Title: A Phase 3, Open-label, Non-controlled, Multi-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with Primary Immunodeficiency Diseases (PID)

NCT Number: NCT04346108

Statistical analysis plan Approve Date: 06-APR-2022

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

STATISTICAL ANALYSIS PLAN

Study Number: TAK-664-3001

Study Title: A Phase 3, Open-label, Non-controlled, Multi-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) in Japanese Subjects with Primary Immunodeficiency Diseases (PID)

Phase: 3

Version: Final 2.0

Date: 06-Apr-2022

Prepared by: PPD

Based on:

Protocol Version: Amendment 2

Protocol Date: 28-Sep-2020

Statistical Analysis Plan Signature Page

SAP Final V2.0 (dated 06Apr2022) for Protocol TAK-664-3001.

PPD

Upon review of this document, the undersigned approves this version of the SAP, authorizing that the content is acceptable for the reporting of this study.

PPD

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	12-Feb-2021	[Not Applicable]
Draft 1.1	24-Dec-2021	• Section 6.1.7.3: imputation of missing medical history start dates added. • Section 6.1.7.6: table of Convention for Converting Non-Standard Laboratory Results updated. • Section 6.4.1: age categories added. • Section 6.6.3: serum trough level of specific antibodies section added. • Section 6.7.1: adverse event section updated to add previously missing description of certain summary tables. • Section 6.7.2: analysis of specific antibody test results added. • Section 6.7.5: "Days of exposure" updated to "Days in study" to distinguish from the days of exposure for adverse events. • Section 6.7.6: study drug administration updated to correct the definition of parameters. • Section 6.9.1: summary of bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess updated. • Section 6.9.2: definition of infections updated to accommodate the change of medical dictionary version. • Section 6.10: definition of baseline added for PRO analysis. • Section 6.10.1: details of PEDS-QL added. • Typos corrected.
Draft.1.2	31-Mar-2022	• Section 6.1.3: definition of End of Epoch updated. • Section 6.4.1: clarified the definition of age. • Section 6.7.1.1: occurrence and number of TEAEs section updated to add additional summary tables. • Section 6.7.1.2: TEAEs per infusion/subject/subject-year section updated to add previously missing description of certain summary tables. • Section 6.7.2: description of summary table of specific antibody test results added. • Section 6.7.5: the concept of total dose (mg) received replaced by average dose (mg/kg/week). • Section 6.7.6: description of infusion completion summary added. • Section 6.9.5: description of Poisson estimates added for length of stay per stay and total length of stay per subject. • Section 6.9.6: Concept of number of acute physician visits OR emergency room visits updated. Description of Poisson estimates added.

		• Section 6.11.1: Subgroup Analysis added. • Version number and date updated.
Final 2.0	06-Apr-2022	• Section 6.9.5: removed description of Poisson estimates for length of stay per stay. • Version number and date updated

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ASBI	acute serious bacterial infection
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
$AUC_{0\text{-last}}$	area under the serum concentration-time curve from time zero to the last sampling time at which the concentration is at or above LLOQ
$AUC_{0\text{-tau}}$	area under the concentration versus time curve over a dosing interval (tau)
BLQ	below the level of quantitation
BP	bodily pain
BUN	blood urea nitrogen
CI	confidence interval
CL/F	apparent total body clearance for extravascular administration divided by the fraction of dose absorbed calculated as dose divided by $AUC_{0\text{-tau}}$.
C_{max}	maximum observed concentration obtained directly from the concentration-time profile
C_{min}	minimum observed concentration obtained directly from the concentration-time profile
CTMS	clinical trial management system
eCRF	electronic case report form
EOS	end of study
EQ-5D-3L	EuroQol 5 Dimensions 3 Level
EQ VAS	EQ visual analogue scale
GH	general health
HBV	Hepatitis B Virus
HIB	Haemophilus influenzae
HRQoL	health-related quality of life
IgG	immunoglobulin G
IGIV	intravenous immunoglobulin
IGSC	subcutaneous immunoglobulin
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LQI	Life Quality Index
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	mental health
PCS	physical component summary
PEDS-QL	Pediatric Quality of Life Inventory
PF	physical functioning
PID	primary immunodeficiency disease

PK	pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PRO	patient-reported outcomes
PT	Preferred Term
RE	role emotional
RP	role physical
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SF	social functioning
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
TEAE	treatment-emergent adverse event
T_{max}	Time to reach the C_{max} concentration after multiple dose
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
VT	vitality
WBC	white blood cell count

1.0 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objective

The primary objective to assess serum trough immunoglobulin G (IgG) concentrations following weekly administration of subcutaneous immunoglobulin (IGSC), 20% (Epoch 2) and serum trough IgG concentration after biweekly administration of IGSC, 20% (Epoch 3), in Japanese subjects with primary immunodeficiency disease (PID).

1.1.2 Secondary Objectives

The secondary objectives are listed as below:

- To assess serum trough IgG concentrations following every 3-week or every 4-week administration of intravenous immunoglobulin (IGIV) (Epoch 1) in Japanese subjects with PID.
- To characterize the pharmacokinetic (PK) profiles of IGSC, 20% in Japanese subjects with PID following weekly subcutaneous (SC) administration (Epoch 2).
- To evaluate the safety and tolerability of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.
- To evaluate the efficacy of IGSC, 20% (Epoch 2, Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID.
- To assess quality of life aspects, treatment satisfaction, and treatment preference of Japanese subjects with PID (Epoch 1, Epoch 2, Epoch 3).

1.2 Endpoints

1.2.1 Primary Endpoint

The primary endpoint is the total serum trough levels of IgG (total serum trough IgG antibodies) measured during Period 2 of Study Epoch 2 (weekly administration of IGSC, 20%) and during Epoch 3 (biweekly administration of IGSC, 20%).

1.2.2 Secondary Endpoints

1.2.2.1 Secondary PK Endpoints

The secondary PK endpoints are listed as below:

- Total serum trough levels of IgG (total serum trough IgG antibodies) measured during Epoch 1 (every 3 weeks or every 4 weeks administration of IGIV)
- PK parameters for total serum levels of IgG and for IgG subclasses (Epoch 2): Area under the concentration versus time curve (AUC), apparent total body clearance for extravascular

administration (CLss/F), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), and time to reach the C_{max} concentration (T_{max})

- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae [HIB], Hepatitis B Virus [HBV]) (Epoch 1, Epoch 2, Epoch 3)

1.2.2.2 Safety and Tolerability Endpoints

The safety endpoints are listed as below:

- Occurrence of treatment-emergent adverse events (TEAEs), including but not limited to: study drug (IGIV or IGSC)-related and non-related, serious, nonserious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs
- Clinical laboratory outcomes: raw (actual) values and change from baseline
- Vital signs: raw (actual) values and change from baseline and change from pre-infusion to post-infusion

The tolerability endpoint is occurrence of tolerability events related to the infusion of study drug (IGIV or IGSC).

1.2.2.3 Efficacy Endpoints

The efficacy endpoints are listed as below:

- Annual rate of validated acute serious bacterial infections (ASBIs) per subject
- Annual rate of all infections per subject
- Days not able to attend school/work or to perform normal daily activities due to illness/infection
- Days on antibiotics
- Number of hospitalizations due to illness/infection and length of stay (in days)
- Number of acute (urgent or unscheduled) physician visits due to illness/infection

1.2.2.4 Patient Reported Outcomes (PROs) Endpoints

The disease activity and health-related quality of life (HRQoL) endpoints are listed as below:

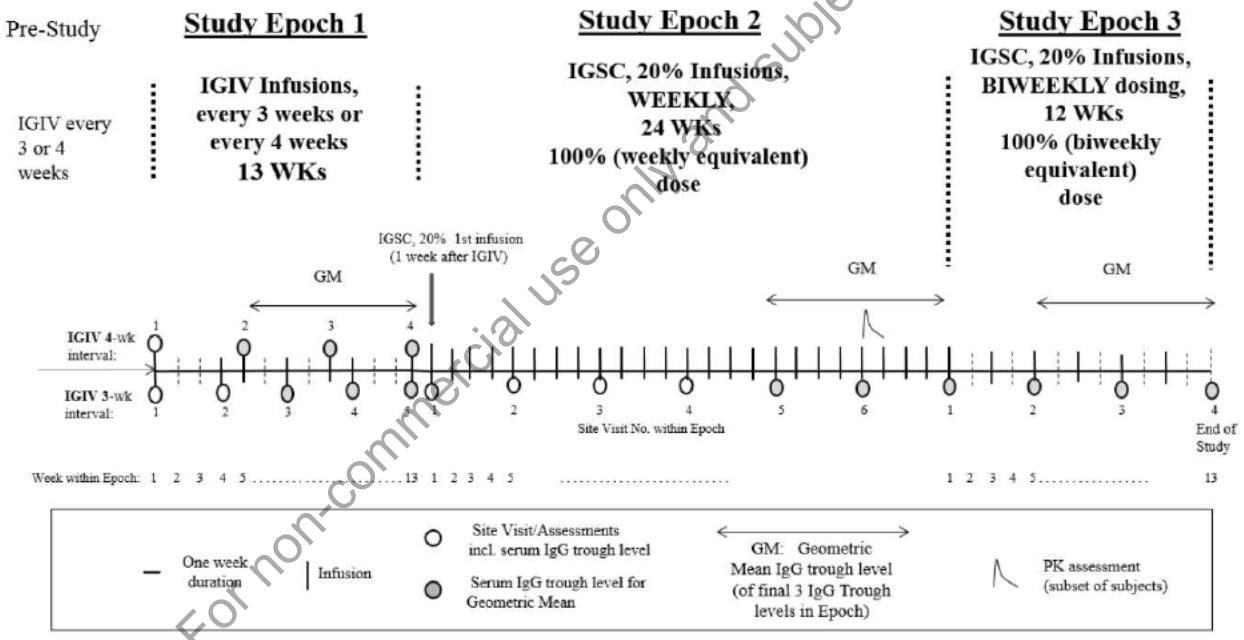
- QoL: Pediatric Quality of Life Inventory (PEDS-QL)[1], 36-Item Short Form Health Survey (SF-36) [2], EuroQol 5 Dimensions 3 Level (EQ-5D-3L) Health Questionnaire [3]
- Treatment Satisfaction (Life Quality Index [LQI], Treatment Satisfaction Questionnaire for Medication-9 [TSQM-9]) [4]
- Treatment Preference (End of Study [EOS]/Early Termination)

2.0 STUDY DESIGN

This is a phase 3, open-label, non-controlled, 3-epoch, multi-dose, multi-center study to evaluate serum trough levels of IgG, PK, efficacy, safety and tolerability of IGSC, 20% (Epoch 2 and Epoch 3) and of IGIV (Epoch 1) in Japanese subjects with PID, as well as to assess disease activity and HRQoL. A total of 16 subjects will be enrolled, of whom 12 subjects are expected to complete Epoch 2 of the study.

A schematic of the study design is provided in Figure 1. Each subject will receive IGIV treatment in Epoch 1 for a total of 13 weeks, then switch to weekly SC treatment with IGSC, 20% in Epoch 2 for a total of 24 weeks; a subset of 7 subjects (of whom 5 subjects are expected to complete, assuming 25% dropout) will continue into Epoch 3 for a total of 12 weeks of biweekly SC treatment with IGSC, 20%.

Figure 1 Study Design



Abbreviations: IGIV = intravenous immunoglobulin, IGSC = subcutaneous immunoglobulin, WKs = weeks, GM = geometric mean, IgG = immunoglobulin G, PK = pharmacokinetic

The study consists of the following evaluation periods:

- Screening: 2 to 8 weeks before the IGIV treatment period
- Epoch 1: IGIV treatment period: 13 weeks

  All subjects will receive either 4 IGIV infusions at 4-week intervals, or 5 IGIV infusions at 3-week intervals, during Epoch 1.
- Epoch 2: IGSC treatment period: 24 weeks (total);

  - Epoch 2, IGSC treatment period 1: 12 weeks of weekly IGSC, 20% dose adjustment period (infusion training will be performed during this period). The dose of IGSC, 20% infusion will be adjusted if necessary, to maintain the target IgG trough level ≥5 g/L.
  - Epoch 2, IGSC treatment period 2: 12 weeks of weekly IGSC, 20% efficacy evaluation period at the dose established in the preceding study period.
- Epoch 3: IGSC, 20% treatment period: 12 weeks of biweekly IGSC, 20%;

There is no follow-up period.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

No statistical hypothesis testing will be performed.

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

The planned total sample size for this study is 16 subjects.

Of the 16 subjects to be enrolled, 12 subjects are expected to complete Epoch 2 of the study, assuming a conservative dropout rate of 25% (overall dropout rates assumed for previous IGSC, 20% PID studies and other PID studies are generally 10%-15%). Subjects who prematurely discontinue the study will not be replaced. The number of subjects expected to complete Epoch 2 (12) is considered adequate for the evaluation of serum trough levels, safety and tolerability, and efficacy of IGSC, 20%, as well as for the assessment of disease activity and HRQoL.

This study is not designed for statistical hypothesis testing and therefore the sample size is not based on statistical considerations such as study power, but instead mainly on consideration of the small size of the Japanese patient population with PID, a group of rare diseases. In Japan, the estimated prevalence of PIDs is 2 to 3 per 100,000 people and the estimated number of people affected is 2,900-3,500. Of the number of PID patients (2,900-3,500), an estimated 1,450- 1,750 would be potential targets for immunoglobulin replacement therapy. In clinical practice, most patients requiring a switch to IGSC (as is required by the study design) are already being treated with the approved IGSC product (Hizentra®). For example, in the Hizentra® NDA review report, the estimated number of patients who could receive

immunoglobulin replacement therapy was 1,155, which is lower than the estimated 1,450-1,750 patients.

Therefore, the number of potentially eligible patients for the planned study is extremely limited, *making it infeasible to enroll a large sample size. Based on feasibility and the Sponsor's clinical* experience with IgG products, a total sample size of 16 subjects (12 completers) is considered adequate for providing reliable estimates of trough levels (study primary objective), as well as reliable estimates of safety and tolerability, efficacy, disease activity and HRQoL (secondary objectives).

5.0 ANALYSIS SETS

5.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent.

5.2 Enrolled Set

The Enrolled Set will contain all subjects in the Screened Set for whom an enrollment number has been assigned.

5.3 All-Treated Set

The All-Treated Set will contain all subjects in the Enrolled Set who received at least 1 dose of study drug (IGIV or IGSC).

5.4 Pharmacokinetic Analysis Set [PKAS]

The Pharmacokinetic Analysis Set (PKAS) will contain all subjects in the all-treated set who have had at least 1 evaluable serum IgG concentration value and have had no major protocol deviations or events that would affect the serum IgG concentration analysis results.

There are 2 separate PK analyses (see Section 6.6):

1. PKAS 1: Total serum IgG trough levels for total serum levels of IgG and IgG subclasses.
2. PKAS 2: PK parameters for total serum levels of IgG and for IgG subclasses in Epoch 2 subjects (5-7 subjects; >= 12 years of age).

Protocol deviations will be reviewed by the study team before database lock to determine exclusion from the PKAS.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Continuous endpoints/outcome measures (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value. Categorical endpoints/outcome measures (e.g., adverse events [AEs]) will be summarized in terms of number and percent of subjects and number of occurrences in each category.

Summaries will be provided, as appropriate, by epoch, by treatment period, by treatment period and visit/timepoint, and overall.

6.1.1 Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study drug (IGIV or IGSC).

If the date of the event is on or after the reference date, then:

- Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then:

- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Section 6.1.7.

6.1.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but AEs and medications commencing after the reference start date and time will be considered post-baseline.

6.1.3 Date of Start/End of Epoch

The date of the start of an epoch is defined as the date of first study drug administration in the corresponding epoch.

The date of end of an epoch is defined as:

- the day before the start date of the subsequent epoch if the subject completes the corresponding epoch and continues in the subsequent epoch;

- the date of end of study if the subject completes the corresponding epoch and the study in accordance with the study protocol or if the subject discontinued the study.

6.1.4 Handling of Treatment Misallocations

For analyses and displays based on the Enrolled Set, subjects will be classified according to treatment allocated.

For analyses and displays based on the All-Treated Set, subjects will be classified according to treatment received.

For analyses and displays based on PKAS, Subjects will be classified according to treatment received.

6.1.5 General Choice of Analysis Sets for Analyses

Background summaries (e.g., subject disposition) will be based on the Enrolled Set.

Analysis of efficacy, safety and tolerability, and disease activity and HRQoL will be based on the All-Treated Set.

Analysis of PK data (serum IgG trough concentrations and PK profiles) will be based on the PKAS.

6.1.6 Multicenter Study

This study will be conducted by multiple investigators at multiple centers. Data from all centers will be pooled together in the analyses and there are no plans to perform an analysis of homogeneity of the results across centers.

6.1.7 Handling of Missing, Unused, and Spurious Data

No imputation for missing data will be applied except for the partial dates for prior/concomitant medications and AEs, the missing severity for AEs and the missing relationship to study drug for AEs.

Imputed data will not be presented in the listings. The original missing data will be presented in the listings.

6.1.7.1 Missing Medication Dates

Partial or completely missing medication dates will be handled as described below to determine if the medications are prior or concomitant. Imputed medication dates will not be presented in the listings.

6.1.7.1.1 Incomplete Start Date

- If a medication start date is completely missing, then the medication will be considered concomitant.

- Missing day and month:

- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

- Missing month only:
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing day only:
  - If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug, then the day of the date of the first dose of study drug will be assigned to the missing day.
  - If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.
  - If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

6.1.7.1.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

- Missing Day and Month
  - 31 December will be assigned to the missing fields.
- Missing Month only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing Day only
  - The last day of the month will be assigned to the missing day.

6.1.7.2 Missing AE Dates

The following approaches will be applied for missing AE dates:

- To facilitate categorization of AEs as treatment emergent, imputation of dates will be used.
- If an AE start date is completely missing, then the AE will be considered treatment-emergent in Epoch 1.
- For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration (e.g., AE start year and month are the same as the year and month of the first dose of study drug), then the AE will be classified as treatment-emergent.
- To facilitate categorization of AEs as treatment emergent, the same imputation of start date used for medication dates will be used of AE start date. See Section 6.1.7.1.1 for details. AE stop dates will not be imputed.

6.1.7.3 Missing Medical History Start Dates

Partial or completely missing medical history start dates will be handled same as missing AE start dates to determine whether a medical history is concurrent or not.

6.1.7.4 Missing Relationship to Study Drug for AEs

If the relationship to study drug is missing for an AE starting on or after the date of the first dose of study drug, a causality of "Related" will be assigned. The imputed values for relationship to study drug will be used for incidence summaries, while the actual values will be presented in data listings.

6.1.7.5 Missing Severity for AEs

If severity is missing for an AE starting prior to the date of the first dose of study drug, then no imputation will be applied. If the severity is missing for an AE starting on or after the date and time of the first dose of study drug, then the worst severity will be assigned, i.e., "Severe". The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

6.1.7.6 Character Values of Clinical Laboratory Variables

Any non-standard laboratory results will be converted to numeric values using the example rules shown in Table 1.

Table 1. Convention for Converting Non-Standard Laboratory Results

Non-Standard Lab Values	Standardized Numeric Values
<0.2	Deduct 0.01 from the reference value. i.e., 0.19
<0.1	Deduct 0.01 from the reference value. i.e., 0.09
>1.045	Add 0.001 to the reference value. i.e., 1.046
<3	Deduct 0.1 from the reference value. i.e., 2.9

6.2 Disposition of Subjects

Number of subjects screened/enrolled will be presented for the Screened Set. Number and percentage of subjects with screen failure and reason for screen failure will also be presented based on the Screened Set.

Number and percentages of subjects treated, ongoing on treatment (for dry runs only), who completed/discontinued early from treatment (including reason for withdrawal), ongoing in study by epoch (for dry runs only), and who completed/discontinued early from the study (including reason for withdrawal) will be provided by epoch and overall based on the Enrolled Set.

Similarly, number of subjects included and excluded from each analysis set (including reason for exclusion) will be summarized based on the Enrolled set. A listing showing inclusion and exclusion of each subject from each analysis set, including reason for exclusion, will be provided.

6.3 Protocol Deviations

Protocol deviations as obtained from a clinical trial management system (CTMS) will be assessed throughout the study. All identified deviations will be reported in the CTMS. Protocol deviations from the CTMS will be coded to severity categories ("critical", "major" and "minor") and provided as part of the CTMS transfer to Biostatistics.

Protocol deviations will be collected at both the site and subject level. Deviations at the site level will be applied to all subjects who were enrolled at that site at the time of the deviation.

Protocol deviations will be summarized by deviation type and severity for the All-Treated Set. All protocol deviations will be included in a subject listing. In particular, protocol deviations identified as exclusion from the PKAS will be flagged in the subject listings. Protocol deviations identified as related to the impact of COVID-19 will be flagged in the subject listings.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics and Other Baseline Characteristics

The following demographic and other baseline characteristics will be reported for this study:

- Age (years)

- Age categories (<18 years / >=18 years)
- Sex
- Ethnicity
- Race
- Weight at baseline (kg)
- Height at baseline (cm)
- BMI at baseline (kg/m^2) - calculated as weight (kg)/ [height $(m)^2$]
- Primary immunodeficiency diagnosis
- Time since diagnosis (years) - calculated relative to date of informed consent
- Age at diagnosis (years)

Age is the age at informed consent date.

Continuous demographic and other characteristics will be summarized using descriptive statistics based by epoch on the All-Treated Set. For categorical demographics, number and percentage of subjects in each category will be provided based on the All-Treated Set.

6.4.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1 or newer, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the All-Treated Set. A subject having more than one surgery/medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT.

All medical history will be listed. Medical histories that started before first dose of study drug AND were on going at the time of the first dose of study drug or ended on the first dose of study drug will be flagged as "ongoing" in the listing.

6.5 Prior and Concomitant Medications/Procedures/Therapies

6.5.1 Prior Medications/Procedures/Therapies

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) dated 01 Sep 2020 or newer. Prior therapies and procedures will be coded using MedDRA Version 23.1 or newer.

Prior medications/procedures/therapies are defined as any medication/procedure/therapy that started and stopped prior to the first dose of study drug.

Partial date imputation for medications is described in Section 6.1.7.1.

The prior medications will be summarized by the number and proportion of subjects within each Anatomical Therapeutic Chemical (ATC) Level 2 therapeutic class and PT for the FAS. The prior therapies and procedures will be summarized by the number and proportion of subjects within each SOC and PT for the All-Treated Set. Multiple medication usage by a subject in the same category (i.e., therapeutic class or PT) will be counted only once.

All prior therapies, procedures and medication will be listed for the All-Treated Set.

6.5.2 Concomitant Medications/Procedures/Therapies

Concomitant medications will be coded using the WHO Drug Dictionary dated 01 Sep 2020 or newer. Concomitant therapies and procedures will be coded using MedDRA Version 23.1 or newer.

Concomitant medications/procedures/therapies are defined as any medication/procedure/therapy that:

- started prior to, on or after the first dose of study drug and started no later than the EOS/Early Termination Visit,
- OR ended on or after the date of first dose of study drug or were ongoing at the EOS.

Partial date imputation for medications is described in Section 6.1.7.1.

Concomitant medications will be summarized by the number and proportion of subjects within each ATC Level 2 therapeutic class, PT and epoch for the All-Treated Set. The concomitant therapies and procedures will be summarized by the number and proportion of subjects within each SOC, PT and epoch for the All-Treated Set. Multiple medication usage by a subject in the same category (i.e., therapeutic class or PT) will be counted only once.

All concomitant therapies, procedures and medication will be listed for the All-Treated Set.

6.6 Pharmacokinetic Analysis

The PK analysis (total serum IgG trough concentrations and PK profiles for PK parameter estimates) will be based on the PKAS (PKAS1 and PKAS2, respectively. See Section 5.4 for the detailed definition).

For Epoch 2 PK parameters will be calculated from total serum IgG concentration-time data using noncompartmental methods and all calculations will be based on actual sampling times.

The serum sample analysis for specified IgG concentrations will be performed according to the relevant Standard Operating Procedures at the contract bioanalytical lab. Total serum IgG concentrations will be measured using the most current validated bioanalytical method.

In addition, selected serum samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate.

The PK analysis of parameter estimates will be conducted by a contract research organization for the Clinical Pharmacology and Pharmacokinetics Department of Shire using Phoenix WinNonlin Version 8.3 or higher (Certara, L.P., Princeton, New Jersey, USA).

6.6.1 Serum IgG Trough Analysis

The total serum trough levels of IgG (total serum trough IgG antibodies) will be listed and summarized for Study Epoch 1 (every 3 weeks or every 4 weeks administration of IGIV), Study Epoch 2 (weekly administration of IGSC, 20%), Study Epoch 3 (biweekly administration of IGSC, 20%), and specific antibodies to clinically relevant pathogens (e.g. Clostridium tetani toxoid, HIB, HBV) (Epoch 1, Epoch 2, Epoch 3).
Values below the lower limit of quantitation (LLOQ) will be replaced as zero for descriptive statistics of serum IgG PK concentrations.

All serum IgG concentration data will be summarized by epoch, IgG, IgG subclass (or specific antibodies) and/or scheduled timepoint, as appropriate, for subjects in PKAS1. Repeated and unscheduled measurements are included in the listings but not used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Individual subject's serum trough levels of IgG and actual sampling time will be listed by nominal sampling timepoint and summarized by epoch, dose, IgG, and IgG subclass with descriptive statistics such as number of observations (n), arithmetic mean, SD, coefficient of variation, geometric mean, geometric coefficient of variation, 2-sided 95% confidence interval (CI) on the geometric mean, median, 2-sided 95% CI on the median, first quartile (Q1), third quartile (Q3), interquartile range (IQR), minimum, and maximum.

Mean (±SD) trough concentrations for IgG and IgG subclass will be presented in a concentration-time plot for each epoch on linear and semi-logarithmic (without SD) scale. Mean (±SD) serial concentration-time profiles for IgG and IgG subclass in Week 21 of Epoch 2 will be presented on linear and semi-logarithmic (without SD) scale. Mean (±SD) concentrations of specific antibodies will be presented across all Epochs on linear and semi-logarithmic (without SD) scale. Individual subject trough concentrations for IgG and IgG subclass will be presented in a concentration-time plot across all Epochs on a linear and semi-logarithmic scale. Individual subject serial concentration-time profiles for IgG and IgG subclass in Week 21 of Epoch 2 will be presented on linear and semi-logarithmic scale.

6.6.2 Pharmacokinetic Parameter Analysis

Subjects identified in the PKAS2 will be included for assessment of PK parameters. Pharmacokinetic parameters will be evaluated and listed for all subjects who provide sufficient concentration-time data per the defined PKAS2. Noncompartmental computation of PK parameters will be performed.

Pharmacokinetic parameters will be estimated in Epoch 2 using non-compartmental analysis methods for total serum-concentration profiles of IgG and IgG subclasses (Epoch 2).

Predose sample concentrations that are below the level of quantitation (BLQ) will be assigned a numerical value of zero for the calculation of parameters. Samples not collected will be identified as missing. Any anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters, even if the anomalous value is greater than 5% of the maximum observed concentration (C_{max}). Serum concentrations of BLQ before the last quantifiable data point will be taken as zero for calculating parameters (i.e., embedded BLQ values will be set to zero). Serum concentrations of BLQ after the last quantifiable data point will be set to 'zero'.

Individual PK parameters will be calculated using unrounded actual sampling times (or using scheduled time if actual time is not available). The predose sample will be considered as if it had been taken simultaneously with the administration of study drug.

Pharmacokinetic parameters will be calculated from serial serum total IgG and IgG subclass concentration-time data based on actual sampling times. Pharmacokinetic parameters will include the following:

$AUC_{0\text{-}tau}$	Area under the concentration versus time curve over a dosing interval (tau = 1 week which is 168 hours) (g*day/L), calculated according to the mixed log linear trapezoidal rule (i.e., linear up/log down)). Only calculated if interpretable i.e., last sample timepoint for dose interval is present, and sample at T_{max} is present. The actual time and associated concentration at the last sample timepoint for the dose interval will be used for calculation of this parameter.
$AUC_{0\text{-}tau}$ /(Dose/Weight)	$AUC_{0\text{-}tau}$ normalized to a g/kg dose [(g*day/L)/(g/kg)].
$AUC_{0\text{-}last}$	Area under the serum concentration-time curve from time zero to the last sampling time at which the concentration is at or above LLOQ (g*day/L), calculated according to the mixed log linear trapezoidal rule (i.e., linear up/log down).
$AUC_{0\text{-}last}$ /(Dose/Weight)	$AUC_{0\text{-}last}$ normalized to a g/kg dose [(g*day/L)/(g/kg)].
C_{max}	Maximum observed concentration (g/L) obtained directly from the concentration-time profile.
C_{min}	Minimum observed concentration (g/L) obtained directly from the concentration-time profile.
CL/F	Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed (mL/kg/day), calculated as dose (in g/kg) divided by $AUC_{0\text{-}tau}$.
T_{max}	Time to reach the C_{max} concentration (h).

Dose/Weight (in g/kg) of Investigational Product (IP) administered will be calculated from administered solution volume as follows:

[Planned IP dose in mg/kg * (actual IP solution volume /planned IP solution volume)] / 1000

Any anomalous concentration values observed at predose will be identified.

Predose total serum IgG concentrations BLQ and BLQ values prior to quantifiable concentrations will be set to zero for both descriptive statistics estimations and PK concentration tables. If the actual time is missing (i.e., not recorded) then the scheduled sampling time will be used for the estimation of the PK parameters, unless otherwise warranted by the data. Samples collected outside the allowable windows will be flagged in the listing.

Pharmacokinetic parameters will be listed and summarized by dose, IgG, and IgG subclass. Descriptive statistics will include: n, arithmetic mean, SD, coefficient of variation, geometric mean, geometric coefficient of variation, 2-sided 95% CI on the geometric mean, median, 95% CI on the median, first quartile (Q1), third quartile (Q3), interquartile range (IQR), minimum, and maximum. The parameter T_{max} will be summarized by n, median, 95% CI on the median, first quartile (Q1), third quartile (Q3), interquartile range (IQR), minimum, and maximum.

Pharmacokinetic parameters of $AUC_{0\text{-}tau}$, $AUC_{0\text{-}last}$, and C_{max} will be presented in box plots when appropriate for each dose, IgG, and IgG subclass.

6.6.3 Serum Trough Level of Specific Antibodies

The serum trough levels of specific antibodies to relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae Type B [HIB] and HBV) will be listed and summarized.

Values below the LLOQ will be replaced as zero for descriptive statistics of serum IgG PK concentrations.

All serum concentration data will be summarized by specific antibody status to relevant pathogens and scheduled timepoint, as appropriate. Repeated and unscheduled measurements are included in the listings but not used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Individual subject's serum trough levels of specific antibody and actual sampling time will be listed by nominal sampling timepoint and summarized by specific antibody status to relevant pathogens with descriptive statistics such as number of observations, arithmetic mean, SD, coefficient of variation, minimum, median, maximum, geometric mean, geometric coefficient of variation, 2-sided 95% CI of the geometric mean, median, 95% CI on the median, first quartile (Q1), third quartile (Q3), interquartile range (IQR), minimum, and maximum.

6.7 Safety Analysis

All safety summaries will be based on the All-Treated Set.

The definition of baseline is provided in Section 6.1.2.

All safety data, including derived data, will be presented in subject data listings.

6.7.1 Adverse Events

AEs will be coded using MedDRA Version 23.1 or newer.

TEAEs are defined as AEs with onset after date-time of first dose of study drug (IGIV or IGSC), or medical conditions present prior to the start of study drug (IGIV or IGSC) but increased in severity or relationship after date-time of first dose of study drug (IGIV or IGSC).

AEs with missing start/stop dates will be imputed as described in Section 6.1.7.2.

Only TEAEs will be analyzed. Non-TEAEs will be listed only.

Related AEs are defined as a*ny AE that is recorded as "possibly related" or "probably related"* to study drug (IGIV or IGSC).

Unrelated AEs are defined as *any AE recorded as "unlikely related" or "not related".*

Temporally associated AEs are defined as any AE that begin during study drug administration or within 72 hours of completion of study drug administration.

Missing relationship to study drug imputation is described in Section 6.1.7.4.

Missing severity imputation is described in Section 6.1.7.5.

6.7.1.1 Occurrence and Number of TEAEs

A TEAE will be counted for a specific epoch only if that AE started during that epoch. The date of start/end of epoch is defined in Section 6.1.3. For AE summaries by epoch, the number of subjects reaching that epoch will be presented and will be used as denominator for percentage calculation.

An overall summary of number and percentage of subjects with any TEAE, any related/unrelated TEAE, any local/systemic TEAE, any related/unrelated local TEAE, any related/unrelated systemic TEAE, any serious TEAE, any serious related/unrelated TEAE, any severe/moderate/mild TEAE, any severe related/unrelated TEAE, any moderate related/unrelated TEAE, any mild related/unrelated TEAE, any temporally associated TEAEs, any temporally associated and related TEAEs, any temporally associated or related TEAEs, any TEAE leading to study drug withdrawn and any TEAE leading to study discontinuation, and any TEAE leading to death as well as the total number of events for each category will be provided for each epoch, combined Epoch 2 and 3, and overall.

The number and percentage of subjects with any TEAE including and excluding infections (the definition of infection is provided in Section 6.9.2), as well as the total number of TEAEs, will be summarized by SOC, and PT for each epoch, combined Epoch 2 and 3, and overall. This summary will be repeated for local TEAEs, systemic TEAEs, related TEAEs, related/unrelated TEAEs excluding infections, severe TEAEs, mild/moderate/severe related TEAEs excluding infections, serious TEAEs including and excluding infections, serious related/unrelated TEAEs including and excluding infections, local TEAEs including and excluding infections, local related/unrelated TEAEs excluding infections, mild/moderate/severe related local TEAEs excluding infections, systemic TEAEs excluding infections, systemic related/unrelated TEAEs

excluding infections, mild/moderate/severe related systemic TEAEs excluding infections, temporally associated TEAEs including and excluding infections, temporally associated and related TEAEs including and excluding infections, temporally associated or related TEAEs including and excluding infections and TEAEs leading to study discontinuation excluding infections for each epoch, combined Epoch 2 and 3, and overall. In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency of the Total column.

The number and percentage of subjects with any TEAE, as well as the total number of TEAEs, will be summarized by PT for each epoch, combined Epoch 2 and 3, and overall. This summary will be repeated for TEAEs excluding infections and infection TEAEs. In the summaries, PT will be sorted in decreasing frequency of the Total column.

A comprehensive summary table of number of subjects, number of events, number of events per infusion and number of events per subject will be provided for any TEAE including infections by PT, location (systemic or local), relationship and severity.

In AE incidence summaries, subjects with multiple events in the same category will be counted only once in the AE category. Subjects with events in more than one category will be counted once in each of the categories.

In AE count summaries, multiple occurrences of the same AE will be counted multiple times.

Subject with multiple severities of the same AE, the maximum severity (most serious severity) of each epoch, combined Epoch 2 and 3, and overall will be used in analysis. Similarly, in subjects with multiple relationships of the same AE, the worst relationship of each epoch, combined Epoch 2 and 3, and overall will be used in the analysis. If a subject experiences multiple severity of the same AE (e.g., 3 occurrences: 1 mild, 1 moderate, 1 severe) all categorized under the same causality assessment (e.g., all related to study drug), the AE with the maximum severity (AE that is severe) will be used in analysis. A subject could have a different maximum severity/relationship in different epochs for the same AE.

If more than 1 AE occurs within the same PT for the same subject during each epoch, combined Epoch 2 and 3, and overall, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to study drug for each and overall. For example, if a subject experienced a mild headache not related to the IP, and a moderate headache related to IP, then the subject will be counted once for headache using the moderate headache related to IP. A subject could be counted by different maximum severity/relationship in different epochs for the same AE.

All AEs will be provided in subject listings. Listings will be presented separately for each epoch.

6.7.1.2 TEAEs per Infusion, per Subject, per Subject-Year

The following summaries will be provided for each epoch, combined Epoch 2 and 3, and overall:

- Number of TEAEs per infusion, by SOC and PT
- Number of TEAEs per subject, by SOC and PT

- Number of TEAEs per subject-year, by SOC and PT

Number of TEAEs per infusion is number of TEAEs divided by total number of infusions administered.

Number of TEAEs per subject is number of TEAEs divided by total number of subjects.

Number of TEAEs per subject-year is number of TEAEs divided by total number of days of exposure, converted into years. Days of exposure will be calculated as (date of last dose - date of first dose) + 1.

Number of TEAEs and TEAEs per subject-years (SYs) will be provided (if analyzable).

The summaries above will be repeated for TEAEs excluding infections, related/unrelated TEAEs excluding infections, local TEAEs including and excluding infections, related/unrelated local TEAEs excluding infections, systemic TEAEs excluding infections, related/unrelated systemic TEAEs excluding infections, mild/moderate/severe related TEAEs excluding infections, serious TEAEs including and excluding infections, serious related/unrelated TEAEs including and excluding infections, temporally associated TEAEs including and excluding infections, temporally associated and related TEAEs including and excluding infections, and temporally associated or related TEAEs including and excluding infections for each epoch, combined Epoch 2 and 3, and overall. In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency of the Total column.

6.7.2 Clinical laboratory outcomes

Laboratory evaluations that are performed at study site visits will be collected and processed via a central laboratory and presented in International System of Units (SI Units).

Clinical laboratory outcomes to be evaluated include the following:

Hematology	hemoglobin, hematocrit, erythrocytes (i.e., red blood cell count), leukocytes (i.e., white blood cell count [WBC]) and differential - basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelet counts, absolute neutrophil counts (ANCs).
Chemistry	sodium, potassium, chloride, bicarbonate, protein, albumin, alanine transaminase (ALT), serum total bilirubin, aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, creatinine phosphokinase (CPK), glucose, haptoglobin, lipase.
Urinalysis	color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.
Hemolysis*	direct antiglobulin test, urine hemosiderin, hemoglobin, LDH, serum haptoglobin *Hemolysis test will only be performed in subjects aged 12 years and older.
Specialty Tests	Hepatitis B Surface Antigen (HbsAg), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV)-1/2.
Specific Antibody Tests	Clostridium tetani toxoid, Haemophilus influenzae Type B (HIB), Hepatitis B virus (HBV)

Hematology, chemistry, urinalysis, hemolysis and specific antibody results will be summarized by epoch and overall as described below. Specialty test results will be listed only.
Raw (actual) clinical laboratory values and changes in raw values from baseline at each post-baseline assessment time point will be summarized for continuous variables. If more than one laboratory result is reported per study visit per parameter, the last non-missing result will be selected for analysis.

Shift from baseline (shift table) to each post-baseline assessment time point will be provided for categorical variables. Summaries of shift-from-baseline will be produced for each laboratory parameter that has a reference range, using the categories: low (below the lower limit of the reference range), normal (within the reference range), high (above the upper limit of the reference range), and missing. Missing data will not be imputed.

Laboratory values for abnormalities for the following parameters will be classified according to a 5-point (Grades 0-4) toxicity grading scale provided in protocol Appendix 6: ALP, ALT, AST, BUN, hemoglobin, lymphocytes, neutrophils, platelet count, potassium, serum creatinine, sodium, serum total bilirubin, WBC. The classification of abnormalities will be performed by the central laboratory and the toxicity grades will be provided in the raw datasets.
Shift-from-baseline to each post-baseline assessment time point and shift-from-baseline to the worse post-baseline assessment within each epoch and overall will be produced for the parameters above by toxicity grade.

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable (e.g., "<X"), a coded value will be used in the analysis instead as specified in Section 6.1.7.6. However, the actual values as reported in the database will be presented in data listings.

All laboratory test results will be presented in subject listings. Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the investigator for a subject across study visits to identify any trends.

6.7.3 Vital Signs

The following vital signs will be measured:

- Height (cm)
- Weight (kg)
- Body temperature (°C)
- Respiratory rate (breaths/min)
- Pulse rate (beats/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

Raw (actual) vital signs, and changes in raw values from baseline at each post-baseline assessment time point, will be summarized. Raw (actual) vital signs and change from pre-infusion to post-infusion will be summarized by study visit.

If more than one vital sign result is reported per time point per parameter, the last non-missing result will be selected for analysis.

6.7.4 Other Safety Data

6.7.4.1 Pregnancy Test

Pregnancy test results will be listed by study visit.

6.7.4.2 Physical Examination

Physical examination will be listed by study visit.

6.7.5 Extent of Exposure and Compliance

Extent of exposure will be summarized by epoch and overall in terms of days of exposure (days) and total dose received (mg) for the All-Treated Set.

Days in study will be calculated as below:

- By epoch: number of days from the date of the first dose of study drug in each epoch to the date of the end of each epoch (See Section 6.1.3 for the definition of end of epoch)
- Overall: number of number of days from the first dose of study drug to the date of the end of the last epoch

Average dose (mg/kg/week) will be calculated as the average of subject's dose (mg/kg) received at each visit during the corresponding period, while the dose received at each visit will be calculated as planned dose (mg/kg) [volume administered at the visit (mL) / planned volume (mL)] / dosing interval (weeks)].

Treatment compliance (%) is defined as the percentage of planned doses received by the subject and will be calculated as number of doses received / number of planned doses * 100.

The number of planned doses is the number of doses planned to be administered up to the date of the end of each epoch or early termination.

Descriptive statistics of days in study, total dose received, total number of doses received by the subject, treatment compliance, and the number and percentage of subjects that received at least 80% of planned doses will be presented by epoch and overall for the All-Treated Set.

6.7.6 Study Drug Administration

Number of infusions per subject, number of infusions per subject-year, number of infusions per month, number of infusion sites per infusion and number of infusion sites per month will be summarized by each epoch and overall for the All-Treated Set.

Number of infusions per month will be calculated as [total number of infusions during the corresponding period / days of exposure] * 30.4 days per month.

Number of infusion sites per infusion will be calculated as total number of infusion sites during the corresponding period / total number of infusions.

Number of infusion sites per month will be calculated as total number of infusion sites /(duration in treatment (days)] / 30.4 days per month).

Descriptive statistics of percentage of infusions completed as planned / with infusion rate reduced / interrupted / stopped / with infusion rate reduced or interrupted or stopped will be summarized by each epoch and overall for the All-Treated Set.

Descriptive statistics of duration of infusion (mins), maximum infusion rate per infusion site, infusion volume, infusion site will be presented by epoch and overall for the All-Treated Set.

A listing of study drug administration and injection report will be provided.

6.8 Tolerability Analysis

6.8.1 Tolerability Events

Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.

An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to study drug (IGIV or IGSC).

An overall summary of number and percentage of subjects with the following tolerability events as well as the total number of tolerability events will be provided for each epoch and overall:

- Any study drug administration with the infusion rate reduced for tolerability concerns or for AEs
- Any study drug administration with the infusion interrupted for tolerability concerns or for AEs
- Any study drug administration with the infusion stopped for tolerability concerns or for AEs
- Any study drug administration with the infusion rate was reduced or interrupted or stopped for tolerability concerns or for AEs

Study drug administration with the infusion rate reduced/infusion interrupted/infusion stopped for tolerability concerns or for AEs are the corresponding events collected by the CRF page "Study Drug Administration - Intravenous" and "Study Drug Administration – Subcutaneous" with "Reason infusion not completed as planned" = "Adverse Event" OR "Device Malfunction" OR "Other Reason".

Number and percentage of subjects with the following events as well as the total number of events will be provided for each epoch and overall:

- Any study drug administration with the infusion rate reduced/infusion stopped with "Reason infusion not completed as planned" = "Adverse Event"
- Any study drug administration with the infusion rate reduced/infusion stopped with "Reason infusion not completed as planned" = "Device Malfunction"
- Any study drug administration with the infusion rate reduced/infusion stopped with "Reason infusion not completed as planned" = "Other Reason"

6.9 Efficacy Analysis

All efficacy summaries will be based on the All-Treated Set.

Efficacy data, including derived efficacy parameters defined in the subsections below, will be presented in subject data listings.

6.9.1 Annual Rate of Validated ASBIs per Subject

ASBIs will include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that are caused by a recognized bacterial pathogen. The diagnostic criteria for ASBIs are included in protocol Appendix 5.

The annual rate of validated ASBIs will be calculated as the mean number of ASBIs per subject per year and be summarized using descriptive statistics by epoch and overall based on the All-Treated Set.

Number of ASBIs per subject per year will be calculated as below:

- By epoch: number of ASBIs / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 1 (See Section 6.1.3 for the definition of start/end of epoch)
- Overall: number of ASBIs / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

Additionally, the generalized linear model procedure for Poisson regression with log link will be used via the SAS procedure PROC GENMOD to estimate ASBI rate per person per year and its one-sided 99% upper confidence bound (or equivalently, the upper bound of the two-sided 98% confidence interval). Subject-year will be calculated for each subject as (duration of study in days/365.25), and the natural log-transformed subject-year will be used in the generalized linear model as an offset variable. To handle over-dispersion, the exponential distribution dispersion parameter will be assumed to be given by the deviance divided by the degrees of freedom and all statistics will be adjusted accordingly. No covariates other than the intercept term will be included in the model. The estimated intercept term and the upper bound of its two-sided 98% CI will be transformed by using the natural exponential function, to provide the point estimate of the ASBI rate per person per year and its one-sided 99% upper confidence bound.

The number and percentage of subjects with bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess for each epoch and overall based on the All-Treated Set.
The diagnosis of ASBIs will be presented in subject listings.

6.9.2 Annual Rate of All Infections per Subject

The preferred terms from MedDRA 23.1 or newer SOC "Infections and infestations" will be used to identify infections.

The annual rate of all infections will be calculated as the mean number of all infections per subject per year and be summarized using descriptive statistics by epoch and overall based on the All-Treated Set. Point-estimate and 95% CI of the annual rate of all infections calculated using a Poisson model with subject-year in study as the offset variable will be provided by epoch and overall based on the All-Treated Set.

Number of infections per subject per year will be calculated as below:

- By epoch: number of infections / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 1 (See Section 6.1.3 for the definition of start/end of epoch)
- Overall: number of infections / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

6.9.3 Days Not Able to Attend School/Work or to Perform Normal Daily Activities Due to Illness/Infection

The days not able to attend school/work or perform normal daily activities due to illness/infection will be collected on the electronic case report form (eCRF) and standardized to per year (365.25 days), and will be calculated as below:

- By epoch: sum of days not able to attend school/work or perform normal daily activities due to illness/infection per subject / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 1 (See Section 6.1.3 for the definition of start/end of epoch)
- Overall: sum of days not able to attend school/work or perform normal daily activities due to illness/infection per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

The mean of days not able to attend school/work or perform normal daily activities due to illness/infection per year will be summarized using descriptive statistics by epoch and overall based on the All-Treated Set. Point-estimate and 95% CI of calculated using a Poisson model with subject-year in study as the offset variable will also be provided by epoch and overall based on the All-Treated Set.

6.9.4 Days on Antibiotics

Antibiotics are defined as any medication under ATC Level 2 therapeutic class "ANTIBACTERIALS FOR SYSTEMIC USE".

Number of days on antibiotics is defined as the number of days that antibiotics were taken as concomitant medications and will be standardized to per year (365.25 days) and will be calculated as below:

- By epoch: sum of the actual number of distinct days that antibiotics were taken per subject / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 1 (See Section 6.1.3 for the definition of start/end of epoch).
- Overall: sum of the actual number of distinct days that antibiotics were taken per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

If a subject took multiple antibiotics on a single day, that day will be counted for only once. Partial date imputation for medications is described in Section 6.1.7.1.

The mean of days on antibiotics per year will be summarized using descriptive statistics by epoch and overall based on the All-Treated Set. Point-estimate and 95% CI of calculated using a Poisson model with subject-year in study as the offset variable will also be provided by epoch and overall based on the All-Treated Set.

6.9.5 Number of Hospitalizations Due to Illness/Infection and Length of stay

Number of hospitalizations will be collected on the eCRF.

Length of stay is defined as the duration of hospitalization and will be calculated as (date of hospital discharge - date of hospital admission) + 1. If the hospitalization is ongoing at the time of EOS/Early Termination Visit, then the hospital discharge date will be imputed with the data cut-off date for the analysis.

Number of subjects with hospitalizations, number of hospitalizations, length of stay per stay and total length of stay per subject will be summarized descriptive statistics by epoch and overall based on the All-Treated Set.

Number of subjects with hospitalization / number of hospitalizations / length of stay per stay / total length of stay per subject will also be standardized to per year (365.25 days) and will be calculated as below:

- By epoch: number of subjects with hospitalization OR number of hospitalizations OR number of days per stay OR number of days of total length of stay per subject / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 1 (See Section 6.1.3 for the definition of start/end of epoch).

- Overall: number of subjects with hospitalization OR number of hospitalizations OR number of days per stay OR number of days of total length of stay per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

Point-estimate and 95% CI of number of hospitalizations per year / total length of stay per subject calculated using a Poisson model with subject-year in study as the offset variable will also be provided by epoch and overall based on the All-Treated Set.

A hospitalization will be counted for a specific epoch only if that hospitalization started during that epoch.

6.9.6 Number of Acute Physician Visits Due to Illness/Infection

Number of acute physician visits and emergency room visits will be collected on the eCRF and summarized descriptive statistics by epoch and overall based on the All-Treated Set.

Number of acute physician visits / emergency room visits per subject will also be standardized to per year (365.25 days) as below:

- By epoch: number of acute physician visits OR emergency room visits per subject / duration of each epoch * 365.25 days per year, where duration of each epoch is calculated as the start date of the epoch – the end date of the epoch + 1 (See Section 6.1.3 for the definition of start/end of epoch).
- Overall: number of acute physician visits OR emergency room visits per subject / duration of study * 365.25 days per year, where duration in study is calculated as the number of days from the first dose of study drug to the date of EOS/Early Termination Visit

Point-estimate and 95% CI of number of number of acute physician visits OR emergency room visits per subject calculated using a Poisson model with subject-year in study as the offset variable will also be provided by epoch and overall based on the All-Treated Set.

6.10 PRO Analysis

All PRO summaries will be based on the All-Treated Set.

All PRO data will be listed in the subject data listings.

For PRO summaries, baseline is defined as the results at Epoch 1 Visit 1.

6.10.1 HRQoL

HRQoL assessment will be performed as part of visits 1 during Epoch 1, Epoch 2 and Epoch 3 and at the EOS/Early Termination Visit.

HRQoL will be analyzed separately for the age groups 2-7 years (PEDS-QL, observer: parent), 8-13 years (PEDS-QL, observer: subject), and 14 years and older (SF-36, observer: subject).

Additionally, all subjects will complete the EQ-5D-3L Health Questionnaire, analyzed separately for the age groups: 2-11 years EQ-5D-3L (observer: parent) and 12 years and older EQ-5D-3L (observer: subject). Age will be defined as the age at screening.

6.10.1.1 PEDS-QL

The PEDS-QL Inventory is a 23-item, brief measure of health-related quality of life in children and young people. The measure can be completed by parents as well as children and young people.

The 23 items in the PEDS-QL comprise 4 Generic Core Scales:

- Physical Functioning (8 items)
- Emotional Functioning (5 items)
- Social Functioning (5 items)
- School Functioning (5 items)

On PEDS-QL for subjects aged 2-4 years, School Functioning only have 3 items. The 4th and 5th question are blanked for subjects aged 2-4 years.

Items on the PEDS-QL will be reverse scored and transformed to a 0-100 scale using the following rules: 0 (Never) = 100; 1 (Almost Never) = 75; 2 (Sometimes) = 50; 3 (Often) = 25; 4 (Almost Always) = 0.

Scale scores will be calculated as the sum of the items over the number of items answered (to account for missing data). If more than 50% of items are missing, the scale score will not be computed.

Total scale score will be calculated as the mean of all items.

Descriptive statistics of total scale score of PEDS-QL and change from baseline (if both scores are available) will be presented by visit and age groups (2-7 years; 8-13 years) for the All-Treated Set.

6.10.1.2 SF-36

SF-36 is a 36-item, patient-reported survey of patient health.

SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).

Two sets of scores will be derived from the SF-36: eight scale scores, and two summary scores: physical component summary (PCS) score and mental component summary (MCS) scores.

PCS score and MCS score can be calculated following the procedure described below:

- Step 1: recode the responses of all items as described in
- Table 2.

Table 2. Original Response and Recoded Values for SF-36 Items

Item Numbers	Original Response Category	Recoded Value
1	1 →	5
	2 →	4.4
	3 →	3.4
	4 →	2.0
	5 →	1.0
6; 9a, 9e, 9d, 9h; 11b, 11d	1 →	5
	2 →	4
	3 →	3
	4 →	2
	5 →	1
3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	1 →	1
	2 →	2
	3 →	3
7	1 →	6.0
	2 →	5.4
	3 →	4.2
	4 →	3.1
	5 →	2.2
	6 →	1
8 (if both 7 and 8 are answered)	1 →	If item 7 original response = 1, then = 6; If item 7 original response = 2-6, then = 5
	2 →	4
	3 →	3
	4 →	2
	5 →	1
8 (if 7 is not answered)	1 →	6.0
	2 →	4.75
	3 →	3.5
	4 →	2.25
	5 →	1
2; 4a, 4b, 4c, 4d; 5a, 5b, 5c; 9b, 9c, 9f, 9g, 9i; 10; 11a, 11c	1 →	1
	2 →	2
	3 →	3
	4 →	4
	5 →	5

- Step 2: use Table 3 to compute simple algebraic sums of the presented final item scores. The developers of the SF-36 suggest a method of gaining scores for missing values, but because of the sample size, missing data will not be imputed.

Table 3. Formulae for SF-36 Scale Scores

SF-36 Scale	Sum Final Item Values (after recoding items as in	Lowest and Highest Possible Raw Scores	Possible Raw Score Range

	Table 2)		
PF	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10, 30	20
RP	4a + 4b + 4c + 4d	4, 20	16
BP	7 + 8	2, 12	10
GH	1 + 11a + 11b + 11c + 11d	5, 25	20
VT	9a + 9e + 9g + 9i	4, 20	16
SF	6 + 10	2, 10	8
RE	5a + 5b + 5c	3, 15	12
MH	9b + 9c + 9d + 9f + 9h	5, 25	20
$\text{Scale Score} = \frac{\text{Actual raw score} - \text{lowest possible raw score}}{\text{Possible raw score range}} \times 100$			

- Step 3: after the eight scale scores are calculated, a z-score will be calculated for each scale by subtracting the general US population mean from a subject's scale score and then dividing by the general US population SD as described below. See Table 4 for the details of the US general means and SDs of each scale.
- Step 4: transform each SF-36 z-score to the norm-based scoring by multiplying each z-score from Step 3 by 10 and adding the resulting product to 50.
    - Norm-Based Score = 50 + (z-score × 10)
- Step 5: An aggregate physical component score will be calculated by multiplying each SF-36 scale z-score by its respective PCS coefficient and summing the eight products, as shown below. Similarly, an aggregate mental component score will be calculated by multiplying each SF-36 scale z-score by its respective MCS coefficient and summing the eight products. See Table 4 for details of PCS/MCS factor score coefficients.
    - AGG_PHYS = (PF_Z × 0.424) + (RP_Z × 0.351) + (BP_Z × 0.318) + (GH_Z × 0.250) + (VT_Z × 0.029) + (SF_Z ×-0.008) + (RE_Z × -0.192) + (MH_Z × -0.221)
    - AGG_MENT = (PF_Z × -0.230) + (RP_Z × -0.123) + (BP_Z × -0.097) + (GH_Z × -0.016) + (VT_Z × 0.235) + (SF_Z ×0.269) + (RE_Z × 0.434) + (MH_Z × 0.486)

Table 4. US Scale Means, SDs and Factor Score Coefficients for PCS and MCS[5]

Scale	Mean	SD	PCS coefficients	MCS coefficients
PF	83.29	23.76	0.424	-0.230
RP	82.51	25.52	0.351	-0.123
BP	71.33	23.66	0.318	-0.097
GH	70.85	20.98	0.250	-0.016
VT	58.31	20.02	0.029	0.235
SF	84.30	22.92	-0.008	0.269
RE	87.40	21.44	-0.192	0.434
MH	74.99	17.76	-0.221	0.486

- Step 6: Transforming each component score to the norm-based scoring by multiplying each aggregate component scale score by 10 and adding the resulting product to 50.
    - PCS score = 50 + (AGG_PHYS × 10)
    - MCS score = 50 + (AGG_MENT × 10)

Descriptive statistics of the PCS score and MCS score and the corresponding changes from baseline will be presented by visit for subjects with age of 14 years and older at screening for the All-Treated Set.

6.10.1.3 EQ-5D-3L Health Questionnaire

EQ-5D-3L Health Questionnaire consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems (Level 1 [L1]), some problems (Level 2 [L2]), and extreme problems (Level 3 [L3]). This part of the EQ-5D-3L provides a descriptive profile that can be used to generate a health state profile. Each health state profile can be assigned a health state index score based on societal preference weights for the health state. Health state index scores generally range from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than death) to 1 (perfect health), with higher scores indicating higher health utility. The health state index score will be calculated from individual health profiles using Japanese value set[6] (see Table 1 for details).

The health state index score h will be calculated using the following formula:

$$h = 1 - (\alpha + \Sigma_d \Sigma_l \beta_{dl} x_{dl})$$

where x_{dl} represents ten dummy variables that indicate the presence of either a Level 2 or a Level 3 in a given dimension of the evaluated state. In other words, d stands for the dimensions: M for mobility, SC for self-care, UA for usual activities, PD for pain or discomfort, AD for anxiety or depression; and l stands for either Level 2 or Level 3. α is constant term representing any move away from perfect health.

Table 5. Japanese Value Set for EQ-5D-3L Health State Index Score

Coefficient	Value
α	0.152
β_{M2} β_{M3}	0.075 0.418
β_{SC2} β_{SC3}	0.054 0.102
β_{UA2} β_{UA3}	0.044 0.133
β_{PD2} β_{PD3}	0.080 0.194
β_{AD2} β_{AD3}	0.063 0.112

For example, assuming there is a subject with health state profile = 11223. The health state index for this subject is calculated as: 1 – 0.152 – 0.044 – 0.080 – 0.112 = 0.612.

EQ VAS is a 0-100 scale where the subjects are asked to self-rate health. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

Descriptive statistics of the health state index score of ED-5D and ED VAS score and change from baseline (if both scores are available) will be presented by visit and age groups (2-11 years; 12 years and older) for the All-Treated Set.

6.10.2 Treatment Satisfaction

Treatment satisfaction (LQI and TSQM-9) will be assessed as part of visits 1 during Epoch 1, Epoch 2 and Epoch 3 and at the EOS/Early Termination Visit.

6.10.2.1 LQI

LQI is an instrument specifically designed to evaluate perceptions of HRQOL, among patients receiving IgG treatment. It consists of 15 items aiming at examining the respondent's perceptions of the impact of the IgG treatment on daily activities. Each item is to be assessed on a 7-point Likert scale ranging from extremely good (=7) to extremely bad (=1).

The LQI can be summarized into four domains: Factor 1 - treatment interference (items 4, 7, 9, 12, 14, 15), Factor 2 - therapy-related problems (items 1, 2, 3, 10), Factor 3 - therapy setting (items 5, 6, 8), and Factor 4 - treatment costs (items 11, 13)[7]. The scores of LQI domains are calculated by summing up item values within each domain and transforming them into scores ranging from 0 to 100 using the following formula:

- LQI factor score calculation: Total raw score = 100 × [(Raw score – Lowest possible raw score) / Possible raw score range]

Higher scores are associated with better IgG treatment specific treatment satisfaction. A score can be computed for a domain only if no more than 50% of the items are missing within that domain.

For example, for the calculation of Factor 1 – treatment interference, lowest possible raw score is 6, maximum is 42, so the range is 36. A subject who has a sum of 24 on these 6 items would have a final score of 100 x ([24-6]/36) = 50.

LQI will be analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older (observer: subject). Age will be defined as the age at screening.

Descriptive statistics of LQI domain scores and change from baseline will be presented by visit and age groups (2-13 years; 14 years and older) for the All-Treated Set.

6.10.2.2 TSQM-9

TSQM-9 is a self-administered, 9-item, validated measure that assesses treatment satisfaction in the following 3 domains: effectiveness (items 1-3), convenience (items 4-6), and global satisfaction (items 7-9).

Items 1-6 and Item 9 will be coded on a scale of 1-7. Items 7 and 8 will be coded on a scale of 1 to 5. The scores of TSQM-9 domains are calculated by summing up item values within each domain and transforming them into scores ranging from 0 to 100 using the following formula[8]:

- Effectiveness
  - If all items are completed: = [(item1 + item2 + item3) - 3]/18*100
  - If one item is missing: = [sum of completed items - 2]/12*100
- Convenience
  - If all items are completed: = [(item4 + item5 + item6) - 3]/18*100
  - If one item is missing: = [sum of completed items - 2]/12*100
- Global satisfaction
  - If all items are completed = [(item7 + item8 + item9) - 3]/14*100
  - If either Item 7 or 8 is missing: = [sum of completed items - 2]/10*100
  - If item 9 is missing: = [(item 7 + item 8) -2]/8*100

The TSQM-9 domain scores range from 0 to 100, where higher scores represent better satisfaction on that domain. A score can be computed for a domain only if no more than one item is missing from that domain.

TSQM-9 will be analyzed separately for the age groups: 2-12 years (observer: parent) and 13 years and older (observer: subject). Age will be defined as the age at screening.

Descriptive statistics of TSQM-9 domain scores and change from baseline will be presented by visit and age groups (2-12 years; 13 years and older) for the All-Treated Set.

6.10.3 Treatment Preference

Treatment preference will be assessed at the EOS/Early Termination Visit.

Treatment preference will be analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older (observer: subject). Age will be defined as the age at screening.

Descriptive statistics of each question of treatment preference will be presented by visit and age groups (2-13 years; 14 years and older) for the All-Treated Set.

6.11 Other Analyses

6.11.1 Subgroup Analysis

Subgroup analyses are planned for all efficacy endpoints, overall summary of TEAEs, study drug administration (number of infusions per subject, number of infusions per subject-year, number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of infusion, maximum infusion rate per infusion site/infusion volume/infusion site) and PK endpoints (trough total IgG and IgG subclass concentrations, and specific antibodies).

The subgroups used will be age categories below:

- <18 years
- >=18 years

Age is the age at informed consent date.

6.12 Interim Analysis

No interim analysis is planned for this study.

6.13 Data Monitoring Committee

No data monitoring committee (DMC) is planned for this study.

7.0 REFERENCES

1. Varni, J. W., Seid, M. & Rode, C. A. 1999. The PedsQL: measurement model for the pediatric quality of life inventory. Med. Care, 37, 126-139.

2. Ware, J. E., Jr. & Sherbourne, C. D. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care, 30, 473-483.

3. Shaw, J. W., Johnson, J. A. & Coons, S. J. 2005. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care, 43, 203-220.

4. Daly, P. B., Evans, J. H., Kobayashi, R. H., Kobayashi, A. L., Ochs, H. D., Fischer, S. H., Pirofsky, B. & Sprouse, C. 1991. Home-based immunoglobulin infusion therapy: quality of life and patient health perceptions. Ann Allergy, 67, 504-510.

5. Ware, M.E., Kosinski, M. and Dewey, J.E., 2001. How to score version 2 of the SF-36 health survey (standard & acute forms). Quality Metric Incorporated.

6. Tsuchiya, A., Ikeda, S., Ikegami, N., Nishimura, S., Sakai, I., Fukuda, T., Hamashima, C., Hisashige, A. and Tamura, M., 2002. Estimating an EQ- 5D population value set: the case of Japan. Health economics, 11(4), pp.341-353.

7. Nicolay, U., Haag, S., Eichmann, F., Herget, S., Spruck, D. and Gardulf, A., 2005. Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy. Quality of life research, 14(7), pp.1683-1691.

8. User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM), Version 1.4, 14Nov2019.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There are no meaningful changes in the SAP relative to the study protocol.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Not Applicable.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

9.2.1.1 Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-dd hh:mm:ss.

9.2.1.2 Spelling format

English US.

9.2.1.3 Paper Size, Orientation, and Margins

The size of paper will be letter and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

9.2.1.4 Fonts

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

9.2.1.5 Descriptive Statistics

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum and maximum: N;
- Mean, median, lower and upper bounds of two-sided 95% CI: N + 1;
- SD: N + 2

9.2.1.6 Percentages

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

9.2.1.7 Listings

All listings will be ordered by the following (unless otherwise indicated in the output template):

- Allocated treatment group (or treatment received if it's a safety output);
- Subject ID;
- Parameter, when applicable;
- Date/Time, when applicable.
- Timepoint, when applicable

9.2.2 Definition of Baseline

Definition of baseline is provided in Section 6.1.2.

9.2.3 Definition of Visit Windows

No visit windowing will be performed for this study.

9.3 Analysis Software

All analyses except PK parameter calculation will be conducted using SAS version 9.4 or higher.

PK parameter calculation will be conducted using Phoenix WinNonlin Version 8.3 or higher (Certara, L.P., Princeton, New Jersey, USA).