will be summarized separately.

5 SUBJECT DISPOSITION

Subject disposition will include the number of subjects screened, number of subjects treated, number and percentage of subjects in each analysis population, and number and percentage of subjects completing the study by study phase and overall. Subject disposition will also be summarized by age group and overall.

The number and percentage of subjects discontinuing early from the study will be summarized for primary reasons of discontinuation by study phase and overall. 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 (ie, minor or major) will be summarized and listed.

7 DEMOGRAPHY AND MEDICAL HISTORY

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, race, ethnicity, age, age categories (≥2 - ≤5, >5 - ≤12, >12 - ≤16, >16 [with sub-categories: >16 - <65, ≥65] years), height, weight, baseline total IgG level, subject entry status, and frequency of the IV dose at entry will be summarized for the Safety population. The primary immunodeficiency and IgG treatment history will also be summarized. The summaries will be provided by age 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 age group and overall.

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 (ie, ATC level 2) and medication sub-class (ie, 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 study phase (concomitant medications). Prior medications are defined as any medication ended prior to the start of study treatment (ie, start of the infusion at Run-In Visit 1 for subjects who are enrolled into the Run-In Phase, or at IV#1 for subjects who are enrolled directly into the IV Phase). 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 (ie, 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 (ie, 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 (ie, “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 imputed medication end date/time will then be compared with the start of study treatment to determine if the medication is prior or concomitant.

Note the imputed end date/time will only be used to determine whether a medication is prior or concomitant. The start/end dates/times reported on the eCRFs will be presented in the listings.

8.2 Extent of Study Treatment Exposure and Compliance

8.2.1 Extent of Study Treatment Exposure

Duration of exposure will be determined for each study phase.

Duration of exposure in days

Run-In Phase

For subjects who completed the Run-In Phase, the duration of exposure in days will be calculated as:

Infusion date of IV#1 – First infusion date of the Run-In Phase

For subjects who prematurely discontinued from the study during the Run-In Phase, the duration of exposure in days will be calculated as follows:

[(Last infusion date of the Run-In Phase – First infusion date of the Run-In Phase) + 21], for subjects on an every-3-week IV dosing schedule

[(Last infusion date of the Run-In Phase – First infusion date of the Run-In Phase) + 28], for subjects on an every-4-week IV dosing schedule

IV Phase

For subjects who completed the IV phase, the duration of exposure in days will be calculated as:

Infusion date of SC#1 – Infusion date of IV#1

For subjects who prematurely discontinued from the study after IV#2 and before SC#1, the duration of exposure will include an additional 7 days to account for the planned duration of 7 days between IV#2 and SC#1. It will be calculated as:

(Infusion date of IV#2 – Infusion date of IV#1) + 7

For subjects who prematurely discontinued from the study after IV#1 and before IV#2, the duration of exposure in days will be calculated as:

(Infusion date of IV#1 – Infusion date of IV#1) + 21 = 21 days, for subjects on an every-3-week IV dosing schedule

(Infusion date of IV#1 – Infusion date of IV#1) + 28 = 28 days, for subjects on an every-4-week IV dosing schedule

SC Phase

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

(Last infusion date during SC Phase – Infusion date of 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 study phase, 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, infusion interruptions will be summarized. The distribution and number of SC infusion sites will be separately summarized. The summaries will also be provided by age group and overall.

The initial and revised (if applicable) dose adjustment factor(s) for all subjects collected on the eCRF will be listed.

8.2.2 Compliance

Infusion compliance, treatment compliance, and overall compliance will be calculated separately for each study phase. For the SC Phase, compliance will be calculated based data obtained with the final dose adjustment factor.

Infusion Compliance

Infusion compliance (%) will be calculated as:

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

For subjects who completed the study, the number of infusions expected will be 2 for the IV Phase and 24 for the SC Phase. In addition, if subjects are required to enter the Run-In Phase, then the number of infusions expected for the Run-In Phase will be determined as follows:

IV Dosing Schedule	Duration of Run-In Phase	Number of Infusions Expected
Every 3 weeks	3 Months	4
Every 3 weeks	4 Months	5
Every 4 weeks	3 Months	3
Every 4 weeks	4 Months	4

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 study phase in which the discontinuation occurred. For example, if a subject prematurely discontinued from the study after the SC#17 infusion and before the SC#18 infusion, then the number of infusions expected for the SC Phase is 17.

Similarly and if applicable, for subjects who were required to enter the Monthly Extension Visit(s) during the SC Phase, the number of infusions expected is the week number of the last infusion of the SC Phase (including the Monthly Extension Visit[s]).

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 collected on the eCRF (Run-In and IV Phases) or in the eDiary (SC Phase).

The total volume expected will be derived as follows:

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

For the Run-In and IV Phases

Dose expected (mg/kg) x Weight (kg) / Concentration of 100 (mg/mL)

For the SC Phase

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

If at any visits the dose expected and/or weight is not collected, the latest available values among the prior visits will be used.

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

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 study phase. The number and percentage of subjects with compliance between 80% and 120% will also be summarized. The summaries will also be provided by age 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. For example, subjects' treatment or infusion compliance (%) during the 4 consecutive weeks prior to SC#13 PK assessment, ie, from SC#10 to #13, will be evaluated. 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

The IgG population will be used for the analyses of trough total IgG concentrations, mean trough total IgG concentrations, trough IgG subclasses, and trough antibody titers. The analyses of serial total IgG concentrations and PK parameters will be based on the PK population.

9.1 Analysis of IgG concentration and dosing data

9.1.1 Analysis of trough total IgG, IgG subclasses, and antibody titers data

Trough concentrations of total IgG during the Run-In Phase, the IV Phase, and the SC Phase will be summarized.

Summaries will be provided for trough concentrations of IgG subclasses (IV#1, IV#2, SC#9, SC#17, Final/Early Termination Visit, and Monthly Extension Visit (wherein IgG subclass and specific antibody titers are every 8 weeks, if applicable). Summaries of trough level concentrations of antibody titers against *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus) will also be provided (collected at these same time points).

Trough measles antibody titers (functional assay at IV#2 and Final/Early Termination Visit) will be summarized as an exploratory variable for informational purposes.

All summaries will be provided by study phase and visit for the IgG population. The summaries will also be provided by age group and overall.

9.1.2 Analysis of mean trough total IgG data

The steady-state mean trough total IgG concentration following IV administrated IGIV-C 10% will be calculated as the average of the steady-state trough concentrations obtained at the IV#1 visit and at 21 or 28 days after the IV#1 IGIV-C 10% dose (depending on dosing interval), ie, immediately prior to the administration of IV dose at the IV#2 visit.

The steady-state mean trough total IgG concentration following SC administrated IGSC 20% will be calculated as the average of all steady-state trough concentrations obtained at the following visits: SC#13, #14, #17, and #21.

Mean trough data will be summarized by study phase. Mean trough summary and analysis will be based on the IgG population. The summaries will be provided by age group and overall.

9.1.3 Analysis of serial total IgG data

The analyses of serial total IgG concentrations will be based on the PK population.

Serial total IgG concentrations immediately prior to and after the IV#1 or SC#13 infusion will be presented in a listing by subject, study phase, 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 IV#1 or SC#13 infusion (scheduled and nominal times as shown in Section 4.1.1.1), 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 study phase 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 IV#1 or SC#13 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 study phase. For all subjects combined, mean or median total IgG concentration vs. time curves will be presented in one figure with the nominal time (see Section 4.1.1.1) plotted on the x-axis. All total IgG concentration vs. time curves will be plotted on both the linear and the semi-log scale.

9.2 Calculation of PK parameters

The PK parameters of serial total IgG following the IV#1 or SC#13 infusion will be determined as appropriate and as data permits. The PK parameters include $AUC_{0-\tau}$, C_{max}, and t_{max}.

Pharmacokinetic parameters will be calculated by [redacted] using Phoenix® WinNonlin® software, version 6.3 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 (eg, 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 21 days for subjects on an every-3-week IV dosing interval or 28 days for subjects on an every-4-week IV dosing interval in the IV Phase, or 7 days for subjects on weekly SC dosing interval in the SC Phase.
C_{max}	the observed maximum total IgG concentration following drug infusion obtained directly from the experimental data without interpolation, expressed in concentration units (eg, 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.

9.3 Descriptive Statistics of PK Parameters

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

Depending on the number of subjects being dosed on IGIV-C 10% at every-3-week or every-4-week dosing intervals, subgroup analyses may be performed to summarize the PK parameters by IV dosing interval. Additional subgroup analyses will be conducted to summarize the PK parameters by age group, sex, race, ethnicity and other factors as appropriate.

9.4 Statistical Analysis of Primary PK Parameter

The primary PK objective is to demonstrate that the final dose of weekly SC administered IGSC 20% produces steady-state AUC of total IgG that is non-inferior to that of the regularly administered IV dose of IGIV-C 10% in PI subjects. The primary PK parameter is the steady-state AUC of total IgG over the regular dosing interval (τ):

- AUC in the IV Phase: Steady-state AUC of total IgG over the regular dosing interval (τ), either every 3 weeks or every 4 weeks (ie, $AUC_{0-\tau, IV}$ or $AUC_{0\text{-}21\ days, IV}$ or $AUC_{0\text{-}28\ days, IV}$, respectively) in PI subjects
- AUC in the SC Phase: Steady-state AUC of total IgG over a weekly SC dosing interval (τ) (ie, $AUC_{0-\tau, SC}$ or $AUC_{0\text{-}7\ days, SC}$) in PI subjects

Because the dosing intervals are different between the IV and SC Phases, prior to the statistical comparison, the $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$ from the IV Phase will be adjusted/standardized to $AUC_{0\text{-}7\ days}$ as follows:

$AUC_{0\text{-}7\ days,\ IV} = AUC_{0\text{-}21\ days,\ IV} / 3$, for subjects on an every-3-week IV dosing schedule

$AUC_{0\text{-}7\ days,\ IV} = AUC_{0\text{-}28\ days,\ IV} / 4$, for subjects on an every-4-week IV dosing schedule

Non-inferiority of steady-state AUC of total IgG between the final SC dose of IGSC 20% and the regularly administered IV dose of IGIV-C 10% will be tested based on established regulatory guidelines for bioequivalence testing.

The null hypothesis for the non-inferiority test 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 geometric least-squares mean (LSM) of $AUC_{0\text{-}7\ days}$ in the SC Phase and μ_R is geometric LSM of $AUC_{0\text{-}7\ days}$ in the IV Phase. The test will be performed with a one-sided α=0.05.

Natural log-transformed $AUC_{0\text{-}7\ days}$ values will be analyzed by analysis of variance (ANOVA) with a mixed-effect model. The analysis will include study phase as a fixed effect, and subject as a random effect.

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

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

where study_phase, log(AUC), and subjid represent study phase (IV Phase or SC Phase), 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 IV Phase will be considered as the Reference study phase, and the SC Phase will be treated as the Test study phase. The ANOVA will include calculation of LSMs, differences between LSMs, and the standard error associated with these differences. The administration effect between SC and IV will be assessed by exponentiation of the difference in LSMs for $AUC_{0\text{-}7\ days}$ between study phases (Test-Reference) and the corresponding 90% CI for the geometric LSM ratio between study phases (Test/Reference) and the corresponding 90% CI for the ratio. The Test (SC Phase) is considered non-inferior to Reference (IV Phase) if the lower bound of the 90CI 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 without the first six subjects who are analyzed in the interim analysis, and repeated for subjects who had serial PK profile in both the IV and SC Phases.

No inferential statistical analyses will be performed on any other PK parameters listed in Section 9.2.

10 EXPLORATORY ANALYSIS

Details on the analyses of the following exploratory PK variables can be found in Section 9:

- t_{max} (time to reach C_{max}) and C_{max} (maximum concentration) in PI subjects at steady state
- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *S. pneumoniae*, *H.influenzae*, and *C. tetani* (tetanus)
- Trough measles antibody titers (functional assay) for informational purposes

Other exploratory variables include the following:

- Rate of SBIs
- All infections of any kind (serious/nonserious 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, eg, 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
- Number of days of work/school/daily activities missed due to infections and their treatment

For these exploratory variables, 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. All other exploratory 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, hospitalizations, and days of work/school/daily activities missed 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 IV and SC infusions by season will be generated to explore potential seasonal effect on these exploratory variables.

11 SAFETY ANALYSIS

Safety analyses will be based on the Safety population.

11.1 Adverse Events

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

AE causality will be classified and assessed by the investigator. If the causality is “definite”, “probable”, “possible”, or “doubtful/unlikely”, the event will be defined as a suspected adverse drug reaction (ADR). A suspected ADR with a causal relationship of “definite” will be defined as an adverse reaction (AR); thus, ARs are a subset of suspected ADRs. If the

causal relationship is labeled as “unrelated”, then it will be considered that the AE is not imputable to the study treatment and it is not a suspected ADR.

For summary purposes, AEs will be classified as treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start of study treatment (ie, start of the infusion at Run-In Visit 1 for subjects who are enrolled into the Run-In Phase, or at IV#1 for subjects who are enrolled directly into the IV Phase). A TEAE will be defined as an AE which occurred on or after the start of study treatment. For adverse events with incomplete start dates/times, the same algorithm for missing or partial date/time information described in Section 8.1 (Prior and Concomitant Medication) will be used for the determination of treatment emergent or not. Non-TEAEs will be summarized separately from TEAEs. TEAEs will be further characterized within each study phase based on the onset date/time relative to the first infusion date/time in each study phase. In this manner TEAEs occuring during subcutaneous IP (IGSC 20%) administration can be categorized separately.

The incidence of AEs, suspected ADRs, ARs, non-serious AEs, SAEs, and AEs by severity and causal-relationship to the investigational product will be summarized by study phase using descriptive statistics. At each level of summation, a subject will only be counted once per system organ class or preferred term using the most severe or highest causal relationship AE. All infections and local infusion site reactions that meet the definition of an AE (see Section 4.3.1 of the protocol for details) will be summarized with other AEs.

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. 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 phase 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 including infections 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.

11.2 Laboratory Assessments

Hematology (hemoglobin, hematocrit, platelets, red blood cell count including red blood cell morphology, white blood cell count with differential, absolute reticulocyte count [ARC]), clinical chemistry (sodium, potassium, creatinine, chloride, calcium, blood urea nitrogen [BUN], bicarbonate, albumin, lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], glucose, total bilirubin, indirect bilirubin), special tests (direct antiglobulin test [DAT], serum free hemoglobin, haptoglobin), serum pregnancy test, and urinalysis (pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase [with microscopic examination of the urine if abnormal]) will be collected for all subjects if applicable at the assigned visits according to the protocol. The urine pregnancy test performed at IV#1 for the determination of subjects' eligibility will be analyzed by a local laboratory. All other laboratory panels above will be stored and/or analyzed by a central laboratory.

The hematology, clinical chemistry, special tests, serum pregnancy, 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 IV Visit #1, and change from SC Week #1 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: $1/mm^3 = 1/uL = 0.001 \times 10^3/uL$)
- 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.

Virus safety (viral NAT and viral serology) retain samples will be collected at the SC#1 Visit, but will be tested only if the subject exhibits clinical signs and symptoms consistent with viral infection while participating in the study. Virus safety samples will be retained until all analyses in support of the study are complete. Additional samples for viral NAT and viral serology testing may be collected and tested during the study only if the subject exhibits clinical signs and symptoms consistent with viral infection while participating in the study. If any virus safety testing was conducted, all available results will be listed.

All laboratory data will be presented in data listings.

11.3 Specific Signs/Symptoms Check, D-dimer, and Wells Score

Specific Signs/Symptoms Check (SSC) data will be summarized with counts and percentages per category by study phase and visit. D-dimer and total scores of the Wells Score for Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) will be summarized with number of subjects, mean, SD, median, minimum, and maximum values by study phase and visit. Summaries will be presented for the original value, change from Screening, and change from SC Week #1.

All SSC, D-dimer, and Wells Score data will be presented in data listings.

11.4 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 study phase and visit. Summaries will be presented for the original value and change from Screening, change from IV Visit #1, and change from SC Week #1. Body weight and height will be similarly summarized.

All vital sign data will be listed.

11.5 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. Physical assessment change findings after the Screening Visit will be summarized with numbers and percentages per category of the change findings.

All physical assessment data will be listed.