Official Title:	**A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects With Primary Immunodeficiency**
NCT Number:	NCT02806986
Document Date:	SAP Version 1: 16 July 2019

STATISTICAL ANALYSIS PLAN (SAP)

IGSC 20% / GTI1503

Title: A Multi-Center, Open-Label, Single-Arm Trial to Evaluate Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects with Primary Immunodeficiency

Author's Name and Address: ████████, PhD

Grifols Therapeutics LLC

79 TW Alexander Drive

Research Triangle Park, NC 27709

Author's Telephone Number: ████████

Version/Date: Final V1.0 / 16 JUL 2019

Approved by: _____ Date: 16/07/2019

    Name: ████ PhD
    Title: ████████
    ████████

Approved by ████████ Date: 16/7/2019

    Name: ████, MD
    Title: ██

Approved by ████████ Date: 16 JUL 2019

    Name: ████
    Title: ████

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0-7days}$	Area under the concentration-time curve from 0 to 7 days
BLQ	Below the limit of quantification
BUN	Blood urea nitrogen
CI	Confidence interval
C_{max}	Maximum concentration
CSR	Clinical Study Report
CV	Coefficient of variation
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
dL	Deciliter
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
HR	Heart rate
IgG	Immunoglobulin G
IGSC 20%	Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (Grifols)
IP	Investigational product
IVIG	Intravenous Immune Globulin (generic terminology)
kg	Kilogram
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NAT	Nucleic acid amplification technology
PI	Primary immunodeficiency
PK	Pharmacokinetic(s)
PT	Preferred term
RR	Respiration rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBI	Serious bacterial infection

SBP	Systolic blood pressure
SCIG	Subcutaneously delivered immune globulin or subcutaneous immunoglobulin (generic terminology)
SD	Standard deviation
SOC	System Organ Class
T	Temperature
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to reach C_{max}
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1   INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol GTI1503 Version 3.0, dated 21 Mar 2017. The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables and figures which will be produced, are appropriate and complete to support valid conclusions regarding the study objectives and the completion of Clinical Study Report (CSR). Additional post-hoc or unplanned analyses, which are not defined in this SAP, may be performed to support the clinical development program. Such analyses will be documented in the CSR.

2   STUDY DESIGN AND OBJECTIVES

2.1   Study Design

This is a prospective, multi-center, open-label, single-arm, efficacy, pharmacokinetic (PK), safety and tolerability study of Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) in subjects with primary immunodeficiency (PI). Approximately 60 subjects will be enrolled in order to have approximately 20 adult subjects (> 16 years) and 20 pediatric subjects (≤ 16 years) treated with subcutaneously (SC) administered IGSC 20% who complete the entire study. This study will include 3 study stages: Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1 (13 IGSC 20% weekly doses), and IGSC 20% Treatment Stage 2 (39 IGSC 20% weekly doses).

Subjects who are receiving intravenous immune globulin (IVIG) at a dose of at least 200 mg/kg per infusion every 3 or 4 weeks at Screening must be on a stable Immunoglobulin G (IgG) regimen (dose and dosing interval) for at least 3 consecutive months prior to Screening. Subjects who are receiving subcutaneously delivered immune globulin (SCIG) must also be on a stable regimen for at least 3 consecutive months prior to Screening; there is no prerequisite minimum dose for subjects entering study on an SCIG regimen. Subjects who have never received IVIG or SCIG treatment (treatment naïve) will not be eligible for entry into the study.

Previous Regimen Phase:

- Subjects will be infused with their current ongoing ("previous regimen") IVIG/SCIG regimen (pIV/pSC) in the clinic (mandatory) to obtain 2 trough IgG levels (obtained prior to each pIV/pSC infusion) on each subject's "previous regimen". For subjects entering study on SCIG, the second IgG trough level may be obtained at Baseline, immediately prior to starting the initial infusion of IGSC 20%.

- The Screening Visit may coincide with the pIV/pSC infusion on the previous regimen (pIV#1/pSC#1). Product for the previous IgG regimen is not provided by Grifols. pIV subjects will be enrolled in IGSC 20% Treatment Stage 1 one week after completion of the last IgG trough sampling in the Previous Regimen Phase and therefore the subject must have 2 minimum concentration (C_{trough}) samples on their pIV **prior** to the Baseline/Week 1 visit. pSC subjects will be enrolled in IGSC 20% Treatment Stage 1 (Baseline) in accordance with the time interval that they are currently receiving SCIG (ie,

if on a weekly SCIG regimen, Baseline will occur 1 week after completion of the last SCIG infusion and a second IgG trough level will be obtained at Baseline. If the interval between pSC infusions is 2 weeks (or more), then Baseline will occur after that time interval has elapsed, a trough IgG level will be obtained, and the eligible subject may commence IGSC 20% after Baseline assessments are complete).

- Nonconsecutive C_{trough} samples are acceptable for subjects on SCIG. A minimum of 10 days is anticipated for the Screening/Previous Regimen Phase to ensure Screening human immunodeficiency virus (HIV) nucleic acid amplification technology (NAT) test results will be available before the Baseline Visit/Week 1 visit.

20% IGSC Treatment Stage 1:

- The first dose of the investigational product (IP), IGSC 20%, will be administered immediately after Baseline assessments are complete (SC#1). Subjects will be infused with IGSC 20% at a 1:1 dose-equivalent regimen (per equation in Section 3.3.2 of the protocol) from their previous regimen at the clinical site (or a minimum IGSC 20% dose of 100 mg/kg/week if the derived 1:1 dose from the previous regimen is lower).

- All subjects will receive 13 IGSC 20% infusions at weekly intervals and study visits at the clinical site will occur at Baseline/SC#1, SC#2, #3, #5, #9, and #13. IgG trough blood levels will be measured at all of these visits (except SC#3) occurring at the clinical site. All other doses of IGSC 20% may be infused at home (once properly trained) or in the clinic.

- The mg/kg dose of IGSC 20% (ratio of mg per kg) will be adjusted <u>at clinic visits</u> if the trough level in subjects is below 500 mg/dL, a level that is considered as insufficient to protect against serious bacterial infection (SBI); the goal is to avoid repeated dose adjustments. The precise dose adjustment (mg/kg) should not be more than a 15% to 20% increase from the dose producing low IgG trough, per the Investigator's discretion. Any dose adjustments beyond this range will be completed in consultation with the Grifols Medical Monitor. The Treatment Stage 1 dose will continue into IGSC 20% Treatment Stage 2. After the 13th IGSC 20% infusion in IGSC 20% Treatment Stage 1, subjects will enter IGSC 20% Treatment Stage 2 to receive an additional 39 weeks of IGSC 20% therapy.

IGSC 20% Treatment Stage 2:

- The IGSC 20% dose (mg/kg) will remain constant with no dose adjustment permitted in this phase, unless <u>it is absolutely medically necessary to change the dose, and such change requires prior consultation with the Grifols Medical Monitor.</u> Dosing will be based on the subject's most current weight. For the subsequent at home IGSC 20% infusions between clinic visits, the dose will be the same as the total infusion dose calculated at the previous clinic study visit where weight was measured at the clinical site.

- While all subjects will have a SC#17 clinic visit and standard assessments, serial PK sampling will only be performed in a subset of adult subjects: At SC#17, PK profiles in

the first (where possible) 20 adult subjects, will be measured by obtaining blood draws for steady-state PK analyses over a period of 7 days just prior to and post the 17th IGSC 20% infusion through SC#18. These subjects will constitute the PK subset in this study.

- Where possible, the PK subset will comprise the first 20 adult subjects enrolled. Any designated PK subject who undergoes a dose adjustment (mg/kg change in dose) at or after the ninth IGSC 20% infusion (SC#9) which corresponds to at or after Week 9 in Treatment Stage 1 will be permitted to continue within the study, though he/she will not participate in PK profiling; however, an additional PK replacement subject may be recruited.

- Similarly, PK subjects who do not complete the full PK profile may be replaced if deemed necessary.

A total of 52 doses of IGSC 20% will be administered (13 doses of IGSC 20% in Treatment Stage 1 and 39 doses of IGSC 20% in Treatment Stage 2) with a final follow-up visit at Week 53 one week after the last dose at Week 52.

The overall study schema and the specific time points for PK sampling for Previous Regimen Phase and IGSC 20% Treatment Stages are outlined in Figure 2-1, and the schedule of study procedures, PK details, and definitions for the primary endpoint variable, SBIs are provided in Appendix 1 to Appendix 3 of the protocol.
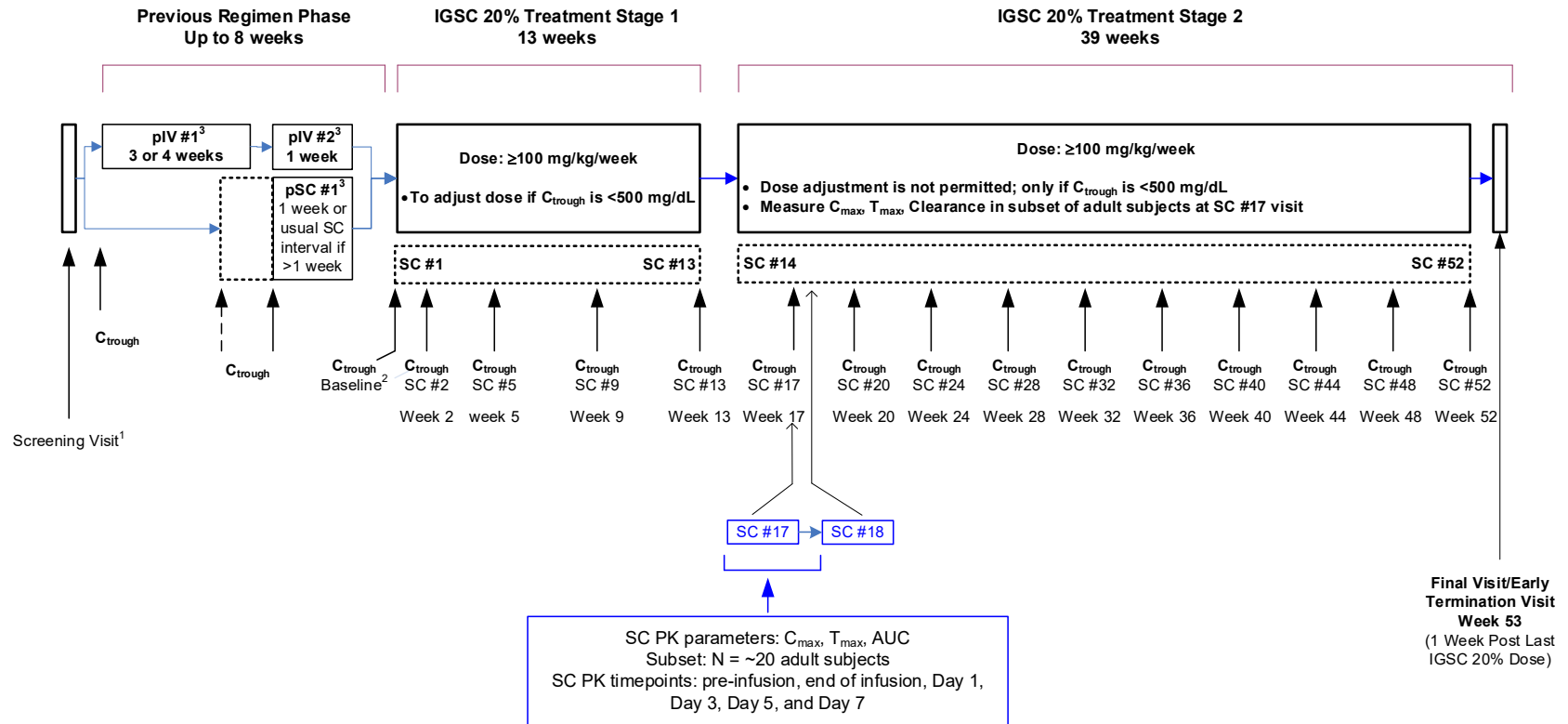
Figure 2-1 Overall Study Schema

2.2   Study Objectives

2.2.1   Efficacy and Pharmacokinetic Objectives

2.2.1.1   Primary Efficacy Objective

The primary objective of this Phase 3 study is to evaluate whether weekly administered IGSC 20% over a one year period will achieve less than 1 SBI per subject per year in PI subjects.

2.2.1.2   Secondary Objectives

- To determine if IGSC 20% replacement therapy maintains mean trough IgG levels that are comparable to the mean trough blood levels with the previous IgG replacement regimen
- To evaluate all infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator

- To evaluate number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic, and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection.

- To evaluate number of hospitalizations due to infection
- To evaluate number of days of work/school/daily activities missed per subject year due to infections and related treatment

2.2.1.3   Other Objectives

- To evaluate trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)

- To evaluate antibody levels for *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Clostridium tetani* (tetanus)

- To evaluate the PK profile for total IgG (area under the concentration-time curve from 0 to 7 days [$AUC_{0-7 \text{ days}}$], maximum concentration [C_{max}], and time to reach C_{max} [t_{max}]) in adult PI subjects at steady state (after approximately 4 months [16 weeks]) of weekly administration of IGSC 20%

- Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes

- 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).

2.2.2   Safety Objectives

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

3   STUDY VARIABLES

3.1   Efficacy and Pharmacokinetic Variables

3.1.1   Primary Efficacy Variable

The primary efficacy variable is the number of SBIs. Also, the percentage of subjects with SBIs will be summarized. SBI definitions (Food and Drug Administration [FDA]/European Medicines Agency [EMA] diagnostic criteria) are provided in Appendix 3 of the protocol.

3.1.2   Secondary Variables

One of the secondary endpoints of this study is trough concentrations of total IgG of previous regimen during the Screening/Previous Regimen Phase and the IGSC 20% Treatment Stages. It is measured to determine if IGSC 20% replacement therapy maintains mean trough IgG levels that are comparable to the mean trough blood levels with the previous IgG replacement regimen.

Other secondary variables include the rate of infection of any kind (serious and non-serious), antibiotic treatment (oral, parenteral, oral plus parenteral, prophylactic, and therapeutic), hospitalizations due to infection, and days lost from work/school/daily activities due to infections and related treatment. The infection of any kind includes acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection?" (verbatim term delineating nature of infection).

3.1.3   Other Variables

Additional PK parameters include average trough concentration of IgG subclasses (IgG1, IgG2, IgG3, and IgG4), and concentration of antibody levels to *S. pneumoniae, H. influenzae*, and *C. tetani* (tetanus). Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes.

For the adult (n~20) PK subset, serial samples will be collected immediately before and after SC#17 infusion at steady state. The PK profile will include total IgG concentrations at timepoints over a 7-day period. PK parameters including $AUC_{0-7days}$, C_{max}, and t_{max} will be determined by a noncompartmental model using WinNonlin.

Another efficacy variable is 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 test) will be analyzed separately.

3.2   Safety Variables

The following safety variables will be assessed in this study:

- AEs, suspected adverse drug reactions (suspected ADRs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
  Note: All infusion site reactions will be recorded in the eCRF. The subset of infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator will be considered as AEs.
- Vital signs during clinic visits (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]).
- Physical assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Laboratory assessments including chemistry, hematology, and urinalysis.

4   GENERAL STATISTICAL CONSIDERATIONS

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

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. The hypothesis testing on the primary efficacy variable of the true rate of the SBIs will be tested at 1-sided with $\alpha=0.01$. All other statistical inferences will be tested at 2-sided with $\alpha=0.05$, if applicable.

Unless otherwise noted, all data collected in the eCRFs or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number) and grouped/sorted by adult vs. pediatric subjects, followed by study phases (Screening/Previous Regimen Phase, IGSC 20% Treatment Stage 1, and IGSC 20% Treatment Stage 2) and visit/time point.

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

For table summaries that are presented by adult vs. pediatric subjects and overall, the following age categorization will be used: adults (>16 years) and pediatrics (≤16 years).

4.1   Data Handling

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

Baseline will be defined as the last measurement taken prior to the start of the IGSC 20% infusion at the Baseline/SC#1 visit.

4.1.1   PK Data Handling

4.1.1.1   Time Window for Pharmacokinetic Analysis

For adult subjects in the PK subset, the time window allowed for serial PK blood sample draws starting at SC#17 (Week 17) and ending at SC#18 (Week 18) in IGSC 20% Treatment Stage 2 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 IGSC 20% SC#17 infusion is shown below.

Scheduled Time	Nominal Time (Hours)	Example Actual Elapsed Time (Hours)
Pre-infusion	0	0
Start of infusion	0	0
Immediately at the completion of the infusion	2	2.15
1 day post-infusion	26	26.50
3 days post-infusion	74	73.86
5 days post-infusion	122	123.20
7 days post-infusion (prior to the IGSC 20% SC#18 infusion)	170	169.75

In addition, the actual duration of the infusion will be calculated.

4.1.1.2   IgG Concentration Missing Values

For PK and IgG concentration analysis, any invalid IgG concentration values will be treated as missing, eg, if the sample was hemolyzed or if a planned trough sample was drawn post-

infusion. If necessary, invalid or missing values will be interpolated or extrapolated using PK principles, as appropriate, and such interpolations or extrapolations will be documented in the CSR.

4.1.1.3   Samples Below the Limit of Quantification (BLQ)

Samples with concentration values below the limit of quantification (BLQ) will be imputed as follows:

- BLQ values will be treated as missing.

4.2   Analysis Populations

Safety population

The Safety population will include all subjects who have received any amount of IGSC 20% and will be used for safety analysis.

Efficacy Evaluable population

The Efficacy Evaluable population will include all subjects who have received at least one dose of IGSC 20% and will be used for efficacy analysis.

IgG population

The IgG population will consist of all subjects who receive any amount of IGSC 20% and have total IgG concentration data to facilitate the comparison of mean trough IgG concentration during the IGSC 20% phase versus the pre-treatment phase.

PK population

The PK population will consist of all adult subjects in the PK subset who have received IGSC 20% and have sufficient serial IgG concentration vs. time data to facilitate calculation of AUC PK parameters. The PK population will be used for the analyses of the PK parameters.

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 (ie, 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

Assuming that the true rate of the SBIs is 0.25 per subject per year, 40 subjects treated for one year for IGSC 20% will provide at least 90% power to reject the null hypothesis of a SBI rate greater than or equal to 1.0 per person per year, using a one-sided test at the 0.01 level.

In order to obtain a total of 40 PI subjects including 20 adult and 20 pediatric evaluable subjects, approximately 60 subjects will be enrolled and treated in the study. This sample size is to allow for a moderate to high early discontinuation rate seen in other similar studies.

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. Subject disposition will also be summarized by adult vs. pediatric subjects and overall.

The number and percentage of subjects discontinuing early from the study will be summarized for primary reasons of discontinuation by study phase and overall. Also, the number and percentage of screening failures will be summarized for primary reasons of ineligibility.

Disposition status will be listed for all subjects.

6   PROTOCOL DEVIATIONS

Protocol deviations will be identified during the study and evaluated before the database lock. The type/category of protocol deviations and severity (ie, minor or major) will be summarized and listed.

7   DEMOGRAPHY AND MEDICAL HISTORY

7.1   Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, race, ethnicity, age, age categories ($\leq$16 [with sub-categories: $\geq$2 - $\leq$5, >5 - $\leq$12, >12 - $\leq$16], >16 [with sub-categories: >16 - <65, $\geq$65] years), height, weight, screening total IgG level, subject entry status, and frequency of the IgG dose at entry will be summarized for the Efficacy Evaluable population. The primary immunodeficiency and IgG treatment history will also be summarized. The summaries will be provided by adult vs. pediatric subjects and overall.

All demographic and baseline characteristics data will be listed.

7.2   Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized/listed. The summaries will be provided by adult vs. pediatric subjects and overall.

8   CONCOMITANT MEDICATION AND TREATMENT

8.1   Prior and Concomitant Medication

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

Prior medications and concomitant medications will be summarized separately either overall (prior medications) or by study phase (concomitant medications). Prior medications are defined as any medication ended prior to the start of study treatment (ie, start of the infusion at Baseline/SC#1). 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 IGSC 20% study phase and overall.

<u>Duration of exposure in days</u>

For the IGSC 20% Treatment Stage 1, the duration of exposure in days will be calculated as:

$$\text{Infusion date of SC\#14} - \text{Infusion date of Baseline/SC\#1}$$

For the IGSC 20% Treatment Stage 2, the duration of exposure will include not only the total time between the first and last SC infusion during the treatment stage, but also include an additional 7 days to take into account total exposure time to the study drug since each SC infusion is administrated weekly. The duration of exposure in days will be calculated as:

$$(\text{Infusion date of SC\#52} - \text{Infusion date of SC\#14}) + 7$$

Similarly, for the overall IGSC 20% treatment phase, the duration of exposure in days will be calculated as:

$$(\text{Infusion date of SC\#52} - \text{Infusion date of Baseline/SC\#1}) + 7$$

For subjects who prematurely discontinued from the study, the duration of exposure in days for the study phase in which the discontinuation occurred and for the overall treatment phase will be similarly calculated as:

$$(\text{Last SC infusion date in the study phase} - \text{First SC Infusion date in the study phase}) + 7$$

<u>Duration of exposure expressed in other units</u>

Duration of exposure in weeks will be calculated as:

$$\text{Duration of exposure in days} / 7$$

Duration of exposure in years will be calculated as:

$$\text{Duration of exposure in days} / 365.25$$

<u>Duration of infusion</u>

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

$$\text{Stop time of infusion} - \text{Start time of infusion}$$

<u>Dose Conversion Factor</u>

In this study, the study drug dose (ie, expected dose as prescribed) in mg/kg/week will be collected on the eCRF at all SC visits.

At each SC visit, the actual dose conversion factor from the previous regimen to IGSC 20% dose will be calculated as follows:

For subjects on previous IV regimen:

Dose (mg/kg) / [pIV dose (mg/kg) / 3 or 4 (pIV dosing interval in weeks between infusions)]

For subjects on previous SC regimen:

Dose (mg/kg) / [pSC dose (mg/kg) / pSC dosing interval in weeks between infusions]

In addition, the actual average dose conversion factor from the previous regimen to IGSC 20% dose will be calculated for each study phase and the overall IGSC 20% treatment phase.

First, the average weekly dose (mg/kg) will be calculated as:

Total dose (mg/kg) / Total number of infusions

The actual average dose conversion factor will then be calculated as follows:

For subjects on previous IV regimen:

Average weekly dose (mg/kg) / [pIV dose (mg/kg) / 3 or 4 (pIV dosing interval in weeks between infusions)]

For subjects on previous SC regimen:

Average weekly dose (mg/kg) / [pSC dose (mg/kg) / pSC dosing interval in weeks between infusions]

For each study phase, the duration of exposure (weeks), the number of infusions received, the total volume infused (mL), and the duration of infusion (minutes) will be summarized. Further, infusion interruptions will be summarized. The distribution and number of SC infusion sites will be separately summarized. The number and percentage of subjects with actual dose conversion factor different from 1 and the actual dose conversion factor will be summarized for each SC visit, each study phase, and the overall IGSC 20% treatment phase. The summaries will also be provided by adult vs. pediatric subjects and overall.

8.2.2   Compliance

Infusion compliance, treatment compliance, and overall compliance will be calculated separately for each IGSC 20% study phase.

Infusion Compliance

Infusion compliance (%) will be calculated as:

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

For subjects who completed the study, the number of SC infusions expected will be 13 for IGSC 20% Treatment Stage 1 and 39 for IGSC 20% Treatment Stage 2. For subjects who prematurely discontinued from the study during IGSC 20% Treatment Stage 1, the number of SC infusions expected will be the SC week number of the last SC infusion for IGSC 20% Treatment Stage 1 and 0 for IGSC 20% Treatment Stage 2. For subjects who prematurely discontinued from the study during IGSC 20% Treatment Stage 2, the number of SC infusions expected will be 13 for IGSC 20% Treatment Stage 1 and (the SC week number of the last SC infusion – 13) for IGSC 20% Treatment Stage 2.

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 SC visit collected in the eDiary.

The total volume expected will be derived as follows:

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

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

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

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

Overall Compliance

The overall compliance (%) will be calculated as:

(Infusion compliance x Treatment compliance) / 100

Infusion compliance, treatment compliance, and overall compliance will be listed and summarized by IGSC 20% study phase and overall. The number and percentage of subjects with compliance between 80% and 120% will also be summarized. The summaries will also be provided by adult vs. pediatric subjects and overall.

Additional consideration regarding compliance will be given when determining legitimacy for inclusion of total IgG concentration data for the calculation of the PK parameters. For example, subjects' treatment or infusion compliance (%) during the 4 consecutive weeks

prior to SC#17 PK assessment, ie, from SC#14 to #17, will be evaluated. Reasons for excluding total IgG concentration data or a subject from the analysis of PK parameters will be documented in the CSR.

9   EFFICACY ANALYSIS

Efficacy analyses will be performed on the Efficacy Evaluable population. All efficacy analyses will be performed by adult vs. pediatric subjects and overall.

9.1   Primary Efficacy Analysis

The primary efficacy variable of SBIs will be analyzed using the Efficacy Evaluable population. The number and percentage of subjects with any SBIs from Week 1 to Week 53 during the IGSC 20% treatment phase, the total number of SBIs, the annualized rate of SBIs for individual subjects, and the rate per person per year of SBIs will be summarized. A listing of SBIs will be provided.

The annualized rate of SBIs for individual subjects will be calculated as:

$$annualized\ rate\ of\ SBIs\ for\ the\ individual\ subject$$

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

The SBI rate for all efficacy evaluable subjects will be compared to the recommended standard rate of 1 SBI per person per year. The following hypothesis testing is performed with one-sided test at alpha = 0.01 level:

$$H_0 : \lambda \geq 1\ SBI\ per\ person\ per\ year$$
$$versus$$
$$H_A : \lambda < 1\ SBI\ per\ person\ per\ year$$

Where λ is the SBI rate during IGSC 20% treatment. Occurrence of SBI is assumed to follow the Poisson distribution.

The generalized linear model procedure for Poisson regression with log link will be used to estimate SBI rate per person per year for IGSC 20% and its one-sided 99% upper confidence bound (or equivalently, the upper bound of the two-sided 98% confidence interval). Person-year during IGSC 20% treatment will be calculated for each subject as (duration of exposure in days/365.25), and the natural log-transformed person-year will be used in the generalized linear model as an offset variable. No covariates but the intercept term are included in the model. The estimated intercept term and 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 SBI rate per person per year for IGSC 20% and its one-sided 99% upper confidence bound. If the one-sided 99% upper confidence bound is less than 1, then the null hypothesis that the SBI rate per person per year is ≥ 1 will be rejected at one-sided alpha = 0.01 level.

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

$$rate\ of\ SBIs\ per\ person\ per\ year$$

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

9.2 Secondary and Other Efficacy Analyses

Secondary and other efficacy variables include the following:

- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) which will be recorded as an AE with the Investigator answering the following question affirmatively in the eCRF: "Is this an infection?" (verbatim term delineating infection).
- 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
- 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 efficacy variables, the number and percentage of subjects with the events, the total number of events or days, the annualized rate of events or days for individual subjects, and the rate of events or days per person per year will be summarized descriptively. All other efficacy data will be listed as well. Similar to the calculation of the annualized rate of SBIs for individual subjects, the annualized rate of events or days for individual subjects can be calculated as follows:

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

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

The rate per person per year of all infections, validated infections, days on antibiotics, hospitalizations, and days of work/school/daily activities missed will be calculated and the two-sided 95% CI will be provided, using the generalized linear model procedure for Poisson regression with log link similar to that used for the primary efficacy analysis. Similar to the calculation of the rate of SBIs, the rate of events or days per person per year can be directly calculated as follows:

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

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

10 PK ANALYSIS

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

10.1 Analysis of IgG concentration and dosing data

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

Trough concentrations of total IgG during the Screening/Previous Regimen Phase, the IGSC 20% Treatment Stage 1, and the IGSC 20% Treatment Stage 2 will be summarized.

Summaries will be provided for trough concentrations of IgG subclasses (Screening, Baseline/SC#1, SC#13, 24, 36, and Final/Early Termination Visit). Summaries of trough level concentrations of antibody titers against *H. influenzae*, *S. pneumoniae,* and *C. tetani* (tetanus) will also be provided (collected at these same time points).

Trough measles antibody titers (functional assay at Baseline/SC#1, SC#20, and SC#52) will be summarized as an exploratory variable for informational purposes.

All summaries will be provided by study phase and visit for the Efficacy Evaluable population. The summaries will also be provided by adult vs. pediatric subjects and overall.

10.1.2   Analysis of mean trough total IgG data

Mean trough total IgG concentration for the IGSC 20% treatment phase will be calculated as the average of all steady state trough concentrations measured during the IGSC 20% Treatment Stage 2, ie, total IgG trough levels measured at the following visits: SC#17, #18, #20, #24, #28, #32, #36, #40, #44, #48, #52, and #53. Comparison will be made to the mean trough total IgG concentration for the previous IgG regimen (either IVIG or other SCIG products) obtained during the Screening/Previous Regimen Phase. For subjects entering study on a previous IVIG regimen, the mean trough for the previous IgG regimen will be calculated as the average of the 2 trough concentrations at pIV#1 and pIV#2. For subjects entering study on a previous SCIG regimen, the mean trough for the previous IgG regimen will be calculated as the average of the 2 trough concentrations at pSC#1 and Baseline/SC#1.

Mean trough data will be summarized by study phase. Mean trough summary and analysis will be based on the IgG population. The summaries will be provided by adult vs. pediatric subjects and overall.

10.1.3   Analysis of serial total IgG data

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

Serial total IgG concentrations prior to and after SC#17 infusion in adult subjects in the PK subset 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 SC#17 infusion (scheduled and nominal times as shown in Section 4.1.1.1), actual collection date 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 the scheduled/nominal time point. The summaries will include n, mean, SD, coefficient of variation (%CV), median, minimum, maximum, and geometric mean.

Total IgG concentration vs. time curves for individual subjects will be presented with the actual elapsed time from the start of the SC#17 infusion plotted on the x-axis. Individual concentration vs. time plots will also be presented for all subjects on the same figure (spaghetti plot). For all subjects combined, mean or median total IgG concentration vs. time curves will be presented in one figure with the nominal time (see Section 4.1.1.1) plotted on the x-axis. All total IgG concentration vs. time curves will be plotted on both the linear and the semi-log scale.

10.2   Calculation of PK parameters

The PK parameters of serial total IgG following the IGSC 20% infusion at SC#17 in adult subjects in the PK subset will be determined as appropriate and as data permits. The PK parameters include $AUC_{0-7days}$, C_{max}, and t_{max}.

Pharmacokinetic parameters will be calculated by Nuventra Pharma Sciences using Phoenix® WinNonlin® software, version 6.3 or later (Certara USA, Inc. [Princeton, NJ]).

The PK parameters of interest are determined as follows:

$AUC_{0-7days}$	area under the concentration vs. time curve from time 0 to 7 days, calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration $\times$ time (eg, mg $\times$ 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.
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 are more than one maximum observed concentration, the t_{max} is the time to the first observed maximum concentration.

10.3   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% CI for the geometric mean will also be calculated for all PK parameters (except t_{max}). The analyses of PK parameters will be based on the PK population.

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

For summary purposes, AEs will be classified as treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start of study treatment (ie, start of the infusion at Baseline/SC#1). A TEAE will be defined as an AE which occurred on or after the start of study treatment. For adverse events with incomplete start dates, the same algorithm for missing or partial date information described in Section 8.1 (Prior and Concomitant Medication) will be used for determination of treatment emergent or not. Non-TEAEs will be summarized separately from TEAEs. TEAEs will be further characterized within each study phase based on the onset date/time relative to the first infusion date/time in each study phase.

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

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

Total number of events / Total number of infusions received

The rate per exposure week will be calculated as:

Total number of events / Total duration of exposure in weeks

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

Temporally-associated AEs defined as those occurring during or within 72 hours following the end of investigational product infusion will be separately summarized. For AEs that occur during study drug infusion, the infusion rate in effect at the time of onset of the AE, the time when the AE is first reported and the time when the AE changes materially in intensity and/or resolves will be listed.

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

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

11.2 Laboratory Assessments

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

The hematology, clinical chemistry, special tests, serum pregnancy, and urinalysis parameters will be summarized at each visit with number of subjects, mean, SD, median, minimum, and maximum values for continuous variables and counts and percentages per category for categorical variables. Change from baseline will be descriptively summarized

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

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

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

At Screening, a sample for HIV NAT testing will be collected and tested for determination of subject eligibility. The subject must be negative for HIV by NAT based on a Screening blood sample. The subject may enter the Previous Regimen Phase while the Screening blood sample is being tested, but will be a Screen Failure and will not undergo Baseline assessments if the HIV result is positive.

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

All laboratory data will be presented in data listings.

11.3 Vital Signs

Vital sign data (SBP, DBP, HR, T, and RR) and their changes from baseline will be summarized with the number of subjects, mean, SD, median, minimum, and maximum values. The vital sign data collected at the pre-infusion time point at the Baseline/SC#1 Visit will be defined as the baseline values. Body weight and height will be similarly summarized.

All vital sign data will be listed.

11.4 Physical Assessments

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

All physical assessment data will be listed.