Official Title:	**A Phase 3, Multicenter, Open-label, Single-sequence, Cross-over, Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of IVIG-PEG compared to Gamunex-C in Subjects with Primary Humoral Immunodeficiency**
NCT Number:	NCT04561115
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STATISTICAL ANALYSIS PLAN (SAP)

IVIG-PEG / GC1902

Title: A Phase 3, multicenter, open-label, single-sequence, cross-over, bioequivalence study to evaluate the pharmacokinetics, safety, and tolerability of IVIG-PEG compared to Gamunex-C in subjects with primary humoral immunodeficiency

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ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0\text{-}21\ days}$	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
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
Cl	Clearance
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
IgM	Immunoglobulin M
IV	Intravenous
IVIG	Intravenous Immune Globulin (generic terminology)
kg	Kilogram
LDH	Lactate dehydrogenase
LSM	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NAT	Nucleic acid amplification technology
PE	Pulmonary Embolism
PI	Primary humoral 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
SD	Standard deviation
SOC	System Organ Class
T	Temperature
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to reach C_{max}
V_d	Volume of distribution
WHO-DD	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol GC1902 Version 4.0, dated 01 Mar 2021. 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 Phase 3, multicenter, open-label, single-sequence, cross-over, bioequivalence clinical study to assess the steady-state pharmacokinetics (PK), safety, and tolerability of IVIG-PEG compared with Gamunex-C in adult subjects with primary humoral immunodeficiency (PI). A total of approximately 35 adult subjects in which a minimum of 6 subjects are planned to be enrolled in each dosing interval (i.e., 3-week dosing interval vs 4-week dosing interval) will be enrolled in order to have 20 evaluable subjects for PK analysis.

The study will include a Screening Phase of approximately 28 days, a Gamunex-C Run-in Phase (intravenous (IV) administration of Gamunex-C) of up to 4.5 months (if applicable), a Gamunex-C PK Phase of 3 or 4 weeks, an IVIG-PEG Treatment Phase of up to 4.5 months, an IVIG-PEG PK Phase of 3 or 4 weeks, and a Final Visit/Early Termination visit.

Prior to enrollment into the study, subjects with PI currently receiving intravenous immunoglobulin (IVIG) replacement treatment will be screened during the Screening Phase. Subjects must meet all the specific inclusion criteria and meet none of the exclusion criteria described in Section 5.1 and Section 5.2 of the protocol, respectively to be enrolled in this study.

Depending on their current IVIG treatment regimen, eligible subjects (those who are on a stable Gamunex-C treatment) may enter directly into the Gamunex-C PK Phase or may be required to enter the Gamunex-C Run-in Phase to receive Gamunex-C treatment (Sponsor provided) to achieve an approximate steady-state condition prior to entering the Gamunex-C PK Phase. Subjects meeting the following conditions are required to enter the Run-in Phase (Section 4.2.2.1 of the protocol):

- Not currently receiving Gamunex-C
- Not on a stable dose of Gamunex-C
- Not receiving Gamunex-C every 3 weeks or 4 weeks

After reaching a stable dose and approximate steady-state (i.e., administration of 5 consecutive doses of Gamunex-C for subjects on every 4 weeks dosing regimen and 6 consecutive doses of Gamunex-C for subjects on every 3 weeks dosing regimen), the subjects

will then enter the Gamunex-C PK Phase to determine the area under the curve (AUC) profile of IV infusions of Gamunex-C.

Subjects receiving Gamunex-C at Screening who have been stable for 4.5 to 5 months (i.e., administration of at least 5 consecutive stable doses for subjects on every 4 weeks dosing regimen and administration of at least 6 consecutive stable doses for subjects on every 3 weeks dosing regimen) at doses between 200 and 800 mg/kg prior to the Screening Visit will directly enter the Gamunex-C PK Phase.

After the Screening Phase or Gamunex-C Run-in Phase, subjects will enter the Gamunex-C PK Phase of 3- or 4-weeks duration depending on the individual dosing interval. PK samples will be drawn 30 minutes prior to the start of the PK Phase Gamunex-C infusion, immediately upon the completion of the PK Phase Gamunex-C infusion (within 10 minutes of infusion completion), and at 1, 3, 6, 24, and 48 hours; and 4, 7, 14, 21, and 28 days (the PK sample drawn at 28 days applies only for subjects on every 4 weeks dosing regimen) after the end of the PK Phase Gamunex-C infusion.

After the completion of the Gamunex-C PK Phase, subjects will enter the IVIG-PEG Treatment Phase. Subjects will receive a total of 5 or 6 consecutive doses of IVIG-PEG according to the subject's previous Gamunex-C dosing interval (i.e., administration of 5 consecutive doses for subjects on every 4 weeks regimen and administration of 6 consecutive doses for subjects on every 3 weeks regimen). The dose of IVIG-PEG administered during this phase will be the same as the subject's dose during the Gamunex-C PK Phase.

Trough immunoglobulin G (IgG) levels will be obtained prior to all infusions in the Screening, Gamunex-C Run-in, and IVIG-PEG Treatment Phases.

At the conclusion the IVIG-PEG Treatment Phase (i.e., after 5 or 6 infusions of IVIG-PEG depending on the individual dosing interval), subjects will enter into the IVIG-PEG PK Phase lasting 3 or 4 weeks in duration depending on the individual dosing interval. Pharmacokinetic samples will be drawn 30 minutes prior to the start of the IVIG-PEG infusion in the PK Phase, immediately upon the completion of the PK Phase IVIG-PEG infusion (within 10 minutes of infusion completion), and at 1, 3, 6 hours (±10 minutes), 24 and 48 hours(±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the PK sample drawn at 28 days applies only for subjects on every 4 weeks dosing regimen) after the end of the PK Phase IVIG-PEG infusion.

At the end of the IVIG-PEG PK Phase, subjects will have their Final Visit.

Treatment visits for the Gamunex-C Run-In Phase, Gamunex-C PK Phase, IVIG-PEG PK Phase and the Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

Some treatment visits for the IVIG-PEG Treatment Phase may also be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare

professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site.

Detailed study schedules are included in Appendix 1 of the protocol, Table A for every 3 weeks dosing regimen, and Table B for every 4 weeks dosing regimen. The specific time points for PK sampling for Gamunex-C and IVIG-PEG administration are outlined in Sections 7.2.1.2.3 and 7.2.1.3.3 of the protocol, respectively.

The overall study diagram is depicted in Figure 2-1 and Figure 2-2 below. 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 the protocol Section 4.2 and Appendix 1.

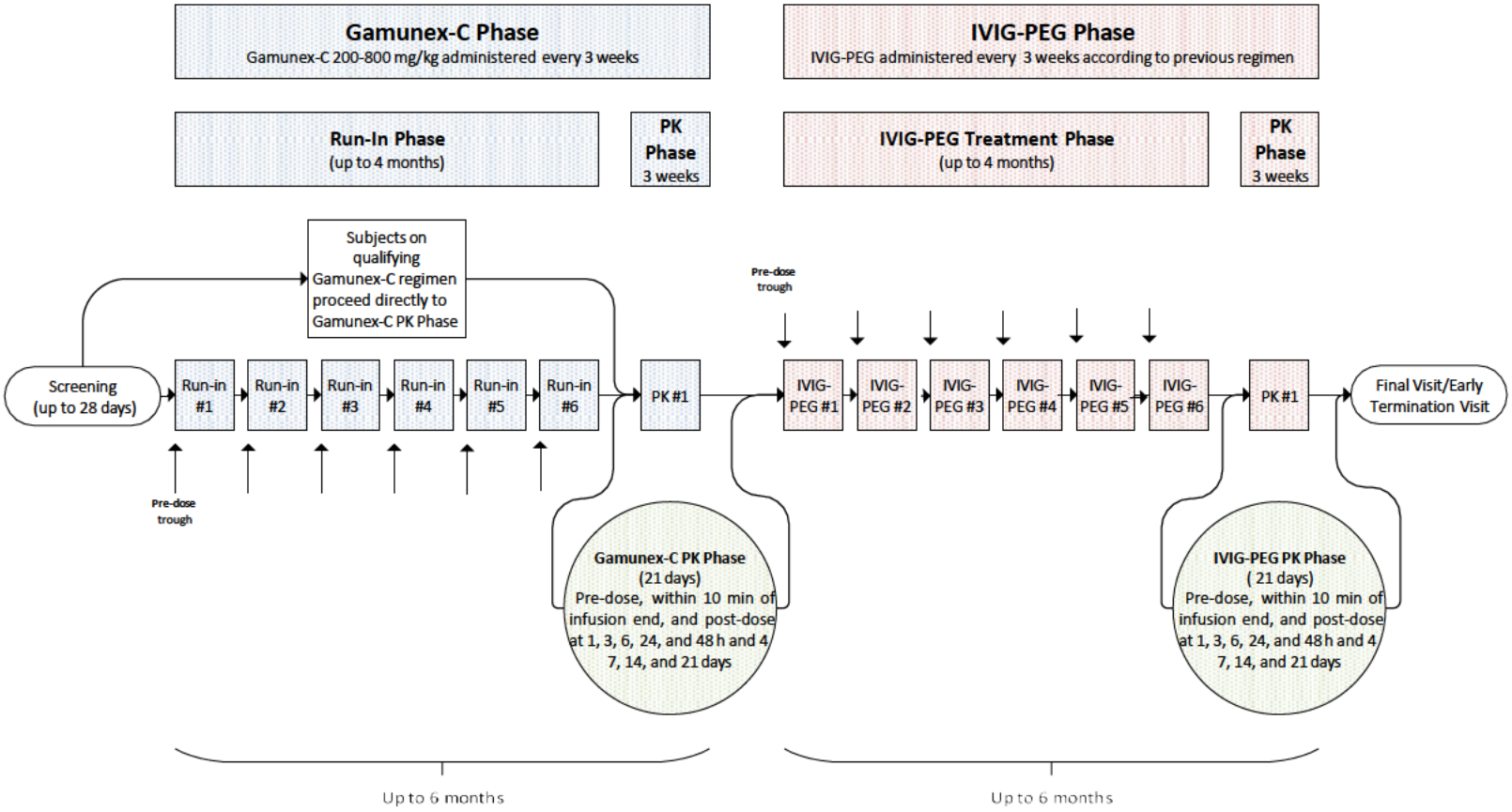

Figure 2-3 Overall Study Schema – Subjects with a Dosing Frequency of Every 3 Weeks

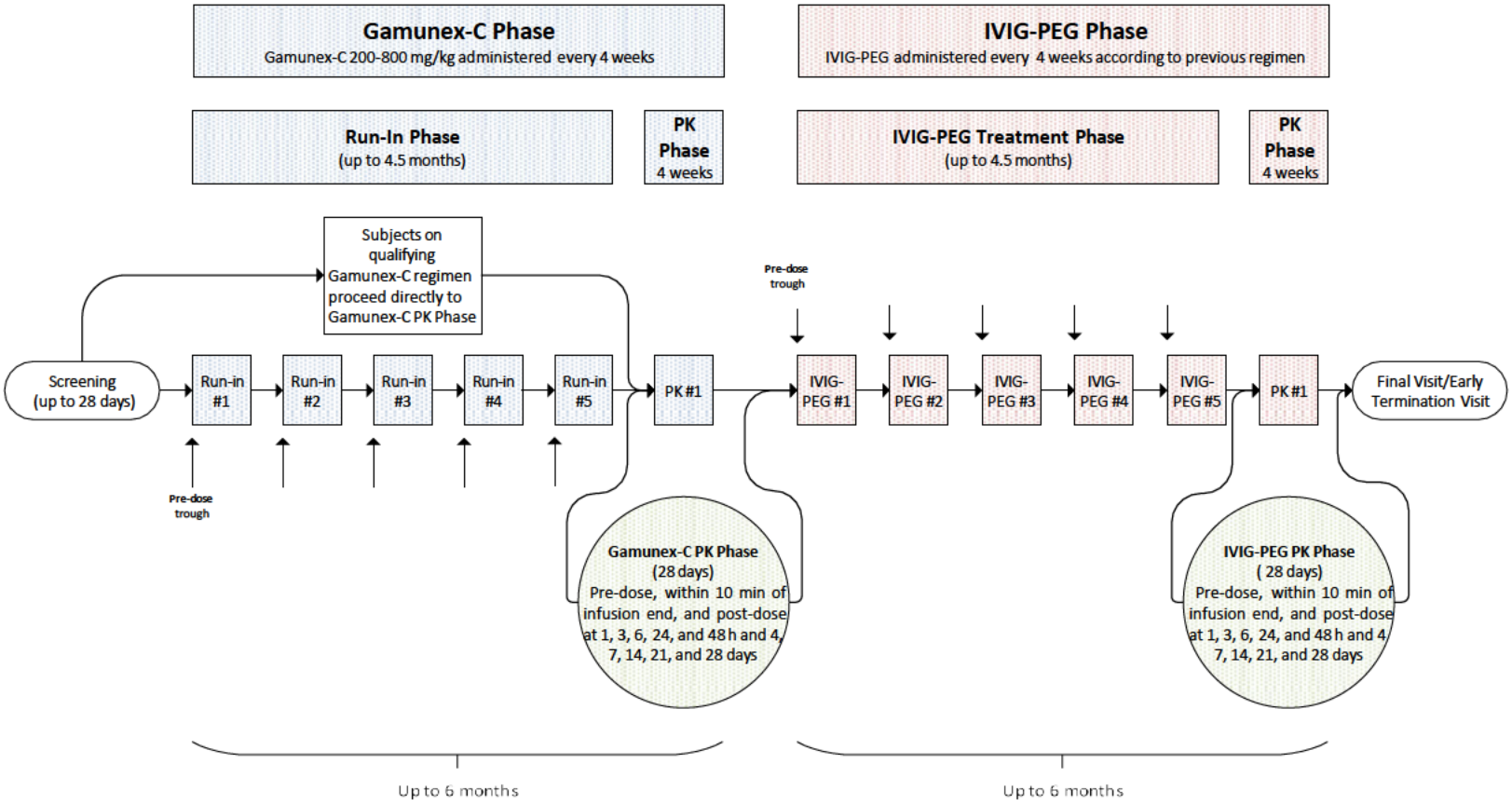

Figure 2-4 Overall Study Schema – Subjects with a Dosing Frequency of Every 4 Weeks

Table 2-1 Subject Entry Criteria

Group	**Subject Populations at Screening Based upon Most Recent IgG Treatment History** (All must have confirmed diagnosis of PI)	**Required Study Entry Point**
1	Receiving stable dose of Gamunex-C between 200 and 800 mg/kg, every 3 or 4 weeks (6 consecutive doses when receiving every 3 weeks administration regimen or 5 consecutive doses when receiving every 4 weeks administration regimen) and have documented trough levels equal to or greater than 500 mg/dL within the previous year documented at the Screening Visit	Gamunex-C PK Phase
2	Receiving IVIG other than Gamunex-C OR Receiving Gamunex-C, but either not on stable dose (≥5 months) OR dose is not between 200 and 800 mg/kg OR interval is not every 3 or 4 weeks	Gamunex Run-in Phase (5 or 6 consecutive doses of Gamunex-C depending on previous dosing regimen)

2.2 Study Objectives

2.2.1 Primary Pharmacokinetic Objective

- To demonstrate bioequivalence of IVIG-PEG with Gamunex-C at steady-state as determined by comparing total IgG area under the concentration time curve during the defined dosing interval ([$AUC_{0-\tau}$] either every 3 weeks [$AUC_{0-21\ days}$] or every 4 weeks [$AUC_{0-28\ days}$]) and maximum concentration in a dosing interval (C_{max}) in subjects diagnosed with PI currently receiving chronic IVIG replacement treatment.

2.2.2 Other Pharmacokinetic Objectives

Other PK objectives include:

- To evaluate the mean steady-state trough IgG levels obtained with IVIG-PEG and Gamunex-C treatment in subjects with PI.
- To evaluate the PK profile for total IgG in the steady-state of IVIG-PEG and Gamunex-C for time of maximum observed concentration (T_{max})
- To evaluate the PK profile for total IgG in the steady-state of IVIG-PEG and Gamunex-C 10% for clearance (Cl) and volume of distribution (V_d)

2.2.3 Secondary Efficacy Objectives

- To evaluate the rate of serious bacterial infections (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

- 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 per subject year due to infections and their treatment

2.2.4 Exploratory Objectives

- To evaluate trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- To evaluate antibody levels for *S. pneumoniae*, *H. influenzae*, and tetanus (*Clostridium tetani* [*C. tetani*])
- 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)
- Trough measles antibody titers (functional assay) is an exploratory variable for informational purposes

2.2.5 Safety Objective

- To evaluate the safety and tolerability of IVIG-PEG as replacement therapy in subjects with PI

3 STUDY VARIABLES

3.1 Primary Pharmacokinetic Variables

The primary PK variables are steady-state total IgG $AUC_{0-\tau}$ (where τ represents the dosing interval of either every 3 weeks [$AUC_{0-21\ days}$] or every 4 weeks [$AUC_{0-28\ days}$]) and C_{max}.

- $AUC_{0-21\ days}$: the AUC over a regular dosing interval of every 3 weeks at an approximate steady-state condition following the regular IV infusion
- $AUC_{0-28\ days}$: the AUC over a regular dosing interval of every 4 weeks at an approximate steady-state condition following the regular IV infusion
- C_{max}: the maximum concentration in a dosing interval (C_{max}) at steady state

3.2 Other Pharmacokinetic Variables

The other PK variables include:

- Mean steady-state trough concentration of total IgG following Gamunex-C administration and following IVIG-PEG administration
- T_{max}: time to reach C_{max}
- Cl: clearance, based on PK profile of total IgG in the steady state
- V_d: volume of distribution, based on PK profile of total IgG in the steady state

3.3 Secondary Efficacy Variables

- 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
- 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 per subject year due to infections and their treatment

3.4 Exploratory Variables

The exploratory variables include:

- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *S. pneumoniae*, *H. influenzae*, and tetanus (*C. tetani*)
- 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)
- Trough measles antibody titers (functional assay) is an exploratory variable for informational purposes

3.5 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), infusional AEs and discontinuations due to AEs
- Criteria for events of special interest: thromboembolic and hemolytic risk assessments

- Vital signs during clinic visits (systolic blood pressure [SBP] and diastolic blood pressure [DBP], heart rate [HR], temperature [T], respiratory rate [RR])
- Physical Assessments
- Laboratory assessments including chemistry, hematology, special tests and urinalysis.

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 alpha level for statistical significance of the bioequivalence test to be used is 0.1 (i.e., alpha=0.05 for one-sided test), or a 90% CI. All other statistical inferences will be tested at 2-sided with α=0.05, if applicable.

Unless otherwise noted, all data collected in the electronic case report form (eCRFs) or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by study phases: Gamunex-C Run-In Phase (including Gamunex-C Run-in visits), Gamunex-C PK Phase (including Gamunex-C PK visit), IVIG-PEG Phase (including IVIG-PEG treatment phase and IVIG-PEG PK phase), subject number (which includes site number) 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.

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 non-missing measurement taken prior to the start of the study treatment as the first Gamunex-C infusion at Gamunex-C Run-in visit #1 for subjects who are enrolled into the Run-In Phase or at Gamunex-C PK Visit for subjects who are enrolled directly into the Gamunex-C PK phase. Where appropriate, additional analyses will be performed for treatment-emergent changes from last non-missing measurement prior to the first infusion of each study phase.

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 Gamunex-C PK Visit and the IVIG-PEG PK Visit 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 Gamunex-C infusion per PK sampling schedule is shown in Table 4-1 below.

Table 4-1 Nominal PK sampling time and an example of actual elapsed time from the start of the Gamunex-C infusion per PK sampling schedule.

Scheduled Time	Nominal Time (Hours)	Example Actual Elapsed Time (Hours)
Pre-Infusion	0	0
Immediately After Infusion	2	2.17
1 Hour Post-Infusion	3	3.00
3 Hours Post-Infusion	5	5.00
6 Hours Post-Infusion	8	8.00
24 Hours Post-Infusion	26	24.03
48 Hours Post-Infusion	50	48.10
4 Days Post-Infusion	98	96.00
7 Days Post-Infusion	170	144.08
14 Days Post-Infusion	338	286.67
21 Days Post-Infusion[†]	506	479.00
28 Days Post-Infusion[§]	674	647.28

[†] Last sample for subjects with dosing interval of every 3 weeks. [§] Only for subjects with dosing interval of every 4 weeks.

In addition, the actual duration of the infusion for the Gamunex-C and IVIG-PEG doses will be calculated.

4.1.1.2 Missing IgG Concentration Values

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

4.1.1.3 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.

In the listing, the actual values will be displayed.

4.2 Analysis Populations

Safety Population

The Safety population will include all subjects who received any amount of study drug(s) (Gamunex-C or IVIG-PEG) and will be used for safety, secondary efficacy, and exploratory analysis.

IgG Population

The IgG population will consist of all subjects who receive study drug(s) and have any valid total IgG concentration data. The validity of total IgG concentrations will be reviewed and determined before database lock based on consideration of treatment compliance and blood sampling/testing issues (such as collection problem). Any invalid total IgG concentrations will be flagged with the reason for invalidity in the subject listing. The summary of total IgG concentration data, mean trough, IgG subclasses, and antibody titers 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 at either the Gamunex-C PK Phase or IVIG-PEG PK Phase to allow calculation of $AUC_{0-\tau}$ and/or C_{max} (the primary PK endpoints).

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 4 quantifiable samples following data imputations (if applicable).

4.3 Sample Size Considerations

A total sample size of 20 subjects achieves at least 90% power at a 0.05 significance level for each one-sided test with the CV of 20% on the primary PK parameter assuming the true ratio of the test to reference is 1.0 and equivalent limits of (0.8, 1.25). An approximate 35 subjects are planned to be enrolled to have 20 evaluable subjects in the PK population for PK analysis.

4.4 Interim Analysis

No interim analysis is planned to be performed.

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.

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 (i.e., minor, major, critical, minor COVID, major COVID, or critical COVID) will be summarized and listed. The three severity levels (minor COVID, major COVID, or critical COVID) are related to PDs due to COVID. The three severity levels (minor, major, or critical) consist of all PDs including all COVID related PDs, and non-COVID related PDs.

7 DEMOGRAPHY AND MEDICAL HISTORY

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including age, age categories (>=18 - <65, >= 65 years), sex, race, ethnicity, height, weight at baseline, total IgG level at baseline, subject entry status, dose frequency at entry will be summarized for the Safety population. The primary humoral immunodeficiency and IgG treatment history will also be summarized.

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 by system organ class (SOC) and preferred terms (PT). Data listing for medical history will also be provided.

Primary Humoral Immunodeficiency and previous IgG replacement therapy will also be summarized separately based on data collected in "Primary Humoral Immunodeficiency" and "Previous IgG Replacement Therapy" CRFs.

8 CONCOMITANT MEDICATION AND TREATMENT

8.1 Prior and Concomitant Medication

All medications as documented by the investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug classification Dictionary (WHO-DD). All medications will be summarized and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (ie, ATC level 4).

Prior medications will be summarized by overall. Concomitant medications will be summarized by study phase. Prior medications are defined as any medication ended prior to the start of study treatment as the start of the Gamunex-C infusion at Run-In Visit #1 for subjects who are enrolled into the Gamunex-C Run-In Phase, or at Gamunex-C PK Visit for subjects who are enrolled directly into the Gamunex-C PK 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 Gamunex-C PK Visit – 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 with dosing frequency of every 3 weeks

[(Last infusion date of the Run-in Phase – First infusion date of the Run-in Phase) + 28], for subjects with dosing frequency of every 4 weeks

Gamunex-C PK Phase

For subjects who completed the Gamunex-C PK Phase, the duration of exposure in days will be calculated as:

First infusion date of the IVIG-PEG Phase - Infusion date of Gamunex-C PK Visit

For subjects who prematurely discontinued from the study after the Gamunex-C PK Visit and before entering the IVIG-PEG Phase, the duration of exposure in weeks will be calculated as follows:

21 days for subjects with dosing frequency of every 3 weeks

28 days for subjects with dosing frequency of every 4 weeks

IVIG-PEG Phase

[(Last infusion date of the IVIG-PEG Phase – First infusion date of the IVIG-PEG Phase) + 21], for subjects with dosing frequency of every 3 weeks

[(Last infusion date of the IVIG-PEG Phase – First infusion date of the IVIG-PEG Phase) + 28], for subjects with dosing frequency of every 4 weeks

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 in hours

Duration of infusion in hours 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), the duration of infusion (hours), and maximum (last) infusion rate achieved (mL/min) will be summarized by dosing frequency. Further, infusion interruptions will be summarized.

8.2.2 Compliance

Infusion compliance, treatment compliance, and overall compliance will be calculated separately for each study phase.

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 are as follows:

Table 8-1 Planned infusion and exposure duration by study phase

Dosing Frequency	Study Phase	Number of Infusions Expected	Exposure Duration Expected (weeks)
Every 3 weeks	Run-in Phase	6	18
Every 4 weeks	Run-in Phase	5	20
Every 3 weeks	Gamunex-C PK Phase	1	3
Every 4 weeks	Gamunex-C PK Phase	1	4
Every 3 weeks	IVIG-PEG Phase	7	21
Every 4 weeks	IVIG-PEG Phase	6	24

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 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 Run-in infusion #4 and before the #5 infusion, then the number of infusions expected for the Run-in Phase is 4.

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.

The total volume expected will be calculated as the sum of the volumes prepared at each visit collected on the eCRF.

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.

9 PHARMACOKINETIC ANALYSIS

PK parameters of total IgG will be generated for Gamunex-C PK Phase and IVIG-PEG PK Phase. Total IgG concentrations in plasma will be measured based on the validated assay. The concentration data will be listed and summarized.

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. The trough total IgG concentrations will be measured by the central lab; whereas the serial PK samples will be measured by the specialty lab.

9.1 Analysis of PK Concentration and Dosing Data

9.1.1 Analysis of mean steady state trough total IgG data

The steady-state mean trough concentrations of total IgG for each subject will be determined as the average value of trough concentration measurements obtained at the PK Visit Day 1 and at PK Visit Day 21 or 28 days (depending on the dosing frequency) prior to IV infusion (within 1 hour prior to the start of infusion)..

Mean trough data will be summarized by study phase. Mean trough summary and analysis will be performed for IgG population.

9.1.2 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 infusion at the Gamunex PK visit or IVIG-PEG PK visit 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 infusion at the Gamunex PK visit or IVIG-PEG PK visit (scheduled and nominal times as shown in Table 1 of Section 4.1.1), 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, %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 infusion at the Gamunex PK Phase and/or IVIG-PEG PK Phase plotted on the x-axis. Individual concentration vs. time plots for all subjects will also be presented 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 Table 2 of Section 4.1.1) 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 infusion at Gamunex PK visit or IVIG-PEG PK visit will be determined as appropriate and as data permits. The PK parameters include $AUC_{0-\tau}$, C_{max}, t_{max}, Cl and V_d.

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

The PK parameters of interest are determined as follows:

$AUC_{0-\tau}$	area under the concentration vs. time curve at steady state over the dosing interval (from time 0 to τ), calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration × time (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 dosing interval τ is 21 days for subjects on an every 3 weeks dosing interval or 28 days for subjects on an every 4 weeks dosing interval.
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.
Cl	clearance, calculated as Dose/$AUC_{0-\tau}$, expressed in unit of mL/h/kg, where Dose is in mg/kg.
V_d	volume of distribution, calculated as Cl × Mean Residence Time (MRT), expressed in unit of mL/kg. MRT is calculated using $((AUMC_{0-\tau} + \tau (AUC_{0-\infty} - AUC_{0-\tau}))/AUC_{0-\tau}) - (T/2)$, expressed in time units (hour), where $AUMC_{0-\infty}$ is the area under the first moment of the concentration vs. time curve from time 0 extrapolated to infinite time, $AUMC_{0-\tau}$ is the area under the first moment concentration versus time curve during a steady state dosing interval, τ is the dosing interval, and T is the infusion duration.

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 for t_{max}). The analyses of PK parameters will be based on the PK population.

Depending on the number of subjects being dosed at dosing intervals of every 3 weeks or every 4 weeks, subgroup analyses may be performed to summarize the PK parameters by dosing frequency. 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 Parameters

The primary PK objective is to demonstrate bioequivalence of IVIG-PEG with Gamunex-C at steady-state as determined by comparing total IgG area under the concentration time curve during the defined dosing interval ([$AUC_{0-\tau}$] either every 3 weeks [$AUC_{0\text{-}21\ days}$] or every 4 weeks [$AUC_{0\text{-}28\ days}$]) and by comparing maximum concentration in a dosing interval (C_{max}) in subjects diagnosed with PI currently receiving chronic IVIG replacement treatment.

For the steady-state AUC of total IgG over the regular dosing interval, prior to the statistical comparison, the $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$ will be adjusted/standardized to $AUC_{0\text{-}7\ days}$ as follows:

$AUC_{0\text{-}7\ days} = AUC_{0\text{-}21\ days} / 3$, for subjects with dosing interval of every 3 weeks

$AUC_{0\text{-}7\ days} = AUC_{0\text{-}28\ days} / 4$, for subjects with dosing interval of every 4 weeks

Bioequivalence of steady-state AUC of total IgG between the IVIG-PEG treatment and Gamunex-C treatment will be tested based on established regulatory guidelines for bioequivalence testing.

The null hypothesis for the bioequivalence test is:

$$H_0 : \frac{\mu_T}{\mu_R} \leq 0.8 \; or \; H_0 : \frac{\mu_T}{\mu_R} \geq 1.25$$

The alternative hypothesis is:

$$H_1 : 0.8 < \frac{\mu_T}{\mu_R} < 1.25$$

Where μ_T and μ_R denote geometric least-squares mean (LSM) of PK parameters of IVIG-PEG phase and Gamunex-C PK phase, respectively. For steady state AUC test: μ is geometric LSM of $AUC_{0\text{-}7\ days}$ of each study phase. For steady state C_{max} test: μ is geometric LSM of C_{max} of each study phase. The test will be performed with a 2-sided α=0.10.

Natural log-transformed PK parameters ($AUC_{0\text{-}7\ days}$ or C_{max}) values will be analyzed by analysis of covariance (ANCOVA) with a mixed-effect model. The analysis will include study phase as a fixed effect, the actual dose at the PK Visit and dosing frequency as covariates and subject as a random effect.

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

```
PROC MIXED;
    Class study_phase subjid dosfreq;
    Model log(PK param) = study_phase dosfreq dose;
    Random subjid;
    Lsmeans study_phase / pdiff cl alpha = 0.1;
    Estimate 'IVIG-PEG vs Gamunex-C' study_phase -1 1 / cl alpha = 0.1;
```

Run;

where study phase, log(PK param), subjid, dosfreq and dose represent study phase (Gamunex-C PK Phase and IVIG-PEG Phase), natural logarithm of the primary PK parameter ($AUC_{0\text{-}7\ days}$, or C_{max}), subject number, dosing frequency and actual dose in mg/kg at the PK Visit, respectively. Only those subjects in the PK population and values determined to be legitimate for inclusion in the statistical analysis during the data review will be included in the mixed-effect model.

The Gamunex-C PK Phase will be considered as the reference study phase, and the IVIG-PEG Phase will be treated as the Test study phase. The ANCOVA will include calculation of LSMs, difference between LSMs, and the standard error associated with the difference. The administration effect between IVIG-PEG and Gamunex-C will be assessed by the anti-log transformed LSM differences of AUC0-7 days or Cmax between study phases (Test-Reference) and the corresponding 90% CI. The resulting ratios will be used in the test for IVIG-PEG / Gamunex-C, which will be considered bioequivalent if the 90% CI for the ratio of the PK parameters ($AUC_{0\text{-}7\ days}$ and Cmax) is within (0.80, 1.25).

Sensitivity analysis will be performed for baseline corrected $AUC_{0\text{-}7\ days}$ and Cmax.

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

10 SECONDARY EFFICACY AND EXPLORATORY ANALYSIS

Trough total IgG concentrations, trough concentration of IgG subclasses and the selected specific antibody titers against H. influenzae, anti-pneumococcal polysaccharide (S.pneumoniae), tetanus (C. tetani) and measles will be summarized separately by study phase and scheduled visit. The summaries will include n, mean and SD, coefficient of variation (%CV), median, minimum, maximum, as well as geometric mean.

Trough total IgG concentrations vs. visits of all subjects will be plotted on the same figure (spaghetti plot) using linear scale for all scheduled visits during all study phases. In addition, mean trough total IgG concentrations vs. visits will be plotted for all scheduled visits during all study phases.

All trough concentrations will be presented in listings by subject, study phase and visit/ sample collection date time using IgG population.

The following secondary efficacy variables based on safety population:

- 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

- 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

The following exploratory variable will be analyzed based on safety population (in addition to the PK exploratory variables):

- 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)

For these secondary efficacy variables and exploratory variable, 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 secondary efficacy and exploratory variables 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. The two-sided confidence interval of the rate per person per year for SBI (98%CI) and other exploratory endpoints (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 will be included in the model. The estimated intercept term and its two-sided CI (98% or 95%) 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 CI (98% CI or 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:

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

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 "definitely related" or "possibly related" the event will be defined as a suspected adverse drug reaction (ADR). A suspected ADR with a causal relationship of "definitely related" will be defined as an adverse reaction (AR); thus, ARs are a subset of suspected ADRs. If the causal relationship is labeled as "unrelated/not related", then it will be considered that the AE is not imputable to the study treatment and it is not a suspected ADR.

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. A non-TEAE is defined as an AE which occurs prior to the start of study treatment. Non-TEAEs will be summarized separately from TEAEs. A TEAE is defined as an AE which occurred on or after the start of study treatment as the first Gamunex-C infusion at Gamunex-C Run-in visit #1 for subjects who are enrolled into the Run-In Phase or at Gamunex-C PK Visit for subjects who are enrolled directly into the Gamunex-C PK phase. 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. For adverse events with incomplete start dates/times, the partial dates will be imputed using the same algorithm for missing or partial end date/time information for prior and concomitant Medication described in Section 8.1. The imputed end date/time will only be used to determine whether an AE is treatment emergent. The start/end dates/times reported on the eCRFs will be presented in the listings.

All AEs, suspected ADRs, ARs, SAEs, and discontinuations due to AEs and SAEs will be summarized by presenting subject incidences and percentages and will also be listed with system organ class and preferred terms.

In addition, TEAEs, including suspected ADRs, will be summarized by study phase, system organ class, preferred term, causal-relationship, intensity (severity) and seriousness (serious versus non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe AE or the AE with the strongest causal relationship to the study drug.

An infusional AEs is defined as any AE that occurred during infusion or within 24 and 72 hours after completion of infusion. Infusional AEs within 24 and 72 hours after completion of the infusion will be separately summarized.

The infusional AE rate per infusion and the proportion of infusions with one or more infusional AEs will be summarized.

Summaries will also be provided for the total number of events, the rate per infusion, and the rate per exposure week for TEAEs, suspected ADRs, AR and infusional AEs. The rate per infusion will be calculated as:

Total number of events / Total number of infusions received

The TEAE rate per person year will be calculated as:

Total number of events / Total duration of each study phase in years,

Where the duration for Run-in phase is between the first dose in Run-in phase and the dose in Gamunex-C PK phase; the duration for Gamunex-C PK phase is between the dose in Gamunex-C PK phase and first dose in IVIG-PEG phase; and the duration from IVIG-PEG phase is between first dose of IVIG-PEG and last study visit in IVIG-PEG Phase.

All AEs will be presented in a data listing. In addition, Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed.

Subjects with TEAEs of special interest (thromboembolic events and hemolytic event) will be summarized separately.

11.2 Laboratory Assessments

Hematology, clinical chemistry, serum pregnancy test, urine pregnancy test, viral safety tests and urinalysis will be collected for all subjects if applicable at the assigned visits according to the protocol. Table 11-1 lists the laboratory tests to be analyzed for each test panel.

Table 11-1. Laboratory Test Panels

Test Panel	Tests	Location
Hematology[a]	Hemoglobin, hematocrit, platelets, red blood cell (RBC) count including RBC morphology, white blood cell (WBC) count with differential; absolute reticulocyte count (ARC)	Central
Hemolysis detection[a,b]	Blood: whole blood Hb, RBC, hematocrit, plasma free Hb, haptoglobin, LDH, DAT, ARC, TBL, indirect and direct bilirubin, and blood smear Urine: urine sediment, measuring of hemoglobinuria, and hematuria	Central (central DAT if feasible)
Thromboembolic events risk[a,b]	D-Dimer	Central
Chemistry[a]	Sodium, potassium, creatinine, chloride, calcium, lactate dehydrogenase (BUN), bicarbonate, albumin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gammaglutamyl transferase (GGT), glucose, total bilirubin (TBL), indirect and direct bilirubin	Central
IgG levels[a]	Total IgG levels will consist of trough (pre-dose) measurements in all subjects, and for PK profiling of IVIG-PEG and a total IgG concentration for safety purposes for subjects prematurely discontinuing the study	Central
IgG subclass levels and antibody titers[a]	Measurement of IgG subclasses (IgG1, IgG2, IgG3, IgG4). Measurement of levels of selected specific antibodies against H. influenzae, anti-pneumococcal polysaccharide (S. pneumoniae), tetanus (C. tetani), and measles	Specialty
Serum pregnancy test[a]	Qualitative serum β-human chorionic gonadotropin (β-HCG) for females of child-bearing potential will be performed at Screening	Central
Urine pregnancy test	Qualitative urine pregnancy test for females of child-bearing potential will be performed prior to the first dose received for each investigational product (IP) as well as prior to each IVIG-PEG infusion, and at the Final Visit/Early Termination Visit	Local
Viral NAT test[a,c]	Collect retain samples for hepatitis A virus (HAV) RNA, Hepatitis B virus (HBV) DNA, Hepatitis C virus (HCV) RNA, Human Immunodeficiency Virus (HIV) RNA, and parvovirus B19 (B19V) DNA testing	Central
Viral serology testing[a,c]	Collect retain samples for hepatitis A antibody differential (IgM/IgG), hepatitis B core antibody differential (IgM/IgG), hepatitis C antibody, HIV-1/-2 + Group O antibody, and B19V antibody differential (IgM/IgG) testing	Central
Urinalysis[a]	Microscopic evaluation is done only with cause. pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of the urine if abnormal), specific gravity, and urine sediment	Central

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

[b] Laboratory samples must be taken prior to administrating Gamunex-C or IVIG-PEG (within 8 hours prior to the infusion) and analyzed as described for monitoring TE and hemolytic AEs in protocol Appendix 3 and Appendix 4 only.

[c] Virus safety (NAT and serology) retain samples collected during the study will only be tested if subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV or B19V infection while participating in the study. Virus safety retain samples will be retained until all analyses in support of the study are complete.

Virus safety retain samples collected during the study will only be tested if subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV or B19V infection while participating in the study. Virus safety retain samples will be retained until all analyses in support of the study are complete. If any virus safety testing was conducted, all available results will be listed.

Hematology, clinical chemistry and urinalysis parameters will be summarized at each scheduled 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 Visit, change from Gamunex-C Run-in Visit #1 pre-dose, and change from IVIG-PEG Visit #1 pre-dose will be descriptively summarized for continuous variables. Shift tables, based on the high/low flags, will also be summarized at each scheduled visit for each parameter with normal ranges. For selected analytes, tabular summaries and listings will be provided of treatment-emergent laboratory abnormalities utilizing the following thresholds of interest which are in some cases relative to the established reference range (multiples of lower limit of normal [LLN] or upper limit of normal [ULN]) and in others an absolute value threshold:

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

All laboratory data will be presented in data listings.

11.3 Thromboembolic Events and Hemolytic Risk Assessments

11.3.1 Thromboembolic Events Risk Assessments

At Screening and during all the infusion visits, subjects will be actively monitored for signs and symptoms of arterial and venous thromboembolic (TE) events. TE events risk will be evaluated using the following assessments

- Measurement of D-dimer blood levels;
- The Wells Score will be utilized to assess the clinical characteristics indicative of possible Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE);

- Evaluation of clinical signs and symptoms of arterial and venous TE (such as, dyspnea, pain, swelling, tenderness and discoloration [paleness or redness] in lower extremities).

D-dimer and total scores of the Wells Score for DVT and PE will be listed and 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 Run-in Visit #1, Gamunex-C PK Visit, and IVIG-PEG Visit #1.

Clinical signs and symptoms of arterial and venous TE will be summarized with counts and percentages per category by study phase and visit.

All D-dimer, Wells Score and clinical signs and symptoms of arterial and venous TE data will be presented in data listings.

11.3.2 Hemolytic Risk Assessments

During all the infusion visits at the timeframes noted below, subjects will be monitored for signs of hemolysis associated with the administration of the IP. Hemolysis will be monitored using the following assessments:

- Blood testing: whole blood hemoglobin, plasma free hemoglobin, haptoglobin, LDH, direct antiglobulin test (DAT), ARC, RBC, hematocrit, total and indirect and direct bilirubin, and blood smear within 8 hours prior to the infusion
- Urine testing: urinary sediment, hemoglobinuria and hematuria within 8 hours prior to the infusion
- Evaluation of clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) evaluated by the Investigator or appropriate study staff (medical doctor) pre and post infusion and 10 days +/- 2 days after each infusion.

The blood and urine testing numerical results for monitoring hemolysis will be listed and will be summarized with number of subjects, mean, SD, median, minimum, and maximum values by study phase and scheduled visit. For those tests with normal ranges, shift tables of out of normal range values from baseline to visit by study phase will be provided.

DAT test results will be summarized with counts and percentages per category by study phase and visit.

All blood and urine testing results and clinical parameters data for monitoring hemolysis will be presented in data listings. A listing of subjects with positive DAT test results will also be provided. Subjects with positive DAT results are defined as those having a positive result for at least one of IgG and C3 (or overall positive result) from Predose Run-in #1 or for Group 1 (Gamunex-C PK #1) through end of study. The listing will include all DAT results for any subject with at least one positive DAT value and will also include all hemoglobin, absolute reticulocyte count, serum/plasma free hemoglobin, haptoglobin, lactate dehydrogenase, and

total and indirect bilirubin values at corresponding time points. Blood smear results (specifically “RBC morphology” whether there is presence of spherocytosis) and “urine blood” with any corresponding entries (eg, “urine RBC/HPF”) on urinalysis will also be included.

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 scheduled visit. The original value and change from Screening Visit for subjects who are enrolled directly into the Gamunex-C PK phase or the Gamunex-C Run-in visit #1 pre-dose for subjects who are enrolled into the Run-In Phase or change from IVIG-PEG Visit #1 pre-dose for IVIG-PEG phase will be descriptively summarized for continuous variables. Body weight, height and BMI will be similarly summarized.

All vital sign data will be listed.

11.5 Physical Assessments

Full physical assessment findings at the Screening Visit and IVIG-PEG Visit #1 will be summarized with numbers and percentages by body system. Entries for 'Other' body systems will be grouped together; a subject with more than one 'Other' entries will be counted only once. Physical assessment change findings (new or worsened clinically relevant findings, and resolved/improved findings) after the screening visit or IVIG-PEG Visit #1 will be summarized with numbers and percentages per category of the change findings by study phase.

All physical assessment data will be listed.

11.6 X-Rays

X-rays finding at screening visit will be listed.