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

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Clinical Study Protocol

Protocol Title:	A Multi-center, Single-Sequence, Open-label Study to Evaluate IGSC 20% Biweekly Dosing in Treatment-Experienced Subjects and Loading/Maintenance Dosing in Treatment-Naïve Subjects with Primary Immunodeficiency
Investigational Product:	IGSC 20% Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified
Sponsor's Name and Address:	Grifols Therapeutics LLC 79 TW Alexander Drive Research Triangle Park, NC 27709
Additional Identifier	IGSC 20% Biweekly and Naïve Subject Study
IND/CTA Number	16528/2018-004475-12
Development Phase:	4
Sponsor Signatories:	[redacted], MD [redacted] Grifols Therapeutics LLC Email address: [redacted] Telephone number: [redacted] [redacted] Instituto Grifols SA Email address: [redacted] Telephone number: [redacted] See Sponsor Signatures on the cover page of the protocol

Investigator Signature Page

The undersigned confirms that he/she agrees to conduct the study under the conditions described in this protocol and comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and all applicable regulatory requirements:

INVESTIGATOR NAME (Please Print)	LOCATION
INVESTIGATOR SIGNATURE	DATE

Title of the Investigator:

Address of the Site:

Telephone Number:

PROTOCOL SYNOPSIS

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

Study Number: GC1906

Phase: 4

Study Objectives:

Primary Pharmacokinetic Objective

- To determine whether biweekly (every 2 weeks) administration of Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) produces a steady-state area under the concentration versus time curve (AUC) of total IgG that is non-inferior to that produced by weekly administration of IGSC 20% in treatment-experienced subjects with primary immunodeficiency (PI)

Secondary Objectives

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

Exploratory Objectives

- To compare treatment burden and treatment satisfaction related to immune globulin therapy using the Life Quality Index (LQI) questionnaire and the Treatment Satisfaction

Questionnaire for Medication (TSQM-9) for IGSC 20% administered weekly or biweekly (every 2 weeks) in treatment-experienced subjects with PI (Appendix 3).

- To survey quality of life (QOL) in subjects with PI using the Short Form Health Survey (12-Item Short Form Health Survey [SF-12] for subjects ≥18 years [observer: subject]in both treatment-experienced and treatment-naïve subjects with PI. (Appendix 3). In addition, 10-Item Short Form Health Survey [SF-10] for treatment-naïve subjects aged 6 to 17 years [observer: parent]) will also be used.

Safety Objectives

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

Overall Study Design and Description:

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

Treatment Experienced Cohort:

The treatment-experienced cohort will enroll subjects with PI already maintained on IgG replacement therapy for at least 3 months who will receive IGSC 20% at 2 different dosing frequencies using a subcutaneous (SC) infusion pump during 2 treatment periods (16 weeks per treatment period).

1) In Treatment Period 1, treatment-experienced subjects will receive 16 weekly IGSC 20% doses from Week 0 to Week 15:
   a) For subjects entering study *on intravenous immune globulin (IVIG),* IGSC 20% will be dosed at 1.37 times the equivalent weekly dose;
   b) Subjects entering *on subcutaneous immune globulin (SCIG)* will receive the same mg/kg equivalent weekly dose as given prior to entry, without using a dose adjustment factor (DAF).
2) In Treatment Period 2, treatment-experienced subjects will receive 9 biweekly IGSC 20% doses (ie, IGSC 20% every 2 weeks at twice the weekly dose) with the first IGSC 20% dose at Week 16 and a final dose at Week 32.

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

Treatment Naïve Cohort:

A separate cohort of treatment-naïve subjects with PI will receive a loading dose of 5 consecutive daily doses of IGSC 20% 150 mg/kg/day (Week 0, Days 1 to 5) followed by

weekly infusions of 150 mg/kg starting Week 1 (Day 8) through Week 32 (end of Treatment Phase). IGSC 20% infusion will be administered using an SC infusion pump.

Number of Subjects Planned:

- Approximately 25 treatment-experienced subjects currently receiving IgG replacement treatment will be enrolled.
- Approximately 6 treatment-naïve subjects will be enrolled.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria **only** for **treatment-experienced subjects:**

A subject must meet all the following inclusion criteria to be eligible for the treatment-experienced cohort.

1. Subjects 18 years to 75 years (inclusive) at screening.
2. Subjects with documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (eg, X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (eg, hyper immunoglobulin M immunodeficiency syndrome). Please also refer to Exclusion Criteria.
3. Subjects have not had an SBI or been hospitalized for infection of any etiology (eg, viral, fungal, parasitic) within the last 3 months prior to screening or during screening.
4. Subjects currently receiving IgG replacement therapy for ≥3 months via intravenous (IV) or SC infusion. Subjects receiving IVIG prior to study must receive a dosage of at least 200 mg/kg per infusion.
5. Subjects whose screening IgG trough levels must be ≥500 mg/dL.

   Note: If screening trough levels are not above this threshold, the subject will be considered a screen failure, but may be rescreened following dose adjustment of their original IgG replacement therapy regimen and maintaining stable dosing for a period of at least 3 months prior to screening a second time.
6. Subjects have signed an informed consent form.

Inclusion criteria **only** for **treatment-naïve subjects:**

A subject must meet all the following inclusion criteria to be eligible for the treatment-naïve cohort.

1. Subjects 6 years to 75 years (inclusive) at screening
2. Subjects with documented and confirmed diagnosis of PI with features of hypogammaglobulinemia requiring IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (eg, X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (eg, hyper immunoglobulin M immunodeficiency syndrome). Please also refer to Exclusion Criteria.

3. Subjects have never received IgG replacement treatment (ie, no prior immune globulin replacement therapy).
4. Subjects whose screening IgG level must be ≤400 mg/dL.
5. Subjects do not have an SBI nor requires hospitalization for infection of any etiology (eg, viral, fungal, parasitic) during screening or at baseline.
6. Subjects have signed an informed consent form.

   Note: The subject must sign the informed consent form (ICF) if at least 18 years old. For children or adolescents, the subject's parent or legal guardian must sign the ICF and if appropriate/applicable, the subject must sign a Child Assent form approved by the Institutional Review Board/Ethics Committee (IRB/EC) per the institution's requirements.

Exclusion Criteria (**all subjects**)

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Subjects with clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may interfere with successful completion of the trial or place the subject at undue medical risk.
2. Subjects have had a known serious adverse reaction (AR) to immunoglobulin or any anaphylactic reaction to blood or any blood-derived product.
3. Subjects have a history of blistering skin disease, clinically significant thrombocytopenia, bleeding disorder, diffuse rash, recurrent skin infections, or other disorders where SC therapy would be contraindicated during the study.
4. Subjects have known isolated IgG subclass deficiency; isolated specific antibody deficiency disorder (SAD) or selective IgG deficiency; or transient hypogammaglobulinemia of infancy.

   Note: Subjects are not to be enrolled if their primary PI diagnosis does not entail an actual quantitative deficit in total IgG. For example, SAD is defined as an impaired specific IgG response to pneumococcal vaccine with normal serum concentrations of IgG, IgM, and IgA. Isolated IgG subclass deficiency is defined as an abnormally low level of 1 or more IgG subclass in subjects with normal levels of total IgG and IgM.
5. Subjects have known Selective Immunoglobulin A (IgA) Deficiency (with or without antibodies to IgA) (Note: exclusion is for the specific diagnostic entity. It does not exclude other forms of humoral primary immunodeficiency which have decreased IgA in addition to decreased IgG requiring IgG replacement).
6. Females of childbearing potential who are pregnant, have a positive pregnancy test at Screening (serum human chorionic gonadotropin-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence*) throughout the study.

Note: *True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)

7. Subjects have significant proteinuria (≥3+ or known urinary protein loss >1 g/24 hours or nephrotic syndrome), has acute renal failure, is on dialysis, and/or has severe renal impairment on screening laboratory testing (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]).
8. Subjects have screening values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory.
9. Subjects have hemoglobin <9 g/dL at screening.
10. Subjects have a history (either 1 episode within the year prior to the Screening Visit or 2 previous episodes over a lifetime) of or current diagnosis of thromboembolism (eg, myocardial infarction, cerebrovascular accident, or transient ischemic attack) or deep venous thrombosis.
11. Subjects are currently receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [eg, dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], and parenteral anticoagulants [eg, fondaparinux]).
12. Subjects currently have a known hyperviscosity syndrome.
13. Subjects have an acquired medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (absolute neutrophil count less than 1000/μL [1.0 x 10^9/L]), or human immunodeficiency virus infection/acquired immune deficiency syndrome.
14. Subjects have a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus or hepatitis C virus infection.
15. Subjects (if <18 years of age) have non-controlled arterial hypertension at a level of greater than or equal to the 90th percentile blood pressure (either systolic or diastolic) for their age and height (see Appendix 5) or the adult subject has non-controlled arterial hypertension (systolic blood pressure [SBP] >160 mmHg and/or diastolic blood pressure [DBP] >100 mmHg).
16. Subjects are receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents; (b) immunomodulators; (c) long-term systemic corticosteroids defined as daily dose >1 mg of prednisone equivalent/kg/day for >30 days.

    Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.
17. Subjects have known substance or prescription drug abuse.
18. Subjects have participated in another clinical trial within 30 days prior to screening (observational studies without investigative treatments [non-interventional] are permitted).

19. Subjects/caregivers are unwilling to comply with any aspect of the protocol, including home SC infusions, blood sampling, and completion of an SC infusion diary for the duration of the study.
20. Subjects who cannot give independent informed consent and/or assent (example: intellectual disability or cognitive disability).
21. In the opinion of the investigator, subjects may have compliance problems with the protocol and the procedures of the protocol.

Investigational Product, Dose and Mode of Administration

Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is the investigational product (IP) administered subcutaneously.

Treatment-Experienced Subjects

In this study, the DAF used for subjects entering study *on IVIG* is 1:1.37. For treatment-experienced subjects *on SCIG at study entry*, there is no DAF. The same equivalent weekly (mg/kg) dose for prior SCIG is used for IGSC 20% weekly dosing in Treatment Period 1.

If a calculation results in an IGSC 20% mg/kg dose per week which is <100 mg/kg/week, then the IGSC 20% dose will be modified to be equivalent to a net dosage of 100 mg/kg/week, which is the minimum weekly IGSC 20% dose.

In Treatment Period 2, the biweekly (every 2 weeks) dose of IGSC 20% (mg/kg) is twice (2×) the weekly dose in Treatment Period 1.

Treatment-Naïve Subjects

Treatment-naïve subjects will receive a loading dose of IGSC 20% consisting of 5 consecutive daily doses of 150 mg/kg/day (Week 0, Days 1 to 5) using a SC infusion pump followed by weekly maintenance infusions of 150 mg/kg IGSC 20% starting Week 1 (Day 8) through Week 32. The weekly frequency will be maintained through Week 32 (end of Treatment Phase).

Duration of Treatment:

Subject participation (from Screening Visit to the Final Follow-up Visit): up to 38 weeks.

Reference Therapy, Dose and Mode of Administration:

None

Key Study Variables:

Primary Pharmacokinetic Endpoint (Treatment-Experienced Subjects):

- AUC in the Biweekly (Treatment Period 2) versus Weekly IGSC 20% (Treatment Period 1) treatment phase, calculated from serial PK sampling for measurement of total IgG levels following Week 14 (weekly) and Week 30 (biweekly) doses:
  - AUC of IGSC 20% administered weekly: Steady-state AUC of total IgG over a regular dosing interval (τ), every week (ie, $AUC_{0\text{-}\tau,\ weekly}$ or $AUC_{0\text{-}7\ days}$) in treatment-experienced PI subjects

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

Secondary Endpoints:

- Steady-state mean trough (predose) concentration of total IgG following SC administration of IGSC 20% given IGSC 20% weekly and biweekly (every 2 weeks) in treatment-experienced subjects
- In the treatment-naïve cohort, ability of a loading dose of IGSC 20% 150 mg/kg/day and maintenance infusion of IGSC 20% 150 mg/kg to achieve and maintain total IgG trough >500 mg/dL through Week 32 (End of Treatment)
- C_{max} and t_{max} of total IgG at steady state given IGSC 20% weekly and biweekly in treatment-experienced subjects
- Total number of SBIs, proportion of subjects who experience SBIs, and rate of SBI as defined in Appendix 4 in all subjects
- All infections of any kind (serious/non-serious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the investigator in all subjects
- 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 (eg, rapid streptococcal antigen detection test) in all subjects
- 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 in all subjects
- Number of hospitalizations due to infection in all subjects

Exploratory Endpoints:

- LQI score in treatment-experienced subjects (Appendix 3) in all subjects
- TSQM-9 score in treatment-experienced subjects (Appendix 3) in all subjects
- SF-12 survey (for subjects ≥18 years [observer: subject]) in both treatment-experienced and treatment-naïve subjects (Appendix 3). In addition, SF-10 for treatment-naïve subjects aged 6 to 17 years [observer: parent or legal guardian]) will also be used.

Safety Endpoints:

- Adverse events including serious adverse events (SAEs), suspected adverse drug reactions (suspected ADRs, potentially related adverse events [AEs]), and ARs (ie, definitely related AEs)

  Note: All infusion site reactions will be recorded in the subject's source documents and electronic case report form (eCRF). The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the

investigator will be considered as AEs.

- Vital signs during clinic visits (SBP and DBP, heart rate [HR], temperature [T], respiratory rate [RR])
- Physical assessments: physical examinations will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Laboratory assessments including chemistry, hematology, urinalysis, haptoglobin, serum/plasma free hemoglobin (central laboratory), and direct antiglobulin test (DAT) (central laboratory) (see Table 7-1).

Key Assessments and Procedures:

Complete schedules of study procedures and events are located in Appendix 1 and Appendix 2 for treatment-experienced and treatment-naïve subjects, respectively.

IgG trough levels will be measured for all subjects during the Screening Visit and treatment phase, and incident SBIs and infections will be continuously monitored. Among treatment-experienced subjects, the sampling for determining PK profiles for weekly IGSC 20% administration will commence at Week 14 (sampling Week 14 to 15), and for biweekly (every 2 week) IGSC 20% administration, full PK profiling will commence at Week 30 (serial sampling period Week 30 to 32).

Statistical Methods:

Descriptive statistics will include the number of nonmissing observations, mean, standard deviation (SD), median, minimum, and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data.

The hypothesis testing for the primary PK analysis of AUC non-inferiority will be tested at 1-sided with α=0.05. When applicable, formal statistical comparisons of other PK parameters will be tested at 2-sided with α=0.10. All other statistical tests will be 2-sided at a significance level of 0.05.

In general, data will be analyzed separately for treatment-experienced and treatment-naïve subjects. For data analysis purpose, treatment groups of interest in this study include weekly dosing regimen of IGSC 20% in treatment-experienced subjects, biweekly dosing regimen of IGSC 20% in treatment-experienced subjects, and loading/maintenance dosing regimen of IGSC 20% in treatment-naïve subjects.

Primary PK Analyses (Treatment-Experienced Subjects, PK Population)

The Primary PK endpoint is the steady-state AUC over a dosing interval defined as follows:

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

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

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

The null hypothesis for the non-inferiority testing is:

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

The alternative hypothesis is:

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

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

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

Secondary Analyses

The steady-state mean trough concentration of total IgG in treatment-experienced subjects will be analyzed as follows. For each treatment period, all pre-infusion total IgG concentrations obtained prior to and at the 12th week of IGSC 20% dosing will be evaluated to determine if an approximate steady-state condition has been achieved by the 12th week of the treatment period. In Treatment Period 1, the steady-state mean trough concentration of total IgG following SC administrated IGSC 20% will be determined as the average value of IgG trough measurements obtained at Weeks 12, 14, and 16. In Treatment Period 2, the steady-state mean trough concentration of total IgG following SC administrated IGSC 20% will be determined as the average value of the IgG trough measurements obtained at Weeks 28, 30, and 32. Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG by treatment group.

The steady-state mean trough will also be analyzed by a mixed-effect model similar to that for the primary PK analysis.

Descriptive statistics will be used to summarize the following secondary variables related to total IgG: 1) trough concentrations of total IgG at individual time points for treatment-experienced subjects, 2) other steady-state PK parameters (C_{max} and t_{max}) of total IgG for

treatment-experienced subjects, and 3) mean and individual trough total IgG values for treatment-naïve subjects.

Secondary variables related to infection will be summarized descriptively for all subjects (treatment-experienced and treatment-naïve subjects will be analyzed separately). The number and proportion of subjects having SBIs, infections, days on antibiotics, and hospitalizations due to infection will be calculated and summarized. Furthermore, the total number of events or days and corresponding annualized rate per subject of SBIs, infections, days on antibiotics, and hospitalizations due to infection will be calculated and summarized. Finally, the rate of events or days per person per year will be analyzed using the generalized linear model procedure for Poisson regression.

Exploratory Analysis

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

For treatment-naïve subjects, analysis of SF-12/SF-10 will compare the subject's perception of state of health from study entry (pre-SC#1 infusion) to Treatment Phase Week 16 and to Treatment Phase Week 32.

Safety Analysis

The safety analyses will be based on the safety population.

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

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

Determination of Sample Size

The planned number of treatment-experienced subjects is 25 treatment-experienced subjects dosed with IGSC 20% to ensure at least 20 subjects provide the primary PK endpoint ($AUC_{0-\tau}$) estimates in both treatment periods, assuming a drop-out rate of 20%. This sample size will provide at least 90% power to demonstrate non-inferiority at a 1-sided alpha level of 0.05,

assuming the %CV of AUC is no greater than 20% and the true ratio between the 2 treatment groups is 1.0. In addition, this sample size will provide clinical experience with up to 400 weekly infusions (16 infusions × 25 subjects) and 225 biweekly infusions (9 infusions × 25 subjects).

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

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GLOSSARY AND ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARC	Absolute reticulocyte count
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
CI	Confidence interval
CJD	Creutzfeldt-Jakob disease
CRF/eCRF	Case report form/electronic case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CXR	Chest x-ray
DAF	Dose adjustment factor
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
HF	Human Factors
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGIV-C 10%	Immune Globulin (Human), 10% Caprylate/Chromatography Purified
IGSC 20%	Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified
IM	Intramuscular
IP	Investigational product
IRB/EC	Institutional Review Board/Ethics Committee
IV	Intravenous
IVIG	Intravenous Immune Globulin (generic terminology)
IWRS	Interactive web response system
LDH	Lactate dehydrogenase

LQI	Life Quality Index
LSM	Least-squares means
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
pH	Potential of hydrogen; acidity/alkalinity measure
PI	Primary immunodeficiency
PK	Pharmacokinetic
QOL	Quality of Life
RBC	Red blood cell
RR	Respiratory rate
SAD	Specific antibody deficiency
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBI	Serious bacterial infection
SBP	Systolic blood pressure
SC	Subcutaneous
SC#1	First subcutaneous infusion
SC#2	Second subcutaneous infusion
SC#3	Third subcutaneous infusion
SCIG	Subcutaneously delivered immune globulin or subcutaneous immunoglobulin (generic terminology)
SD	Standard deviation
SF-10	10-item short form health survey (for pediatric subjects)
SF-12	12-item short form health survey
SF-36	36-item short form health survey
T	Temperature
t_{max}	Time to reach C_{max}
TB	Total bilirubin
TEAE	Treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of the normal range
US	United States
vCJD	Variant Creutzfeldt-Jakob disease
WBC	White blood cell
%CV	Percent coefficient of variation

1 GENERAL INFORMATION

Protocol title and other key study information are provided on the title page. Information regarding additional key personnel and organizations involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the sponsor and at the investigator sites within the study reference manual/file.

Investigators and staff will receive training either via an investigators meeting or other appropriate training session(s).

2 BACKGROUND INFORMATION

In addition to the information provided below, please also refer to the Package Insert (Xembify® [IGSC 20%]) and any additional data supplied by the sponsor.

2.1 Name and Description of the Investigational Product

The investigational product (IP) is Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%), Grifols company designation GRF6017. IGSC 20% is licensed in the United States (US) (XEMBIFY®) for the indication of primary humoral immunodeficiency (PI) in July 2019 as subcutaneous IgG replacement administered weekly or in divided doses at more frequent intervals.

IGSC 20% is a sterile liquid formulation containing 20% human immune globulin (primarily immune globulin G [IgG]) formulated in 0.16 to 0.26 M glycine and 10 to 40 µg/mL polysorbate 80 at pH of 4.1 to 4.8.

IGSC 20% is purified from large pools of human plasma via modifications of the Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C 10%) manufacturing process. The IGIV-C 10% process is licensed in the US (trade name Gamunex®-C, which is a 10% IgG product), in Europe (Gamunex®), and in a number of other countries around the world. See Section 4.3 Study Treatments for details.

2.2 Relevant Findings from Nonclinical and Clinical Trials

2.2.1 Nonclinical Studies

In animal studies, the toxicity profiles of IGSC 20%, and comparator IGIV-C 10% were remarkably similar following single or repeated SC administration in New Zealand White rabbits.

In a single dose toxicity study, the SC dosing was well tolerated and no adverse effects were observed at dose levels as high as 1500 mg/kg. In a repeat dose toxicity study, the safety and toxicity profiles of IGSC 20% and IGIV-C 10% were remarkably similar following 5 consecutive daily SC administrations in New Zealand White rabbits. The repeat dose study employed the daily dosing strategy to minimize xenogeneic immunity issues. This dosing

was essentially cumulative because of the long terminal half-life ($t_{1/2}$) (>100 hours) in rabbits. The final cumulative IGSC 20% doses were 2500, 5000, and 7500 mg/kg, respectively (5 days × 500, 1000, and 1500 mg/kg/day). The final cumulative dose of IGIV-C 10% was 7500 mg/kg (5 days × 1500 mg/kg/day). Clinical signs in the affected animals were only seen after the administration of the fifth and final highest dose levels of IGSC 20% or IGIV-C 10% and the frequency was similar between commercial product IGIV-C 10% and IGSC 20%. Manifestations were morbidity/mortality in several animals dosed at the highest cumulative dose levels of human IGSC 20% and IGIV-C 10% related to immune-mediated hemolytic anemia. Injection site histopathology was similar between the high dose IGSC 20% and IGIV-C 10% groups.

In improper delivery route studies, IGSC 20% administered as a single intravenous (IV), intra-arterial, and perivascular dose of 100 mg/kg was well tolerated in rabbits. Pathological findings in these studies were either considered non-adverse or within standard norms for the given routes of administration in rabbits.

The plasma pharmacokinetic (PK) profile of IGSC 20% in rabbits revealed a dose dependent maximum drug concentration (C_{max}). The time to C_{max} (t_{max}) occurred 72 to 96 hours following SC dosing. The $t_{1/2}$ could not be precisely determined in rabbits and is expected to be long (multiple days) due to sustained plasma levels of human-IgG for up to 12 days following single dosing.

In conclusion, the safety and toxicity profile of IGSC 20% was remarkably similar to subcutaneously administered IGIV-C 10% on a mg/kg basis.

2.2.2 Clinical Studies

Two Phase 3 clinical trials (Study GTI1502 conducted in North America [US and Canada] and Study GTI1503 conducted in the European Union [EU] and Australia) evaluated IGSC 20% in subjects with primary immunodeficiency (PI).

Study GTI1502 (IGSC 20%)

On the basis of the GTI1502 Phase 3 study, IGSC 20% received Food and Drug Administration approval for XEMBIFY® for subcutaneous injection indicated for treatment of PI in patients 2 years of age and older, which includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. XEMBIFY® labeling includes flexible dosing (multiple times per week) in addition to weekly dosing. However biweekly (every 2 weeks at twice the weekly dose) IGSC 20% dosing is not included in the current US product labeling, and so biweekly dosing will be explored and evaluated in this current study (GC1906).

In Study GTI1502, a total of 53 subjects with PI were enrolled. Participants received IGIV-C 10% IV followed by 24 weeks of weekly IGSC 20% administered subcutaneously using an IV to SC dose adjustment factor (DAF) of 1.37. Non-inferiority and bioequivalence of IGSC 20% to IGIV-C 10% were demonstrated in terms of the area under the concentration versus time curve (AUC) comparing IgG PK profiling of IV IGIV-C 10% to SC IGSC 20%

at SC Weeks #13 to 14. The $AUC_{(0\text{-}7days)}$ geometric LSM ratio was 1.04 (90% confidence interval [CI] 1.00, 1.07). Also it was evident that steady state for IGSC 20% had been reached well within this timeframe (serial PK profiles were obtained at SC Weeks #13-14), and this supports the 16-week duration for each crossover period in the current study. In study GTI1502, little variation in IgG trough values was observed during IGSC 20% treatment from SC Week #5 onwards. Average total IgG steady-state mean trough during SC administration of IGSC 20% was 1244.8 mg/dL, demonstrating a 33% increase relative to average steady state mean IgG trough during IV infusions of IGIV-C 10% (957.1 mg/dL). IGSC 20% provided good protection from serious bacterial infections (SBIs) with a rate per person per year of 0.049 (95% CI 0.020, 0.098) (1).

Study GTI1503 (IGSC 20%)

In the second Phase 3 study (GTI1503), subjects received 12 months of IGSC 20% given subcutaneously (SC) at weekly intervals. IGSC 20% was given at an equivalent dose to the subject's previous IgG replacement regimen.

In Study GTI1503, a total of 61 subjects with PI were enrolled, and these included 29 children and 32 adults. Participants received 52 weeks of IGSC 20% administered via SC route. A weekly dose of IGSC 20% equivalent to the subject's previous immune globulin replacement was administered for all prior regimens, both subcutaneous immune globulin (SCIG) and IV immune globulin (IVIG). No DAF was applied for subjects entering on IVIG although a minimum dose of IGSC 20% was set to 100 mg/kg/week.

The primary efficacy endpoint was rate of SBIs per person per year, which was 0.017 on IGSC 20% treatment. The 1-sided 99% upper confidence limit was 0.036, which was less than 1, hence the null hypothesis that the SBI rate per person per year is ≥ 1 was rejected at 1-sided α=0.01 level. Thus the primary efficacy endpoint was met.

The rate of hospitalization due to infection per person per year 0.017 (2-sided 95% confidence interval: 0.008-0.033) overall. Weekly administration of IGSC 20% resulted in mean trough serum concentrations of total IgG that were comparable to the mean trough IgG levels obtained with the previous IgG replacement regimen. The mean trough ratio (SC phase:Previous Regimen phase) was 1.078 (range: 0.83 to 1.54), and the average of the steady state mean trough concentrations of total IgG over all subjects during the Previous Regimen and SC phases were 891.37 mg/dL and 947.64 mg/dL, respectively.

Two Clinical Studies of IGIV-C (060001 and T5004-4001)

Additionally, there are 2 completed clinical studies of SC administration of IGIV-C 10% in subjects with PI (Studies 060001 and T5004-4001). Both studies employed a DAF for IV to SC transition of 1.37 and both demonstrated protection from infection by the IgG replacement regimen. Study 060001 showed that weekly SC administration in 32 adult subjects with PI (including 3 adolescent subjects) resulted in a relatively constant steady-state mean trough plasma concentration of total IgG (1140 mg/dL). There were no SBIs reported during the 24-week SC treatment period (2).

In a completed pediatric study (T5004-4001), weekly SC administration of IGIV-C 10% in 11 pediatric subjects (age range 4-15 years) also resulted in relatively constant steady-state mean trough plasma concentration of total IgG (1330 mg/dL). There was no SBI reported during the 12 weeks of the SC treatment period. These results demonstrated that IGIV-C 10% treatment provided protection against SBIs when administered via the SC route.

2.3 Known and Potential Risks and Benefits to Human Subjects

The SC route of administration of immune globulin offers several advantages over the IV route which constitute material benefit for subjects with PI who require immune globulin. SCIG preparations are beneficial if venous access is difficult. The SC route causes few systemic adverse reactions (ARs) and produces more consistent delivery of IgG with less fluctuation in concentration than IVIG preparations. This translates to maintenance of higher trough IgG levels for SCIG preparations and protection against infections is comparable to IVIG administration. The results of several well-controlled clinical trials with dose equivalent 1:1 dose transitioning from IVIG to SCIG administration illustrate that IgG trough levels on SCIG are slightly higher than IVIG with preserved efficacy against SBIs (3-9).

From the feasibility and tolerability perspective, especially in pediatric patients, SCIG can address difficulty in obtaining venous access which may be an impediment to IVIG therapy, (10,11,12). Systemic ARs associated with IVIG (eg, headaches, fever, chills, and myalgia [13,14]) are diminished with SCIG and repeated SC infusions of IgG cause few systemic ARs. Fewer systemic ARs coupled with the convenience and autonomy of home SC administration has a beneficial impact on quality of life (QOL).

IGSC 20% may be contraindicated in individuals with known anaphylactic or severe systemic hypersensitivity reactions to Immune Globulin (Human). Individuals with severe, selective immunoglobulin A (IgA) deficiencies (serum IgA <0.05 g/L [15]) who have known antibodies against IgA (anti-IgA antibody) should only receive IGSC 20% with extreme caution due to the risk of severe immediate hypersensitivity reactions including anaphylaxis.

In the setting of a PI disease state, live viral vaccines have various contraindications and specific risks/degrees of effectiveness dependent on the type/category of the immune deficiency (Medical Advisory Committee of the Immune Deficiency Foundation [16]). Passive transfer of antibodies from IGSC 20% may transiently interfere with the immune response to live viral vaccines such as measles, mumps, polio, rubella, and varicella in the normal host with an intact immune system. Best medical practices should be followed regarding immunization requirements, particularly for children.

IGSC 20% is made from human plasma and may carry a risk of transmitting infectious agents (eg, viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent, and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). No cases of transmission of viral diseases, vCJD, or CJD have been identified for products manufactured with the same core manufacturing process as IGSC 20%. The risk that IGSC 20% can transmit an infectious agent has been reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview, testing of individual donations and plasma pools, and the

presence in the manufacturing process of steps with demonstrated capacity to inactivate and/or remove pathogens.

Based on the known class effect, caution should be exercised in subjects with underlying pathology which places them at risk of renal insufficiency. Subjects at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity that can cause thrombotic events.

2.4 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s)

2.4.1 Administration of Investigational Products

The IP will be administered to treatment-experienced subjects by ambulatory SC infusion pump during two 16-week treatment periods to evaluate the pharmacokinetic profile of weekly versus biweekly IGSC 20% dosing (see Section 4.3.1 and Section 6). A predecessor study of IGSC 20% (GTI1502) demonstrated bioequivalence based on PK profiling at SC Weeks #13 to 14, indicating that a 16-week duration for each treatment period is adequate in this treatment-experienced subject population to achieve steady state (please see Section 2.2 for further details).

For treatment-naïve subjects, the IP will be administered by ambulatory infusion pump over a 32-week treatment period (see Section 4.3.1 and Section 6).

Section 6.1.1 provides full details regarding infusion rates for administration via pump.

The volume infused, infusion start date/time, infusion end date/time, initial and final infusion rates, number of infusion sites, the location(s), and other SC infusion information will be recorded in the SC infusion diary by the subject/parents/legal guardians, or site personnel as appropriate.

2.4.2 Justification for Selection of Doses/Timing of Investigational Products

IGSC 20% provided a comparable measure of protection against SBIs and non-serious infections as IGIV-C 10% in Study GTI1502, and is currently Food and Drug Administration (FDA) approved for PI. IGSC 20% is manufactured by the same process as IGIV-C 10% with increased IgG concentration allowing lower infusion volume per dosage.

For treatment-experienced subjects *on SCIG prior to study*, the IGSC 20% dose selected will be equivalent on a mg/kg basis to the prestudy dose for each subject. Given that eligibility criteria require an IgG trough level ≥500 mg/dL for a treatment-experienced subject to qualify for study entry, the equivalent dose of IGSC 20% (to previous SCIG regimen) should provide adequate IgG replacement (by definition). Furthermore, as an added safety measure, the minimum dose of IGSC 20% on-study is predefined as ≥100 mg/kg/week).

For treatment-experienced subjects *on IVIG prior to study*, the IGSC 20% dose for Treatment Period 1 will be calculated as the equivalent weekly dose (adjusting IV dosing interval to weekly frequency), and then will be multiplied by a DAF of 1.37. The DAF of 1.37 is based

on the non-inferior and moreover bioequivalent AUC for IGSC 20% compared with IGIV-C 10% in the North American pivotal study GTI1502. The DAF provides an additional buffer for the IV-to-SC transition in dosing route.

This study, Study GC1906, is evaluating the PK and efficacy of biweekly (every 2 weeks) IGSC 20% dosing versus weekly IGSC 20% administration. The aim is to expand the current FDA-approved labeling which allows flexible dosing frequencies of weekly or multiple times per week. If the primary non-inferiority endpoint is achieved in Study GC1906, it may be possible to potentially include a longer, 2-week treatment interval between IGSC 20% administrations in the product labeling.

For treatment-naïve subjects, the implementation of a loading dose over 5 days followed by weekly maintenance dosing is an accepted approach and allows subjects to establish clinical stability on IgG replacement. In most subjects, the 5-day loading dose provides IgG levels that are considered protective at the end of the loading dose period (17). In addition to the modeling results of Rojavin et al (17), IGSC 20% modeling for treatment-naïve subjects supports 5 consecutive days at a loading dose of 150 mg/kg with weekly maintenance dose (150 mg/kg) starting on Day 8 (Figure 2-1). This approach provides rapid attainment of protective IgG trough levels, initially targeted at 700 mg/dL in the model for these newly diagnosed medically delicate patients in simulations for both severely deficient patients (ie, endogenous IgG level 150 mg/dL) and those with a lesser degree of deficiency (ie, presumed endogenous IgG level 400 mg/dL) in the model (18). In GC1906, uniformly applying a dose of 150 mg/kg/day for loading infusions on Days 1 through 5 for all study subjects allows the fastest institution of IgG replacement treatment with the greatest logistical ease and consistency of implementation.

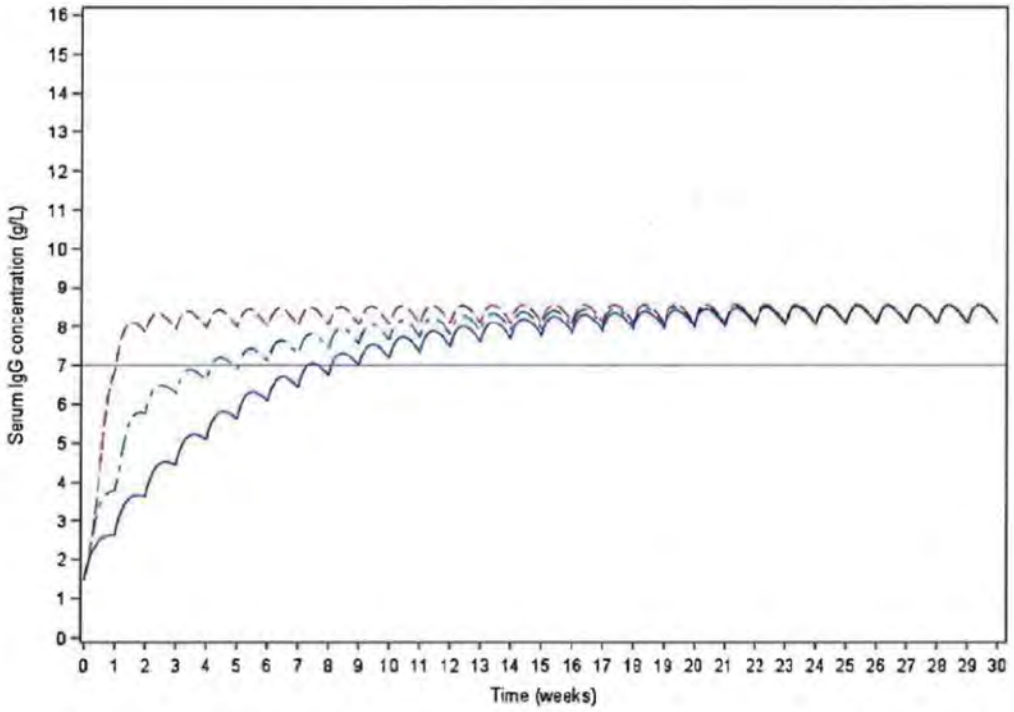


Figure 2-1 Treatment-Naïve Patients Simulated Median IgG Concentration-Time Profiles for Different IGSC 20% Loading Regimens (150 mg/kg, 10.5 g) Assuming Endogenous IgG Level of 1.5 g/L (150 mg/dL)

Legend: Dashed line (top line of figure, best IgG replacement simulation) is loading dose given Day 1 through Day 5 (5 consecutive days) with weekly maintenance starting Day 8.
Long-short-long dashed line is loading dose given 2 times/week on Weeks 1 and 2 (middle line of figure).
Solid line is without any loading dose (bottom line of figure).

2.5 Compliance Statement

This study will be conducted under the conditions described in this protocol and in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and all applicable regulatory requirements.

2.6 Study Population

Eligible participants for this study include male or female treatment-experienced subjects who are 18 to 75 years of age and treatment-naïve subjects aged 6 to 75 years (inclusive) who have a diagnosis of PI requiring IgG replacement treatment. Subjects who initially fail to meet eligibility criteria may be rescreened once. Subjects who fail to meet eligibility criteria upon rescreen will be considered screen failures and will not be eligible to participate in the study.

2.7 Relevant Data and Literature Review

2.7.1 Primary Immunodeficiency

Primary immunodeficiency diseases are a family of congenital disorders of the immune system that lead to an increase in frequency of infections, notably, but not limited to, bacterial infections of the respiratory tract (19). Results from a recent study suggest that in the US alone, 1 in 2,000 children and 1 in 1,200 persons (including adults and children) are diagnosed with PI, yielding a total US PI patient population estimate of approximately 250,000 adults and children (20). Worldwide upper estimates suggest that 6 million people (638,000 in Europe) may be living with PI, although only a fraction of these patients have been identified in registries (21). Patients with inherited deficiencies leading to impaired humoral immunity are highly susceptible to a wide range of infections, most commonly bacterial infections. The efficacy of IgG replacement in the treatment of these disorders has been well established (22,23) since 1952 when the use of serum globulin fraction was reported to reduce the frequency of infections in a patient with agammaglobulinemia (24). The therapeutic management of PI has been carried out via intramuscular (IM), IV, and SC injections of various IgG preparations (10,25).

2.7.2 Immunoglobulin Replacement Therapy

Despite its widespread use, the infusion of IVIG is problematic in some patients, especially those who have poor venous access or develop systemic AEs, such as headaches, fever, chills, or myalgia from this route of administration (13,14). In children, difficulty in obtaining venous access can prevent or delay IVIG therapy (10,11,12). Over the last several years, SCIG has been developed for administration in the home setting for treatment of PI and has become accepted in the clinical setting (11,12,26).

The results of several adult PI studies with SCIG products have shown good efficacy of replacement therapy and control of bacterial infections (3,27,28). Additionally, the results of several pediatric studies also showed that SC infusion of IgG in children (ages 1-15 years) at home was feasible and safe and also resulted in maintenance of the IgG levels above 500 mg/dL (26,29,30), a level that is considered sufficient to protect against SBIs in adult and pediatric PI patients. It is now generally accepted that repeated SC infusions of IgG cause few adverse systemic reactions, and for some patients, including children, the SC route has become a preferred route of administration (4-6,13,31-39).

Advantages of home-based SCIG infusions in adults and children with PI include treatment satisfaction and QOL improvement, specifically, greater independence, better control of the therapy situation, and an overall improvement in daily life afforded by home-based therapy. This has been repeatedly demonstrated in sentinel studies (40,41). Moreover, the technique involved is deemed easy to learn by adults and children (10,25,36,42).

3 STUDY OBJECTIVES AND PURPOSE

3.1 Pharmacokinetic and Efficacy Objectives

3.1.1 Primary Pharmacokinetic Objective

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

3.1.2 Secondary Objectives

- To determine if IGSC 20% replacement therapy maintains steady-state mean trough total IgG levels when administered biweekly (every 2 weeks) that are comparable to steady-state mean trough total IgG levels obtained when IGSC 20% is administered weekly in treatment-experienced subjects with PI.
- To evaluate maximum concentration (C_{max}) and time to reach C_{max} (t_{max}) of total IgG at steady state in given IGSC 20% weekly and biweekly (every 2 weeks) in treatment-experienced subjects.
- To evaluate if a loading dose of IGSC 20% consisting of 5 consecutive daily doses of 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly infusions of IGSC 20% 150 mg/kg

starting Week 1 (Day 8) through Week 32 achieves and maintains total IgG trough >500 mg/dL in treatment-naïve subjects with PI.

- To evaluate the rate of SBIs as defined in Appendix 4 in all subjects.
- To evaluate all infections of any kind as determined by the investigator in all subjects.
- To evaluate validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms eg, bacterial, viral, fungal, or protozoal pathogens (eg, rapid streptococcal antigen detection test) in all subjects.
- To evaluate the number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic) in all subjects.
- To evaluate the number of hospitalizations due to infection in all subjects.

3.1.3 Exploratory Objectives

- To compare treatment burden and treatment satisfaction related to immune globulin therapy using the Life Quality Index (LQI) questionnaire and the Treatment Satisfaction Questionnaire for Medication (TSQM-9) for IGSC 20% administered weekly or biweekly (every 2 weeks) in treatment-experienced subjects with PI. (42,43,44). (Appendix 3)
- To survey QOL in subjects with PI using the Short Form Health Survey (12-Item Short Form Health Survey [SF-12] for subjects ≥18 years [observer: subject] in both treatment-experienced and treatment-naïve subjects with PI. (Appendix 3). In addition, 10-Item Short Form Health Survey [SF-10] for treatment-naïve subjects aged 6 to 17 years [observer: parent or legal guardian]) will also be used.

3.2 Safety Objectives

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

4 STUDY DESIGN

4.1 Study Design and Plan

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

4.1.1 Treatment-Experienced Cohort

The Screening Period is up to 5 weeks to accommodate treatment-experienced subjects who may enter the study on commercial IVIG or HYQVIA with a monthly dosing schedule. The treatment-experienced cohort will enroll subjects with PI already maintained on IgG replacement therapy for at least 3 months who will receive IGSC 20% at 2 different dosing frequencies using an SC infusion pump during 2 treatment periods (16 weeks per treatment period).

Treatment Period 1:

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

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

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

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

Treatment Period 2:

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

Final follow-up Visit:

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

The overall study schema for the treatment-experienced subjects is shown in Figure 4-1.

4.1.2 Treatment-Naïve Cohort

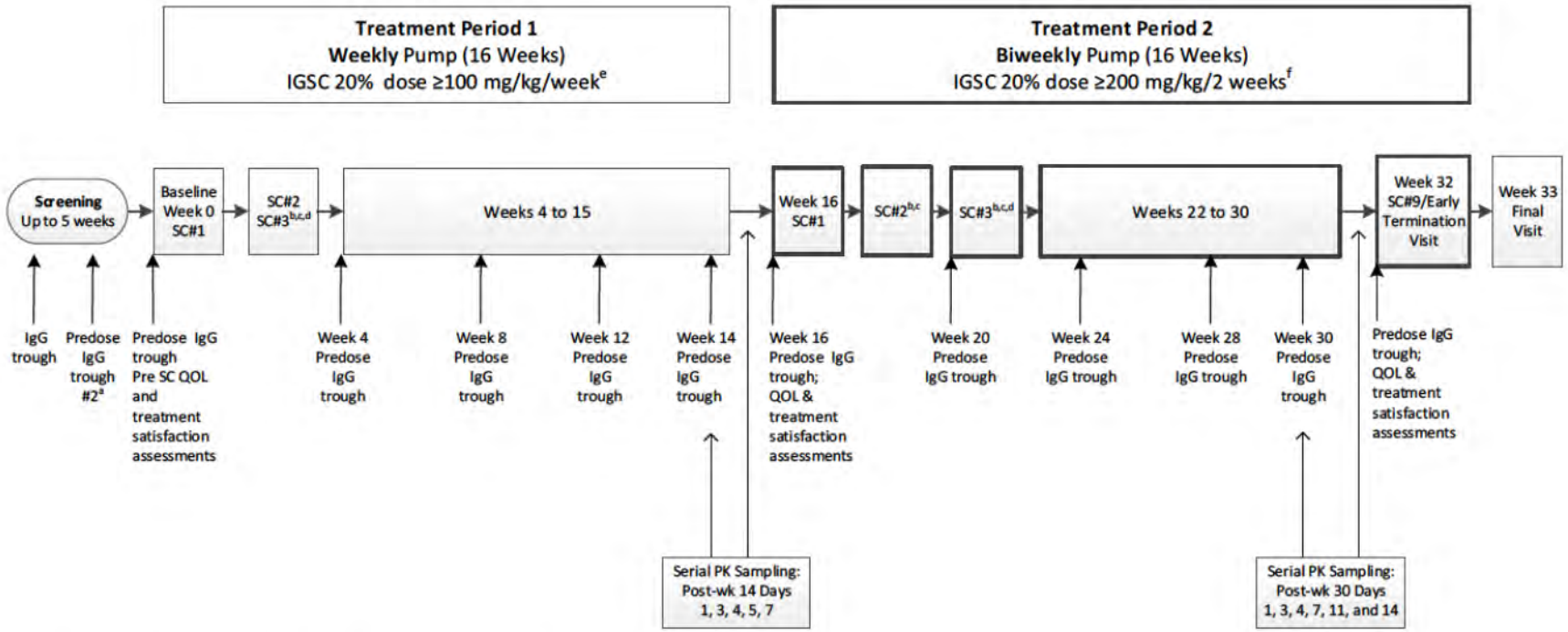
For treatment-naïve subjects, the Screening Period should be as short as possible in order to facilitate rapid commencement of IGSC 20% as IgG replacement treatment.

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

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

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

The study schema for treatment-naïve subjects is shown in Figure 4-2.



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

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

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

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

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

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

Figure 4-1 Overall Study Schema – Treatment-Experienced Subjects

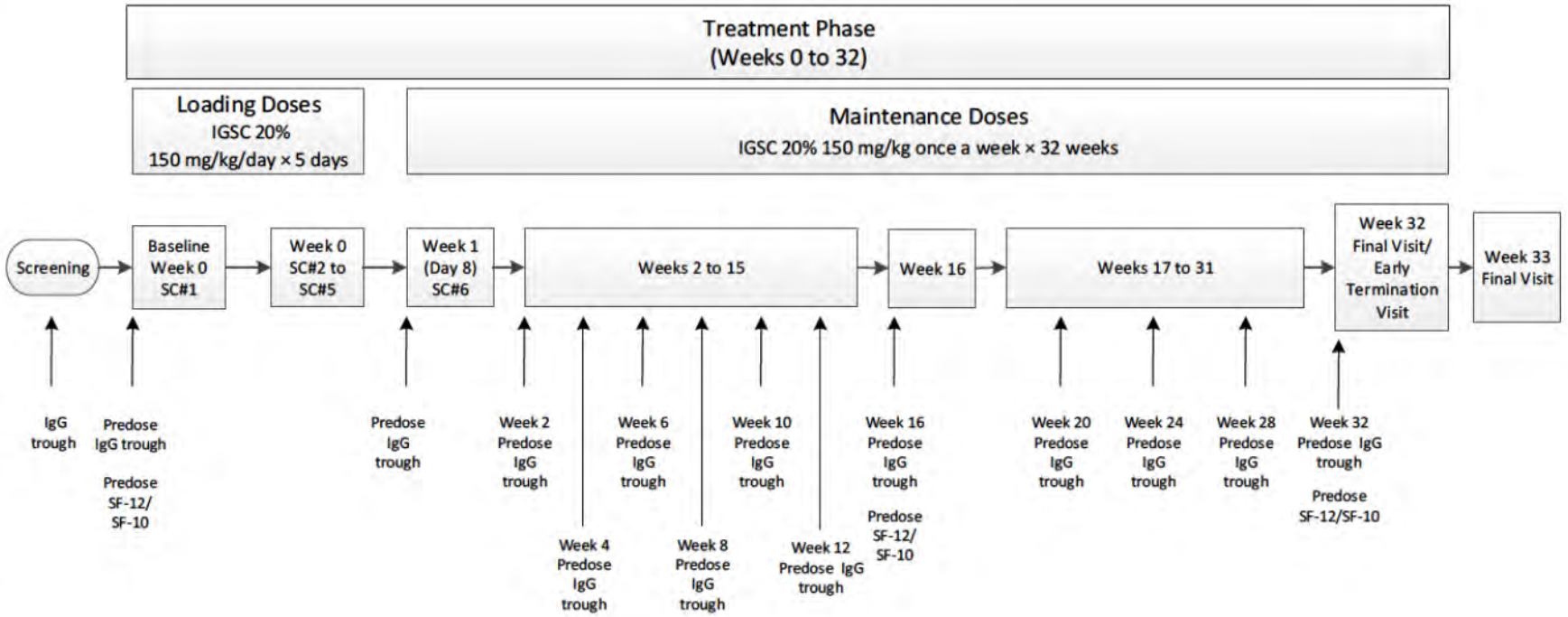


Figure 4-2 Overall Study Schema – Treatment-Naïve Subjects

4.1.2.1 Algorithm for Treatment-Naïve Cohort Enrollment

Treatment-naïve subjects will be enrolled one at a time in a sequential fashion.

Each individual subject not meeting the optimal target IgG trough level ≥700 mg/dL after 5 consecutive loading infusions are complete (and not meeting discontinuation criteria below) will have dose adjustment of IGSC 20% as detailed in Section 4.1.2.2 based on IgG trough level and investigator judgment in order to reach an IgG trough ≥700 mg/dL *before* Week 8. See also Appendix 7.

Stopping rules for the entire Treatment-Naïve Cohort are detailed in Section 4.5.3 and individual subject discontinuation criteria are fully described in Section 5.3.2. The figure in Appendix 8 illustrates the algorithm for treatment-naïve individual IGSC 20% dosing and cohort recruitment based on IgG trough levels.

Treatment-naïve subjects will be enrolled sequentially per the following algorithm which will be repeated for the 3rd, 4th, 5th and 6th treatment-naïve subjects based on the predecessor subject's IgG trough values:

- A second treatment-naïve subject may be enrolled, if the IgG trough result drawn at Week 1 (Day 8) is ≥600 mg/dL following 5 consecutive daily loading infusions for the first enrolled treatment-naïve subject.
  - If the IgG trough is >500 mg/dL, but < 600 mg/dL for the first subject, then further cohort recruitment is deferred until the review of the Week 6 IgG trough level results.
  - If the IgG trough is ≤500 mg/dL, then the subject must discontinue, and recruitment in the Treatment-Naïve Cohort will end.
- Deferral of additional recruitment to Week 6 IgG trough result received:
  - If the target IgG trough of ≥700 mg/dL is achieved for the first subject upon review of the Week 6 IgG trough level results, then a second treatment-naïve subject may be enrolled.
  - If the target IgG trough of ≥700 mg/dL *is not achieved before* the Week 8 Visit, then the first subject must prematurely discontinue from the GC1906 study. *However, a second treatment-naïve subject may still be enrolled provided that the first subject at least achieved an IgG trough value of ≥600 mg/dL before Week 8.*

This pattern will be repeated for all subsequent treatment-naïve subjects; for example, enrollment of a third treatment-naïve subject will be based on the IgG trough values of the second subject enrolled based on these rules. In this manner, treatment-naïve subject enrollment will be carefully staggered by intervals of not less than 2 weeks.

4.1.2.2 Algorithm for Individual Treatment-Naïve Subject IGSC 20% Dose Adjustment Based on IgG Trough Levels

Following 5 daily IGSC 20% loading infusions, if the Week 1 (Day 8) IgG trough value is >500 mg/dL but <700 mg/dL, a new IGSC 20% dosage will commence at Week 2 using the equation for dose adjustment provided below (**) for an optimal target IgG trough value of ≥700 mg/dL.

Subsequently, if the previously drawn Week 2 or Week 4 IgG trough level is <700 mg/dL dose adjustments may occur at the next clinic visit (Week 4 or Week 6, respectively). So an IGSC 20% dose adjustment may occur at any time from Week 2 through Week 6 if the investigator considers the prior IGSC 20% dosage insufficient based on best clinical judgment (IgG trough ≥700 mg/dL must be reached *before* Week 8 for a subject to continue).

The equation (**) can be used to calculate dose adjustments at these study visits for target IgG trough ≥700 mg/dL, provided that the 'current IgG trough mg/dL' entered in the equation is drawn on the subject's current IGSC 20% regimen.

Any dose adjustment made at the Week 2 visit will not be reflected in the Week 2 IgG trough result which is drawn prior to the Week 2 IGSC 20% infusion. Therefore, careful investigator consideration is needed if a dose adjustments is made at Week 4 after an earlier Week 2 dose adjustment.

Similarly, effects of a dose adjustment at Week 4 will not be evident until the IgG trough is drawn at Week 6, with results available after the Week 6 visit.

** The equation below provides the new mg/kg IGSC 20% dose to achieve the optimal target IgG trough of ≥700 mg/dL for subjects with a Week 1 (Day 8) IgG trough > 500 mg/dL but <700 mg/dL. The equation should be used to calculate a new dose at Week 2 or any subsequent visit through Week 6 using a current IgG trough *value that was drawn on the subject's current IGSC 20% dosage.*

Dose Adjustment Calculation providing new increased IGSC 20% dose in mg/kg:

$$1)\ \left(700\,\frac{mg}{dL} - current\ IgG\ trough\,\frac{mg}{dL}\right) \div 6.6 = \frac{mg}{kg}\,dose\ increase\ required$$

$$2)\ Current\,\frac{mg}{kg}\,dose + \frac{mg}{kg}\,dose\ increase\ required\ (Step\ 1\ total) = New\,\frac{mg}{kg}\ dose\ per\ week$$

The New volume of IGSC 20% to be administered each week may be calculated as:

$$(New\,\frac{mg}{kg}\,dose\ \times body\ weight\ (kg)) \div 200\,\frac{mg}{mL} = New\ total\ volume\ (mL)$$

For example, if a subject with a body weight of 70 kg has an actual IgG trough level of 600 mg/dL and the target level is 700 mg/dL, this results in a difference of 100 mg/dL. The

mg/kg dose increase required would be 15.2 mg/kg (= 100 ÷ 6.6). If the subject were receiving 150 mg/kg/week, then the new IGSC 20% dose would be 165.2 (= 150 + 15.2) mg/kg per week, which can be rounded to the nearest whole number.

See also Appendix 7 which contains a tabular guide for dose adjustment in terms of volume (mL) as an additional reference.

Refer to Section 5.3.2 for premature discontinuation criteria for individual treatment-naïve subjects.

4.2 Measures Taken to Minimize/Avoid Bias

4.2.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers will be generated beginning with the study center number (3 digits, assigned by the sponsor) followed consecutively with a unique number for each subject (4 digits, beginning with the number "1"). For example, if the investigator's center number is 301, subject number will be 3011001, 3011002, 3011003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

If a subject is re-screened (see Section 5.3.1), a different subject number will be assigned to this subject.

4.2.2 Interactive Web Response System

Subjects will not be randomized; however an IWRS will be used for clinical trial material surveillance of all subjects. Furthermore, recruitment of treatment-naïve subjects will be controlled by the IWRS (see Section 4.1.2).

4.2.3 Blinding

This is an open-label study with no blinding.

4.3 Study Treatments

4.3.1 Treatments to Be Administered

Immune Globulin Subcutaneous (Human), 20% Caprylate/Chromatography Purified (IGSC 20%) is a sterile liquid formulation of immunoglobulin that has been purified from human plasma via a multi-step process. IGSC 20% is manufactured using the same process as for IGIV-C 10% (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified [IGIV-C]), and is further concentrated by ultrafiltration to a higher IgG concentration (20%). IGSC 20% vials will be supplied in 20 and 50 mL vial size containing a 20% solution of immunoglobulin (ie, a concentration of 20 g/100 mL [200 mg/mL]).

IGSC 20% must be inspected visually before being administered. The solution must not be used if the solution is cloudy or turbid. Solution that has been frozen should not be used. The

investigator, or designee, is responsible for immediately reporting any issues noted with IGSC 20% to the study monitor.

Detailed IP administration instructions are provided in Section 6.

4.3.2 Labeling and Packaging of Investigational Product

Investigational products will be labeled according to the requirements of local law and legislation. Label text will be approved according to Grifols procedures, and a copy of the labels will be made available to study sites.

4.3.3 Storage of Investigational Product

IGSC 20% must be stored in a secure area accessible to study personnel authorized by the investigator, such as the study staff responsible for the preparation and dispensing of IP.

IGSC 20% must be stored at temperatures of 2°C to 8°C (36°F to 46°F) and protected from light. Do not freeze or partially freeze. Investigators, or designees, are responsible for maintaining storage temperature records and for immediately reporting deviations in temperature to the study monitor.

Details for the storage are located in the Pharmacy Manual provided to each site and instructions will also be provided to participating subjects.

4.4 Expected Duration of Subject Participation in the Study

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

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

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

4.5 Discontinuation Criteria for Individual Subjects and Study

4.5.1 Discontinuation Criteria for Individual Subjects

See Section 5.3 Subject Withdrawal Criteria.

4.5.2 Premature Termination of Study/Closure of Center

The sponsor, Institutional Review Board/Ethics Committee (IRB/EC), and/or regulatory authorities have the right to close this study or a study center, and the investigator/sponsor

has the right to close a center, at any time, although this should occur only after consultation between involved parties. The IRB/EC must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

The reasons a study center can be closed include, but are not limited to, the following:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with ICH GCP

4.5.3 Stopping Rules for the Treatment-Naïve Cohort

Criteria for discontinuation of the entire Treatment-Naïve Cohort are the following:

1. If 3 or more treatment-naïve subjects fulfill individual subject discontinuation criteria (1), (2), or (3) as outlined in Section 5.3.2, then the Treatment-Naïve Cohort will be terminated from participation in the study.
2. If 3 or more treatment-naïve subjects are unable to complete 5 consecutive day loading infusions due to tolerability issues (ie, AEs), then the Treatment-Naïve Cohort will be terminated from participation in the study.
3. If any subject fails to reach an IgG trough level of >500 mg/dL at Week 1 (Day 8), further recruitment into the Treatment-Naïve Cohort will be discontinued due to failure of 5 consecutive loading IGSC 20% doses to achieve minimum IgG trough.

If any of the stopping criteria for the Treatment-Naïve Cohort are met, no further enrollment into the Treatment-Naïve Cohort will occur, but ongoing treatment-naïve subjects successfully receiving IGSC 20% maintenance infusions may continue at the investigator's discretion.

Criteria #1 and #2 for discontinuation of the entire Treatment-Naïve Cohort are based on the fact that if 3 or more out of the possible total of 6 treatment-naïve subjects were non-responders (ie, those who did not meet the IgG or tolerability success criteria as stipulated above), then the upper limit of the exact 95% CI for the proportion of responders will be below 90% (maximum = 88.2%), equivalent to rejecting the null hypothesis that the true proportion of responders is at least 90% at a 1-sided alpha level of 0.025, as shown in Table 4-1.

Table 4-1 Point Estimates and Exact 95% CIs for Proportion of Responders

Total Number of Subjects	Number of Non-Responders[a]	Number of Responders[a]	Proportion of Responders (%)	
			Point Estimate	Exact 95% CI[b]
6	0	6	100.0	(54.1, 100.0)
6	1	5	83.3	(35.9, 99.6)
6	2	4	66.7	(22.3, 95.7)
6	3	3	50.0	(11.8, 88.2)
6	4	2	33.3	(4.3, 77.7)
6	5	1	16.7	(0.4, 64.1)
6	6	0	0.0	(0.0, 45.9)

[a] Non-responders and responders are defined as treatment-naïve subjects who did not meet and met, respectively, the IgG or tolerability success criteria.
[b] The 95% CI was calculated using the exact (Clopper-Pearson) method for binomial proportion.

4.6 Accountability Procedures for Investigational Product

Investigational product is to be used only for the study in accordance with the directions given in this protocol. The investigator, or designee such as the study pharmacist, is responsible for the distribution of the IP in accordance with directions given in the protocol and Pharmacy Manual.

The investigator is responsible for maintaining accurate records of the IP for his/her site. Investigational product inventory/dispensing documentation verifying the receipt, dispensing, destruction, or return must be maintained and kept current by the investigator, or designee. The IP and supplies inventory must be made available to the monitor. Investigational product supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to IP return or destruction. Written documentation of any used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols.

4.7 Maintenance of Treatment Randomization Codes

This study is not a randomized trial; randomization codes are not applicable.

4.8 Data to Be Recorded Directly on the Electronic Case Report Forms

Not applicable. For QOL and treatment satisfaction scales, the diary or form employed will be considered source documentation.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

Inclusion Criteria **only** for **Treatment-Experienced Subjects**

A treatment-experienced subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Subjects 18 years to 75 years (inclusive) at screening
2. Subjects with documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (eg, X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (eg, hyper immunoglobulin M immunodeficiency syndrome).
3. Subjects have not had an SBI or been hospitalized for infection of any etiology (eg, viral, fungal, parasitic) within the last 3 months prior to screening or during screening.
4. Subjects currently receiving IgG replacement therapy for ≥3 months via IV or SC infusion. Subjects receiving IVIG prior to study must receive a dosage of at least 200 mg/kg per infusion
5. Subjects whose screening IgG trough levels must be ≥500 mg/dL.

   Note: If screening trough levels are not above this threshold, the subjects will be considered a screen failure, but may be rescreened following dose adjustment of their original IgG replacement therapy regimen and maintaining stable dosing for a period of at least 3 months prior to screening a second time.
6. Subjects have signed an informed consent form.

Inclusion Criteria **only** for **Treatment-Naïve Subjects**

A treatment-naïve subject must meet all the following inclusion criteria to be eligible for participation in the study:

1. Subjects 6 years to 75 years (inclusive) at screening.
2. Subjects with documented and confirmed diagnosis of PI with features of hypogammaglobulinemia requiring IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (eg, X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (eg, hyper immunoglobulin M immunodeficiency syndrome).
3. Subjects have never received IgG replacement treatment (ie, no prior immune globulin replacement therapy)
4. Subjects whose screening IgG level must be ≤400 mg/dL
5. Subjects do not have an SBI nor requires hospitalization for infection of any etiology (eg, viral, fungal, parasitic) during screening or at baseline.
6. Subjects have signed an informed consent.

   Note: The subject must sign the informed consent form (ICF) if at least 18 years old. For children or adolescents, the subject's parent or legal guardian must sign the ICF and if appropriate/applicable, the subject must sign a Child Assent form approved by the IRB/EC per the institution's requirements.

5.2 Exclusion Criteria (All Subjects)

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

1. Subjects with clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may interfere with successful completion of the trial or place the subject at undue medical risk.
2. Subjects have had a known serious AR to immunoglobulin or any anaphylactic reaction to blood or any blood-derived product
3. Subjects who have a history of blistering skin disease, clinically significant thrombocytopenia, bleeding disorder, diffuse rash, recurrent skin infections, or other disorders where SC therapy would be contraindicated during the study.
4. Subjects have known isolated IgG subclass deficiency; isolated specific antibody deficiency (SAD) or selective IgG deficiency; or transient hypogammaglobulinemia of infancy.

   Note: Subjects are not to be enrolled if their primary PI diagnosis does not entail an actual quantitative deficit in total IgG. For example, SAD is defined as an impaired specific IgG response to pneumococcal vaccine with normal serum concentrations of IgG, IgM, and IgA. Isolated IgG subclass deficiency is defined as an abnormally low level of 1 or more IgG subclass in subjects with normal levels of total IgG and IgM.
5. Subjects have known Selective IgA Deficiency (with or without antibodies to IgA) (Note: exclusion is for the specific diagnostic entity. It does not exclude other forms of humoral primary immunodeficiency which have decreased IgA in addition to decreased IgG requiring IgG replacement).
6. Females of childbearing potential who are pregnant, have a positive pregnancy test at screening (serum human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study.

   Note: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
7. Subjects have significant proteinuria (≥3+ or known urinary protein loss >1 g/24 hours or nephrotic syndrome), has acute renal failure, is on dialysis, and/or has severe renal impairment on Screening laboratory testing (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]).
8. Subjects have screening values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory.
9. Subjects whose hemoglobin level is <9 g/dL at screening.

10. Subjects have a history (either 1 episode within the year prior to the Screening Visit or 2 previous episodes over a lifetime) of or current diagnosis of thromboembolism (eg, myocardial infarction, cerebrovascular accident or transient ischemic attack) or deep venous thrombosis.
11. Subjects are currently receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [eg, dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], and parenteral anticoagulants [eg, fondaparinux]).
12. Subjects currently have a known hyperviscosity syndrome.
13. Subjects have an acquired medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (absolute neutrophil count less than 1000/µL [1.0 x 10^9/L]), or human immunodeficiency virus infection/acquired immune deficiency syndrome.
14. Subjects have a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus or hepatitis C virus infection.
15. Subjects (if <18 years of age) have non-controlled arterial hypertension at a level of greater than or equal to the 90th percentile blood pressure (either systolic or diastolic) for their age and height (See Appendix 5) or the adult subject has non-controlled arterial hypertension (systolic blood pressure [SBP] >160 mmHg and/or diastolic blood pressure [DBP] >100 mmHg).
16. Subjects are receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents; (b) immunomodulators; (c) long-term systemic corticosteroids defined as daily dose >1 mg of prednisone equivalent/kg/day for >30 days.

    Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.
17. Subjects have known substance or prescription drug abuse.
18. Subjects have participated in another clinical trial within 30 days prior to screening (observational studies without investigative treatments [non-interventional] are permitted).
19. Subjects/caregivers are unwilling to comply with any aspect of the protocol, including home SC infusions, blood sampling, and completion of a SC infusion diary for the duration of the study.
20. Subjects who cannot give independent informed consent and/or assent (example: intellectual disability or cognitive disability).
21. In the opinion of the investigator, subjects may have compliance problems with the protocol and the procedures of the protocol.

5.3 Subject Withdrawal Criteria

5.3.1 Screen Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment. Subjects who fail to meet eligibility criteria during screening evaluations will be allowed to be rescreened once. If a subject fails the screening evaluation upon rescreening, the subject will be considered a screen failure and will not eligible to participate in the study.

5.3.2 Removal of Subjects

The reasons a subject may withdraw or be withdrawn from the study include, but are not limited to, the following:

- At their own request or at the request of their legally acceptable representative.
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- At the specific request of the sponsor.

Also, subjects must be withdrawn for the following reasons:

- Subjects with an occurrence of a concomitant disease, or any medical condition which, either because of its severity or duration or necessary change in treatment, contravenes the condition of the study or puts the subject at unnecessary risk or harm.
- Subjects with an occurrence of an AE which in the opinion of the investigator and/or subject requires termination of treatment.
- Subjects who are noncompliant with the protocol (including noncompliance with IGSC 20% dosing) per the investigator's discretion.
- Pregnancy (Note: If a subject becomes pregnant during the study, the subject must be withdrawn from IP administration and the study prior to dosing with a commercially available IgG product. See Section 8.3.9.2).

Additionally, criteria for the discontinuation of individual treatment-naïve subjects based on IgG trough levels are as follows:

1. If a treatment-naïve subject's Week 1 (Day 8) IgG trough value is ≤500 mg/dL following 5 consecutive days of loading infusions, then the subject will be discontinued from the study.
2. If a treatment-naïve subject's IgG trough value drawn at Week 6 is <700 mg/dL, then the subject must be withdrawn.
3. If a treatment-naïve subject develops an SBI considered suboptimally managed by the IGSC 20% treatment regimen in the opinion of the investigator or sponsor, then the subject must be withdrawn.

Additionally, treatment-naïve subjects may be withdrawn from the study at any time by the investigator if it is considered the best medical management to prematurely discontinue the subject from the study and treat them with commercial IgG product for infection prophylaxis.

In all cases, the reason for withdrawal must be recorded in the subject's source documentation and electronic case report form (eCRF).

5.3.3 Subject Replacement

Treatment-experienced subjects will not be replaced.

Treatment-naïve subjects who discontinue prior to Week 16 may be replaced.

5.3.4 Follow-up of Subjects Withdrawn from Study

Subjects who receive any amount of IP and discontinue early from the study will be requested to return for the Early Termination Visit prior to starting commercial IgG treatment. The assessments at the Early Termination Visit will be the same as those performed at the Week 32 Visit, and IP dosing for subjects who prematurely discontinue will be at the discretion of the investigator. If IP dosing is administered at the early termination visit, the final dose should be consistent with the frequency and dosing of IGSC 20% in effect when the subject withdrew from the study.

6 TREATMENT OF SUBJECTS

6.1 Administration and Timing of Investigational Product for Each Subject

The volume infused, infusion start date/time, infusion end date/time, and initial and final infusion rates will be recorded in the subject's source documentation and eCRF. The number of infusion sites, the location(s) of each infusion site, and other SC infusion information will be recorded in the SC infusion diary by the subject/parents or legal guardians or site personnel as appropriate. Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

Treatment-Experienced Subjects

The volume (ie, total infusion dose administered) of IGSC 20% prepared for each SC infusion will be individualized for each treatment-experienced subject based on dose-equivalence with their previously established (prestudy) regimen (documented at screening) using body-weight-based dosing.

A DAF of 1.37 will be applied to subjects entering study on IVIG for the IV-to-SC transition to weekly IGSC 20% administration in Treatment Period 1. This means for subjects entering on IVIG, to obtain the IGSC 20% dose per week, the equivalent weekly dose will be multiplied by 1.37.

A DAF is not used for subjects entering study on SCIG, and the equivalent weekly dose will be the same as previous SCIG regimen adjusted for weekly dosing interval.

If the equivalent weekly dose (based on prior commercial IgG dose) is <100 mg/kg/week, then the IGSC 20% dose will be modified to be equivalent to a net dosage of 100 mg/kg/week. The minimum IGSC 20% dose in GC1906 is 100 mg/kg/week.

Dose calculations are described in further detail below. See Appendix 6 for sample calculations based on dosing frequency.

Dose Calculation

- For any prior IgG treatment regimen, the initial calculation is to establish the equivalent weekly dose.

This is calculated as follows for prior IgG dosing intervals greater than or equal to 1 week (IVIG, SCIG including HYQVIA):

Equation A:

$$\textbf{\textit{Equivalent Weekly Dose}} = \frac{\textbf{\textit{Previous IVIG or SCIG dose (mg/kg)}}}{\textbf{\textit{Number of weeks between IVIG or SCIG doses (weeks)}}}$$

This is calculated as follows for prior IgG dosing intervals <1 week (some SCIG regimens):

Equation B:

$$\textbf{\textit{Equivalent Weekly Dose}} = \left(\textbf{\textit{Previous SCIG dose}}\ \left(\frac{mg}{kg}\right)\right) \times\ (\textbf{\textit{number of times given per week}})$$

- Treatment Period 1:
  - For subjects entering on IVIG, multiply the equivalent weekly dose by the 1.37 DAF to obtain the mg/kg IGSC 20% dose per week.
  - For subjects entering on SCIG, there is no DAF. The dose in mg/kg of IGSC 20% per week is exactly the same as the Equivalent Weekly Dose.
- Treatment Period 2:
  - The IGSC 20% dose is to be given every 2 weeks (Biweekly).
  - Multiply the calculated IGSC 20% weekly dose by 2.

Treatment-naïve Subjects

The treatment-naïve cohort will receive a loading dose consisting of 5 consecutive daily doses of IGSC 20% 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly infusions of IGSC 20% 150 mg/kg starting Week 1 (Day 8) through Week 32. The weekly frequency will be maintained through Week 32.

For Treatment-Naïve Cohort and individual subject IGSC 20% dose adjustment algorithms, see Sections 4.1.2.1 and 4.1.2.2, and Appendix 8.

6.1.1 Subcutaneous Administration Procedures of Investigational Product with Infusion Pump

The ambulatory infusion pump should initially employ an infusion rate no greater than 25 mL/hour/site as tolerated by the subject and as per the investigator's discretion. The investigator will tailor the pump infusion configuration for each individual subject. Subjects who are naïve to SC infusion for IgG replacement (ie, receiving IVIG at study entry) may start at a lower pump SC infusion rate per site initially while transitioning from the IV to SC route of administration. In the event that the subject is not able to tolerate the set infusion rate, the rate may be decreased for better tolerability.

If the pump infusion rate is well tolerated during 2 infusions (with an initial target of ≤25 mL/hour/site), the infusion rate for subsequent infusions can be increased in a stepwise manner at the investigator's discretion (eg, at intervals of at least 10 minutes) to a maximum of 60 mL/hour/site during observation at a clinic visit (which may occur between scheduled visits). If the infusion at the maximum pump rate is well tolerated, subsequent infusions can begin at the maximum tolerated rate without any stepwise increments (ie, if the first 2 infusions at the initial target of 25 mL/hour/site are well tolerated, the third infusion will initiate at 25 mL/hour/site and will be incrementally increased, at investigator's discretion, while the subject is in clinic to a maximum of 60 mL/hour/site. If the third infusion is well tolerated at 60 mL/hour/site in clinic, the fourth infusion will commence at the maximum rate of 60 mL/hour/site, without stepwise increments either at home or in clinic per the investigator's discretion).

The stepwise increases must not exceed 60 mL/hour/site, the maximum infusion rate for all sites combined is ≤240 mL/hour, and the volume per site must be ≤60 mL/site. The infusion rate should not be increased at the subject's home.At higher infusion rates, infusion sites must be rotated with each administration and are recommended to be spaced at least 10.2 cm (4 inches) apart, and avoiding bony prominences.

Reference the Pharmacy Manual/study manual for detailed instructions for IGSC 20% preparation and administration.

6.2 Prior and Concomitant Therapy

Prior and concomitant medications must be recorded in the subject's source documentation and eCRF, including the trade or generic names of the medication, the therapeutic indication for the medication, the dose, the route of administration, frequency, and the duration of the medication. All IgG treatments administered for the 12 months prior to screening should be recorded.

6.2.1 Prohibited Medications Prior to Study Participation

Use of the following medications, as specified below, would exclude a subject from participating in this study:

- At the time of screening, receiving systemic corticosteroids (long-term daily doses of >1 mg of prednisone equivalent/kg/day for >30 days) (intermittent courses of not more than 10 days would not exclude subject). Note: Inhaled or topical corticosteroids are allowed.
- At the time of screening, receiving immunosuppressants including chemotherapeutic agents or immunomodulators.
- At the time of screening, receiving anti-coagulation therapy which would make SC administration inadvisable (vitamin K antagonists, nonvitamin K antagonist oral anticoagulants [eg, dabigatran etexilate targeting Factor IIa, rivaroxaban, edoxaban, and apixaban targeting Factor Xa], parenteral anticoagulants [eg, fondaparinux]).

6.2.2 Prohibited Concomitant Medications during the Study

Use of the following medications is prohibited during the study participation.

- Any IgG replacement therapy other than IGSC 20% provided in this study
- Corticosteroids in excess of stipulations delineated in Section 6.2.1
- Anti-coagulant therapy as outlined in Section 6.2.1
- Immunosuppressants including chemotherapeutic agents or immunomodulators
- Investigational product that is not part of this study

6.2.3 Restricted Concomitant Medications during the Study

This section describes medications that are restricted, but not prohibited during the study participation:

For subjects receiving a permissible stable dose of systemic steroids (defined above), it is recommended to maintain the same dose throughout the study.

The medications listed below are not allowed during the study as premedication to IP administration; however, these medications are allowed during the study for general use (eg, to treat an AE):

Oral or Parenteral medications:

- Ibuprofen
- Acetaminophen
- Acetylsalicylic acid
- Antihistamines

Topical medications at infusion site locations:

- Steroids
- Antihistamines

6.2.4 Drug Interactions

In the setting of a PI disease state, live viral vaccines have various contraindications and specific risks/degrees of effectiveness dependent on the type/category of the immune deficiency (Medical Advisory Committee of the Immune Deficiency Foundation [16]). Passive transfer of antibodies from IGSC 20% may transiently interfere with the immune response to live viral vaccines such as measles, mumps, rubella, and varicella in the normal host with an intact immune system. Best medical practices should be followed regarding immunization requirements, particularly for children during the course of this study.

6.3 Treatment Compliance

Reasons for any deviation from the administration of less than 100% of the IP dose as prepared by the pharmacist, or designee, must be recorded in the subject's medical records and eCRF.

7 ASSESSMENT OF PHARMACOKINECTICS AND EFFICACY

7.1 Study Variables

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

7.1.1 Primary Pharmacokinetic Variable

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

7.1.2 Secondary Variables

- Steady-state mean trough (predose) concentration of total IgG following SC administration of IGSC 20% given IGSC 20% weekly and biweekly (every 2 weeks) in treatment-experienced subjects.
- C_{max} and t_{max} of total IgG at steady state given IGSC 20% weekly and biweekly in treatment-experienced subjects.

- In the treatment-naïve cohort, ability of a loading dose of IGSC 20% 150 mg/kg/day and maintenance infusion of IGSC 20% 150 mg/kg to achieve and maintain total IgG trough >500 mg/dL through Week 32 (End of Treatment).

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

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

7.1.3 Exploratory Variables

- LQI score in treatment-experienced subjects.

  The LQI covers 3 domains: treatment interference, therapy-related problems, and therapy settings (39,43,45-49). Change in LQI from Pre-SC#1 Week 0 to Week 16 , and from Week 16 to Week 32 will be analyzed (Appendix 3).

- TSQM-9 score in treatment-experienced subjects.

  This questionnaire is a measure of treatment satisfaction in 3 categories of effectiveness, convenience, and global satisfaction (44,50,51). Change in TSQM-9 from Pre-SC#1 Week 0 to Week 16, and from Week 16 to Week 32 will be analyzed (Appendix 3).

- SF-12 survey (subjects ≥18 years [observer: subject]) which measures dimensions of health analogous to the 36-item short form health survey (SF-36) (52,53) in both treatment-experienced subjects and treatment-naïve subjects. In addition, 10-Item Short Form Health Survey [SF-10] for treatment-naïve subjects aged 6 to 17 years [observer: parent]) will also be used.

  In treatment-experienced subjects, change in SF-12 from Pre-SC#1 Week 0 to Week 16 (end of Treatment Period 1), and from Week 16 to Week 32 (end of Treatment Period 2) will be analyzed (Appendix 3). In the treatment-naïve cohort, the time points for comparison SF-12/SF-10 will be change from Pre-SC#1 Week 0 (before first loading dose) to Week 16 and to Week 32 (End of Treatment).

In all questionnaires, higher scores indicate higher satisfaction.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Pharmacokinetic and Efficacy Parameters

7.2.1 Observations and Measurements

The following is a description of the procedures/assessments to take place at each study visit. See the Schedules of Study Procedures and Events for treatment-experienced subjects (Appendix 1) and for treatment-naïve subjects in Appendix 2.

7.2.1.1 Screening Period (**All Subjects**)

The Screening Period is up to 5 weeks to accommodate treatment-experienced subjects who may enter the study on commercial IVIG or HYQVIA with a monthly dosing schedule. For treatment-experienced subjects receiving IVIG and HYQVIA, commercial immune globulin will be infused twice during the Screening Period. The first commercial infusion will occur at the initial Screening Visit, and the second commercial infusion will be at the IgG Trough #2 Visit either 3 or 4 weeks later depending on the subject's treatment interval. Both infusions will occur after the laboratory samples are collected (inclusive of IgG trough). The first IGSC 20% infusion (Baseline Visit) is 1 week after the IgG Trough #2 Visit (last IVIG or HYQVIA dose).

For treatment-experienced subjects entering on commercial SCIG, the Screening Period can be shortened in accordance with the subject's dosing schedule (eg, weekly) and receipt of qualifying laboratory values for eligibility.

For all treatment-experienced subjects, the Screening Visit will occur on the same day as the subject's normally scheduled commercial IgG infusion so that an IgG trough value can be drawn before the infusion occurs.

For treatment-naïve subjects, the Screening Period should be as short as possible in order to facilitate rapid commencement of IGSC 20% as IgG replacement treatment. Baseline can occur as soon as qualifying laboratory values are received and eligibility is confirmed.

The medical records for all subjects should be available to document diagnosis, previous infections, and treatment.

The following will be performed at the Screening Visit (**All Subjects**):

- Informed consent
- Assess inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively) to determine subject eligibility.
- Assign subject number.
- Medical history (record relevant medical history defined as any history impactful on the subject's condition in terms of current functioning, disability, treatment or management)
- Demographics

- Record specific type of PI diagnosed, date of diagnosis, and for treatment-experienced subjects, dose of current IgG replacement regimen and date initiated.
- Full physical exam (excludes breast and genitourinary exam)
- Vital signs (temperature [T], respiratory rate [RR], pulse [HR], blood pressure [SBP, DBP])
- Height and body weight
- Blood and urine samples (see Section 7.2.2) (in treatment-experienced subjects this should occur prior to standard of care commercial dose)
  - Hematology: Hemoglobin, hematocrit, platelets, red blood cell (RBC) count, white blood cell (WBC) count with differential, absolute reticulocyte count (ARC)
  - Clinical chemistry: Sodium, potassium, creatinine, chloride, calcium, BUN, lactate dehydrogenase (LDH), AST, ALT, alkaline phosphatase (ALP), total bilirubin (TB), indirect bilirubin
  - Haptoglobin
  - Serum pregnancy test (potential child-bearing females only)
  - Blood sample for IgG trough level
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Blood sample for central laboratory direct antiglobulin test (DAT) and serum/plasma free hemoglobin assessments
- Record AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections (*if this occurs during the Screening Period, the subject will be considered a screen failure*).
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.
- Record prior and concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).

IgG Trough #2 Screening Visit (only for treatment-experienced subjects receiving commercial IVIG or HYQVIA):

- Pre-dose blood sample for IgG trough. Blood sample will be drawn within 8 hours of the IVIG or HYQVIA dose (trough sample collection must precede dosing)

  Note: This visit will occur at the next scheduled commercial dose after the Screening visit and 1 week prior to SC#1.

- Record AEs, SBIs, infections, and concomitant medications as indicated immediately above.

7.2.1.2 Treatment Periods

Treatment-Experienced Subjects

Treatment-experienced subjects will receive weekly IGSC 20% in Treatment Period 1, given at the same equivalent weekly dose for subjects on SCIG at study entry, or if the subject enters study on IVIG, at 1.37 times the equivalent weekly dose (ie, using a1.37 DAF for IV-to-SC transition).

The IgG dose may be adjusted only for safety reasons in Treatment Period 1 before Week 9 in the event the IgG trough level is less than or equal to 500 mg/dL or at the investigator's discretion. The dose adjustment (mg/kg) should not be more than a 20% increase from the dose producing the low IgG trough, per the investigator's discretion. Any dose adjustments beyond this range will require consultation with the Grifols Medical Monitor. No dose adjustments should occur at or after Week 9 except in extenuating circumstances after discussion with the Grifols Medical Monitor.

At Week 16, the subject will transition to biweekly (every 2 week) IGSC 20%; the 1st biweekly mg/kg dose will be administered at Week 16. Since dosing in Treatment Period 2 is every 2 weeks, the mg/kg/2 week dose is twice (2×) the weekly IGSC 20% dose in Treatment Period 1. The transition from weekly IGSC 20% dosing to biweekly IGSC 20% dosing will occur after the predose Week 16 assessments are complete.

The first SC infusion (SC#1) in Treatment Period 1 and in Treatment Period 2 will be performed in the investigator's clinic or under medical supervision to assure the subject fully understands the dosing methodology and technique. Subjects demonstrating proficiency with the administration method at the first clinic visit, as per the investigator's judgment, may administer SC#2 and SC#3 of each treatment period at home under the supervision of a healthcare provider (home health aide). Healthcare provider monitoring of SC#2 and SC#3 of each treatment period is required for subjects who were receiving IVIG treatment prior to study entry (naïve to SCIG administration), and is also recommended for subjects receiving SCIG treatment prior to study entry given transitions in method and frequency of administration. Note that increases in pump infusion rates, eg, stepped escalation in pump infusion rate during an infusion, must be performed at a clinic visit. IGSC 20% infusions may be administered at home thereafter, once the subject (or parent/guardian if the subject is a child) has been properly trained and demonstrated competence in administering infusions.

Ambulatory pump dosing will occur every week for a total of 16 doses in Treatment Period 1, and biweekly (every 2 weeks at twice the weekly dose) for a total of 9 doses in Treatment Period 2, with the last IGSC 20% dose given at Week 32.

Note that all clinic visits designated in the Schedule of Study Procedures in Appendix 1 should coincide with an anticipated IgG dosing time point unless otherwise specified, eg, serial PK draws at specific time points post dose.

Treatment-Naïve Subjects

Treatment-naïve subjects will receive a loading dose of IGSC 20% consisting of 5 consecutive daily doses of IGSC 20% 150 mg/kg/day (Week 0, Days 1 to 5) with weekly infusions of IGSC 20% 150 mg/kg starting Week 1 (Day 8) through Week 32. The weekly frequency will be maintained through Week 32.

The IgG dose may be adjusted for safety reasons in the Treatment Phase before Week 9 in the event the IgG trough level is less than 700 mg/dL or at the investigator's discretion. The dose adjustment algorithm is delineated in Section 4.1.2.2 (see also Appendix 8).

In this section, the standard planned dosage of 150 mg/kg for treatment-naïve subjects is referenced throughout.

7.2.1.2.1 BASELINE WEEK 0, DAY 1, SC#1 (TREATMENT PERIOD 1 FOR TREATMENT-EXPERIENCED SUBJECTS AND START OF TREATMENT PHASE [FIRST LOADING DOSE] FOR TREATMENT-NAÏVE SUBJECTS)

- Schedule Baseline Visit.

  For treatment-experienced subjects entering the study on SCIG, the Baseline Visit should be scheduled at the time point when the subject would ordinarily receive a SCIG dose (the exception is HYQVIA, see instructions below). On the day where commercial SCIG would ordinarily be given, commercial SCIG would be held, blood would be drawn for IgG trough and the subject will then be dosed with IGSC 20%.

  For treatment-experienced subjects entering the study on IVIG or HYQVIA, the Baseline Visit should be scheduled 1 week after their IgG Trough #2 Visit (their last IVIG or HYQVIA dose). If there are logistical issues requiring schedule adjustment for IGSC 20% administration, the first SC#1 dose may be scheduled 7±2 days after last commercial IVIG or HYQVIA dose.

  For treatment-naïve subjects, schedule Baseline Visit as soon as feasible following confirmation that eligibility criteria are met in order to assure medically vulnerable subjects commence IgG replacement treatment with IGSC 20% as soon as feasible. The first loading infusion will be administered on Week 0, Day 1, SC#1.
- Re-assess inclusion and exclusion criteria (if a subject develops an SBI [defined in Appendix 4] or is hospitalized for infection of any kind, subject will be a screen failure).
- Record vital signs (T, RR, HR, SBP, DBP).
- Record body weight (used to calculate IGSC 20% dosage).

- Predose blood sample for IgG trough level.
- Urine qualitative pregnancy (β-HCG) test for women of childbearing potential (to be performed locally at the investigative site)
- Treatment-experienced subjects only: Predose LQI and TSMQ-9
- All subjects: Predose SF-12 (subjects ≥18 years [observer: subject]). Treatment-naïve subjects who are 6 to 17 years: SF-10 (observer: parent)
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

Following completion of predose baseline assessments, the subject will receive the first IGSC 20% dose (SC#1) in Treatment Period 1 (for treatment-experienced subjects) or first loading dose (for treatment-naïve subjects) at the investigator's site during the same visit.

- For treatment-experienced subjects: calculate IGSC 20% dosage (mg/kg) based on the subject's weight at baseline and prior (commercial) IgG replacement regimen documented at screening as described in Section 6.1 adjusted for the assigned dosing interval (equivalent weekly dose), and in the case of subjects entering on IVIG multiplying by the 1.37 DAF.
- For treatment-naïve subjects: calculate IGSC 20% dose based on weight at baseline (150 mg/kg). This will be the first loading dose of 5 consecutive daily loading infusions of IGSC 20%.
- For All subjects: train subjects/caregivers to administer IGSC 20% using an infusion SC pump.
- Document infusion start date/time and stop date/time, total volume infused, infusion rate for pump infusion and, if necessary, any infusion interruption with explanation.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).

- SC infusion diaries: SC/IgG infusion diaries will be provided to each subject at the Baseline Visit which may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF. All local infusion site reactions will be recorded in the subject's source documents and eCRF.

7.2.1.2.2 TREATMENT-NAÏVE SUBJECTS: TREATMENT PHASE VISITS FOR SC#2, SC#3, SC#4, SC#5 (WEEK 0, DAYS 2-5), AND ON WEEK 1 (DAY 8) FIRST MAINTENANCE DOSE SC#6

- Treatment-naïve subjects will receive loading doses SC#2 through SC#5 consisting of consecutive daily doses of IGSC 20% 150 mg/kg/day (Week 0, Days 2-5) in clinic (to assure complete delivery of the critical loading dose in inexperienced untreated subjects).
- At Week 1 (Day 8) only: Predose blood sample for IgG trough level

  Note: Regardless of clinic visit time window, trough samples must be drawn within 8 hours prior to dosing and occur on the same day.
- The first weekly maintenance dose (SC#6) of IGSC 20% (150 mg/kg) will be administered on Week 1 (Day 8) in clinic.
- At each visit, observe (or re-train) subjects/caregivers to self-administer IGSC 20% using an infusion SC pump.
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, infusion rate for pump infusion and, if necessary, any infusion interruption with explanation.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and CRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

7.2.1.2.3 TREATMENT-EXPERIENCED SUBJECTS: TREATMENT PERIOD 1 SC#2 AND SC#3 AND TREATMENT PERIOD 2 SC#2 AND SC#3 (INITIAL 3 DOSES UNDER MEDICAL SUPERVISION)

Note: Subjects demonstrating proficiency with the administration method at the first clinic visit as per the investigator's judgment may administer SC#2 of both treatment periods and SC#3 for Treatment Period 1 at home under the supervision of a healthcare provider (home health aide). The Week 20 visit (Treatment Period 2 SC#3) must be performed in clinic. Healthcare provider monitoring of SC#2 and SC#3 of each treatment period is required for subjects who were receiving IVIG treatment prior to study entry (naïve to SCIG administration), and is also recommended for subjects receiving SCIG treatment prior to study entry given transitions in method and frequency of administration. Note that increases in pump infusion rates (eg, stepped escalation in pump infusion rate during an infusion) must be performed at a clinic visit.

- Observe (or re-train) subjects/caregivers to self-administer IGSC 20% using an infusion SC pump.
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, infusion rate for pump infusion and, if necessary, any infusion interruption with explanation.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

7.2.1.2.4 TREATMENT-NAÏVE SUBJECTS: TREATMENT PHASE VISITS FOR WEEK 2±2 DAYS, WEEK 6±2 DAYS, WEEK 10±2 DAYS

- Predose blood sample for IgG trough level. Note: Trough samples must be drawn within 8 hours prior to dosing and occur on the same day.
- At Week 2 (±2 days), if the Week 1 (Day 8) IgG trough level is ≤500 mg/dL, then the subject must discontinue the study (Section 5.3.2). If the IgG trough level is >500 mg/dL and <700 mg/dL, adjust the IGSC 20% dose as described in Section 4.1.2.2.
- At Week 6 (±2 days), if the Week 4 IgG trough level is <700 mg/dL, dose adjustment of IGSC 20% may be made at the investigator's discretion (see Appendix 8 and Section 4.1.2.2).
- At each visit observe (or re-train) subjects/caregivers to self-administer IGSC 20% using an infusion SC pump at a weekly maintenance dose of 150 mg/kg or calculated dose according to Section 4.1.2.2 if dose adjustment was required.
- Document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, infusion rate for pump infusion and, if necessary, any infusion interruption with explanation.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and CRF that this

is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

7.2.1.2.5 TREATMENT PERIOD 1 WEEK 4 (±2 DAYS), TREATMENT PERIOD 2 WEEK 20 (±2 DAYS)) FOR TREATMENT-EXPERIENCED SUBJECTS AND CORRESPONDING TREATMENT PHASE WEEK 4 (±2 DAYS) AND WEEK 20 (±2 DAYS) FOR TREATMENT-NAÏVE SUBJECTS

- Vital signs (T, RR, HR, SBP, DBP)
- Predose blood sample for IgG trough level. Note: Trough samples must be drawn within 8 hours prior to dosing and occur on the same day.
- Treatment-naïve subjects: At Week 4 (±2 days), review IgG trough level drawn at Week 2. If this IgG trough level is <700 mg/dL, dose adjustment of IGSC 20% may be made at the investigator's discretion (see Appendix 8 and Section 4.1.2.2).
- Observe (or re-train) subjects/caregivers to self-administer IGSC 20% using an infusion SC pump.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment (see Section 7.2.1.2.1 for details).

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administered with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

7.2.1.2.6 TREATMENT PERIOD 1 WEEK 8 (±2 DAYS), TREATMENT PERIOD 2 WEEK 24 (±2 DAYS) FOR TREATMENT-EXPERIENCED SUBJECTS AND CORRESPONDING TREATMENT PHASE WEEK 8 (±2 DAYS) AND WEEK 24 (±2 DAYS) FOR TREATMENT-NAÏVE SUBJECTS

- Abbreviated physical examination
- Vital signs (T, RR, HR, SBP, DBP)
- Body weight (used to calculate IGSC 20% dosage)
- Predose blood sample for IgG trough level. Note: Trough samples must be drawn within 8 hours prior to dosing and occur on the same day.
- Predose blood and urine samples (see Section 7.2.2)
  - Hematology: Hemoglobin, hematocrit, platelets, RBC count, WBC count with differential, ARC
  - Clinical chemistry: Sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, TB, indirect bilirubin
  - Haptoglobin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Blood sample for predose central laboratory DAT and serum/plasma free hemoglobin assessments
- Treatment-naïve subjects: The Investigator should review the IgG trough level drawn at Week 6 at or before the Week 8 (±2 days) visit. If it is <700 mg/dL, then the subject must discontinue study (see Section 5.3.2).
- Observe (or re-train) subjects/caregivers to self-administer IGSC 20% using an infusion SC pump.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local

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

- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example acute, sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.
- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

7.2.1.2.7 TREATMENT PERIOD 1 WEEK 12 (±1 DAY); TREATMENT PERIOD 2 WEEK 28 (±1 DAY) FOR TREATMENT-EXPERIENCED SUBJECTS AND CORRESPONDING TREATMENT PHASE WEEK 12 (±2 DAYS) AND WEEK 28 (±2 DAYS) FOR TREATMENT-NAÏVE SUBJECTS

- Vital signs (T, RR, HR, SBP, DBP)
- Predose blood sample for IgG trough level. Note: Trough samples must be drawn within 8 hours prior to dosing and occur on the same day.
- Observe (or re-train) all subjects/caregivers to self-administer IGSC 20% during this visit using an infusion SC pump.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.

- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.
- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

7.2.1.2.8 TREATMENT-EXPERIENCED SUBJECTS: TREATMENT PERIOD 1 WEEK 14 (±1 DAY); TREATMENT PERIOD 2 WEEK 30 (±1 DAY) – START OF PHARMACOKINETIC PROFILING

- Predose blood sample for serial PK IgG trough level (within 0.5 hour of infusion start). Note: this sample is the same as the predose serial PK sample, as described below.
- Observe (or re-train) all subjects/caregivers to self-administer IGSC 20% during this visit using an infusion SC pump.
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this

is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

PK samples for PK profiling will commence at Week 14 (Treatment Period 1) and Week 30 (Treatment Period 2) for all treatment-experienced subjects.

- Blood samples for Week 14 Serial PK assessments are at the following time points:
  - Prior to the Week 14 IGSC 20% infusion (within 0.5 hour of infusion start [predose]). Note: This sample also serves as the trough IgG measurement at Week 14.
  - 1 day (± 4 hours) post end of Week 14 infusion
  - 3 days (± 4 hours) post end of Week 14 infusion
  - 4 days (± 4 hours) post end of Week 14 infusion
  - 5 days (± 8 hours) post end of Week 14 infusion
  - 7 days (+1 day) post end of Week 14 infusion (which is equivalent to Week 15). Note: This sample must be drawn prior to the Week 15 infusion.

  NOTE: To facilitate the collection of serial PK blood samples, samples for IgG concentration taken at 1, 3, 4, 5, and 7 days following completion of Week 14 IGSC 20% infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (eg, subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

- Blood samples for Week 30 Serial PK assessments are at the following time points:
  - Prior to the Week 30 IGSC 20% infusion (within 0.5 hour of infusion start [predose]). Note: This sample also serves as the trough total IgG measurement at Week 30.
  - 1 day (± 4 hours) post end of Week 30 infusion
  - 3 days (± 4 hours) post end of Week 30 infusion
  - 4 days (± 4 hours) post end of Week 30 infusion
  - 7 days (±1 day) post end of Week 30 infusion (which is equivalent to Week 31)
  - 11 days (± 1 day) post end of Week 30 infusion
  - 14 days (+1 day) post end of Week 30 infusion Note: This sample will be drawn at the Week 32 visit and must be drawn prior to the Week 32 infusion. Additionally, this sample will serve as the trough IgG measurement at Week 32.

NOTE: To facilitate the collection of serial PK blood samples, samples for IgG concentration taken at 1, 3, 4, 7, and 11 days following completion of Week 30 IGSC 20% infusion may be drawn at the study site, or, if deemed appropriate, at an alternate site (eg, subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

7.2.1.2.9 WEEK 16 (+1 DAY): FOR TREATMENT-EXPERIENCED SUBJECTS - TRANSITION FROM TREATMENT PERIOD 1 WEEKLY IGSC 20% TO TREATMENT PERIOD 2 BIWEEKLY IGSC 20% (EVERY 2 WEEKS) (SC#1); WEEK 16 (±2 DAYS) FOR TREATMENT-NAÏVE SUBJECTS - REGULAR MAINTENANCE VISIT

- Abbreviated physical exam
- Vital signs (T, RR, HR, SBP, DBP)
- Body weight (used to calculate IGSC 20% dosage)
- Predose blood sample for IgG trough level. Note: Trough samples must be drawn within 8 hours prior to dosing. The trough sample collection MUST precede dosing and occur on the same day.
- Predose blood and urine samples(see Section 7.2.2)
  - Hematology: Hemoglobin, hematocrit, platelets, RBC count, WBC count with differential, ARC
  - Clinical chemistry: Sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, TB, indirect bilirubin
  - Haptoglobin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Blood sample for predose central laboratory DAT and serum/plasma free hemoglobin assessments
- Treatment-experienced subjects only: Predose LQI and TSMQ-9
- All subjects: SF-12 (subjects ≥18 years [observer: subject]). Treatment-naïve subjects who are 6 to 17 years: SF-10 (observer: parent)
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

- Record concomitant medications assessments (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administration with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.
- For treatment-naïve subjects, observe (or re-train) subjects/caregivers to self-administer IGSC 20% during this visit using an infusion SC pump (dose and frequency remain static at 150 mg/kg/week)

Following completion of predose assessments, the transition for treatment-experienced subjects will occur from weekly IGSC 20% to biweekly IGSC 20% with the first biweekly dose administered at Week 16 (twice the weekly mg/kg dose).

- For treatment-experienced subjects only, train subjects/caregivers to transition to biweekly (every 2 weeks) IGSC 20% dosing using an infusion SC pump.
- For all subjects, document total infusion volume prepared, infusion start date/time and stop date/time, total volume infused, and, if necessary, any infusion interruption with explanation.

7.2.1.2.10 WEEK 32 (+1 DAY) FOR TREATMENT-EXPERIENCED SUBJECTS OR WEEK 32 (±2 DAYS) FOR TREATMENT-NAÏVE SUBJECTS /EARLY TERMINATION VISIT (ALL SUBJECTS)

- Abbreviated physical examination
- Vital signs (T, RR, HR, SBP, DBP)
- Pre-dose blood sample for IgG trough level sample. Note: Trough samples must be drawn within 8 hours prior to dosing. Note: For treatment-experienced subjects, this is the same as the 14 days post end of Week 30 infusion serial PK sample (see Section 7.2.1.2.8).
- Blood and urine samples(see Section 7.2.2)

  - Hematology: Hemoglobin, hematocrit, platelets, RBC count, WBC count with differential, ARC
  - Clinical chemistry: Sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, TB, indirect bilirubin
  - Haptoglobin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)
- Blood sample for predose central laboratory DAT and serum/plasma free hemoglobin assessments
- Treatment-experienced subjects only: Predose LQI and TSMQ-9
- All subjects: SF-12 (subjects ≥18 years [observer: subject]). Treatment-naïve subjects who are 6-17 years: SF-10 (observer: parent).
- Observe subjects/caregivers self-administer final IGSC 20% during this visit using an infusion SC pump (all subjects).
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.
- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- Review SC infusion diary and infusion details from IGSC 20% administered with subjects/caregivers. Diaries may be used to record items including but not limited to: local infusion site reactions, antibiotics (prophylactic and therapeutic), and details of IgG drug administration (location and number of sites, date/clock time of start and end of infusion, dose/volume, duration and rates of infusion). Diaries will be collected at clinic visits, filed as source documentation, and entered into the eCRF.

- After all study related assessments for Week 32 are complete, execute plans to start commercial IgG replacement regimen per investigator discretion.

Note for Early Discontinuations: Subjects who receive any amount of IP and discontinue early from the study will be requested to return for the Early Termination Visit prior to starting commercial IgG treatment. The assessments (for early terminations) will be the same as those performed at the Week 32 visit except that IP dosing will be at the discretion of the investigator for subjects prematurely discontinuing. IP dosing should be consistent with the IGSC 20% dosing interval in effect when the subject withdrew from the study (eg, one week after last dose if receiving weekly IP).

7.2.1.2.11 WEEK 33 (±1 DAY) FINAL FOLLOW-UP VISIT

- Abbreviated physical examination
- Vital signs (T, RR, HR, SBP, DBP)
- Record AEs including infusion reactions and clinical observation of signs and symptoms suggestive of any significant disease or condition (eg, thrombosis, anemia, etc.). All local infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Record any SBIs (defined in Appendix 4) and hospitalizations due to infections. The evaluations performed to fulfill diagnostic categories specified in Appendix 4 and the results must be recorded in the subject's source documents and eCRF.
- Record non-serious infections (by category) and antibiotic treatment.

  These include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc., with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.
- Record concomitant medications (for antibiotics, distinguish between prophylactic use and use for treatment of an episode of infection).
- .

7.2.2 Description of Laboratory Tests and Procedures

Detailed descriptions of laboratory test procedures are located in the study Laboratory Manual. Table 7-1 provides an example summary of the laboratory tests conducted for this study.

Table 7-1 Name, Description, and Location of Laboratory Tests and Procedures

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

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

7.2.3 Immunoglobulin G Assessments

All subjects will have trough (predose) total IgG measurements performed at each clinical visit prior to IGSC 20% dosing except SC#2 and SC#3 of each treatment period, and for treatment-naïve subjects there is no trough measurement before daily loading doses SC#2 through SC#5. These measurements are an important measurement to ensure that adequate IgG concentration levels are maintained (not less than 500 mg/dL) to avoid serious infection. Dose adjustments will be allowed for treatment-experienced subjects before Week 9 to ensure sufficient IgG concentration is maintained. Samples will be retained until all analyses in support of the study specified in Section 7.2.1.2 are complete.

For treatment-experienced subjects, serial total IgG samples will be collected from Week 14 to Week 15 in Treatment Period 1, and from Week 30 to Week 32 in Treatment Period 2. Detailed sampling schedules are described in Section 7.2.1.2.8.

7.2.4 Assessment and Recording of Infections

Serious and non-serious infections (by category) will be recorded, including infections of any kind (eg, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.), which will be recorded with the investigator indicating affirmatively in the subject's source documents and eCRF that this is an infection (verbatim term, delineating nature of infection). Also record 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 (eg, rapid streptococcal antigen test). The specific evaluations performed to validate infections and the results must be recorded in the subject's source documents and eCRF.

8 ASSESSMENT OF SAFETY

8.1 Safety Variables

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

- Adverse events (AEs) including serious AEs (SAEs), suspected adverse drug reactions (suspected ADRs, potentially related AEs), and ARs. All infusion site reactions will be recorded in the subject's source documents and eCRF. The subset of local infusion site reactions where the symptoms/signs lead to infusion interruption or discontinuation, require concomitant medication, or have an impact on the general condition of the subject as judged by the investigator will be considered as AEs.
- Vital signs during clinic visits (SBP and DBP, HR, T, RR)
- Physical assessments: physical examinations will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded
- Laboratory assessments including chemistry, hematology, urinalysis, haptoglobin, serum/plasma free hemoglobin (central laboratory), and DAT (central laboratory) (see Table 7-1)

8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Physical assessments, safety laboratory parameters, vital signs, assessment and recording of infections, and AEs will be performed for all subjects during the Screening Visit, Treatment Period 1 and Treatment Period 2 for treatment-experienced subjects or Treatment Phase for treatment-naïve subjects inclusive of the Week 32/Early Termination Visit and Final Follow-up Visit (Week 33) as detailed in Section 7.2.1, Appendix 1, and Appendix 2.

8.2.1 Adverse Events

Adverse events (includes suspected ADRs) occurring at any time between signing of the subject's ICF and the last day of the subject's participation in the clinical trial will be reported and recorded in the subject's medical records and eCRF entry.

It is investigator's responsibility to ensure that all AEs are appropriately recorded.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

8.2.2 Clinical Laboratory Evaluations

All clinical laboratory data will be listed for each clinical trial subject. Results will be recorded in source documents and on the subject's eCRF.

The investigator will be required to classify laboratory results out of the normal range reported by the laboratory as clinically significant or not according to his/her judgment.

Laboratory results out of the normal range judged by the investigator as clinically significant will be considered AEs. If a specific diagnosis is made based on the clinically significant laboratory values, the diagnosis will become the AE.

8.2.3 Vital Signs

Vital signs will be measured by a medically certified individual or a nurse according to his/her standard clinical practice. Vital signs will be measured at the following visits: screening, baseline, Weeks 4, 8, 12, 16, 20, 24, 28, and 32. The following vital signs will be assessed:

- Temperature
- Blood pressure: SBP and DBP
- Heart rate
- Respiration rate

Vital signs will be routinely monitored by the study staff as detailed in Appendix 1 and Appendix 2. The investigator will be required to classify vital signs abnormalities as clinically significant or not according to his/her judgment. Results will be recorded in source documents and on the subject's eCRF. Vital signs abnormalities judged by the investigator as clinically significant will be considered AEs. If a specific diagnosis is made based on the clinically significant vital sign values, the diagnosis will become the AE.

8.2.4 Physical Examinations

A full physical exam will be performed (excluding breast and genitourinary exam) at screening, and an abbreviated physical exam will be performed at Weeks 8, 16, 24, and 32 (Early Termination Visit) targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and inspection of previous IGSC 20% administration sites. Results will be recorded in source documents and on the subject's eCRF. Physical examination abnormalities judged by the investigator as clinically significant will be considered an AE.

8.3 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Event and Intercurrent Illnesses

8.3.1 Warnings/Precautions

For complete information on IGSC 20% refer to the Xembify Package Insert.

8.3.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to the IP.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

8.3.3 Adverse Event Definitions

8.3.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any medical or surgical procedures should not be regarded as AEs. The condition that led to the procedure is the AE.

A pre-existing disease, condition, or laboratory abnormality that does not worsen from baseline should not be considered as an AE.

8.3.3.2 Suspected Adverse Drug Reactions/Adverse Reactions

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility; that is, the relationship cannot be ruled out.

In the framework of this study, a suspected ADR with a causal relationship of "definite" will be labeled as an AR; thus, ARs are a subset of suspected ADRs.

An AE will be considered a suspected ADR when either the sponsor or an Investigator considers that the drug might have caused the AE.

8.3.4 Assessment of Causality of Adverse Event

The investigator is required to provide a causality assessment for each AE reported to the sponsor. The assessment of the causal relationship of an AE to the administration of IP must be a clinical decision based on all available information at the time of the completion of the CRF/eCRF and/or SAE form. The sponsor will consider the investigator's causality assessment and also provide its own assessment.

Causal relationship to the IP will be established according to medical judgment on whether there is a **reasonable possibility of a causal relationship between the AE and the IP administration**:

The investigator must determine and classify the AE causality according to the following categories:

Unrelated/Not related: there is not a reasonable possibility of causal relationship between the AE and the IP.

Possibly related: there is evidence to suggest a causal relationship between the IP and the AE.

Definitely related: there is a reason to conclude that the IP caused the AE.

Criteria to assess the causal relationship should take into account the following conditions: 1) a plausible temporal sequence from the IP administration to the AE onset; 2) whether the event follows a known response pattern to the suspected treatment; 3) whether the AE could be reasonably explained by the subject's clinical state, comorbidities, or concomitant medications, as well as 4) the occurrence of improvement on stopping/reducing the treatment (positive dechallenge) and/or reappearance of the event on repeated exposure (positive rechallenge).

For expedited safety reporting purposes, AEs assessed as either "possibly related" or "definitely related" will be considered POTENTIALLY RELATED or just RELATED.

For any subject, all AEs that occur at any time from the beginning of IP administration until the final follow-up visit of the clinical trial will be considered treatment-emergent AEs (TEAEs).

8.3.5 Severity of Adverse Event or Suspected Adverse Drug Reaction

Adverse events and suspected ADRs will be classified depending on their severity according to the following definitions:

Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.

Moderate: an AE that interferes with the subject's normal activities.

Severe: an AE that prevents the subject from performing their normal activities.

Adverse events and suspected ADR severity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate, or severe but not necessarily serious in all these cases.

The investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account current criteria included in this section.

8.3.6 Expectedness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "unexpected" if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness shall be determined by the sponsor according to the reference document (ie, Xembify Package Insert) for any serious ADRs (potentially related SAEs) for expedited safety reporting purposes.

8.3.7 Seriousness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization*
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above).

  *Hospitalization is to be considered only hospital admission (including emergency room stay) for equal or more than 24 hours. The following hospitalizations should not be reported as SAEs:

Hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol or as part of a routine procedure followed by the center.

Admissions not associated with an AE (eg, social hospitalization for the purpose of respite care, survey visits, or annual physicals).

Elective or pre-planned hospitalizations for a pre-existing condition that had not worsened from baseline (eg, elective or scheduled surgery arranged prior to start of the study).

This definition permits either the sponsor or the investigator to decide whether an event is "serious." If either the sponsor or the investigator believes that the event is serious, the event must be considered "serious" and evaluated by the sponsor for expedited reporting.

8.3.8 Adverse Event Documentation

All AEs and SAEs occurring after the subject has **signed the ICF through the Final Follow-up Visit (ie, end of study)** must be fully recorded in the subject's eCRF, and SAE report form (if serious) as well as in the medical record. If no AE has occurred during the study period, this should also be indicated in the eCRF.

It is the responsibility of the investigator to ensure that AEs are appropriately recorded.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded in the subject's source documentation and AE eCRF:

- The verbatim term (a diagnosis is preferred)
- Date/time of onset
- Date/time of resolution
- Severity (mild, moderate, severe)
- Causality (unrelated, possibly related, definitely related)*
- Seriousness (yes, no)
- Action taken (with regard to IP)
- Other action (to treat the event)
- Outcome and sequel (follow-up on AE)

*Causality assessment will be made only when the AE occurs after the subject has initiated at least one infusion of the IP. An AE occurring before subject's exposure to IP will be always labeled as "unrelated".

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured in the eCRF.

In addition to the investigator's own description of the AEs, each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA®).

For example, a laboratory test abnormality considered clinically significant, eg, causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged clinically significant in the context of the subject's medical history by the investigator, should be reported as an AE. Each event must be described in detail along with start and stop dates, severity, relationship to IP, action taken and outcome. Each

event must be adequately supported by documentation as it appears in the subject's medical or case file.

8.3.9 Reporting of Serious Adverse Events

8.3.9.1 Reporting of Serious Adverse Events

Any SAE (see Section 8.3.7) that occurs after **signing the study ICF through the Final Follow-up Visit (ie, end of study)** must be expeditiously reported whether or not considered attributable to the IP. Each SAE must be fully recorded in the subject's eCRF and SAE Report Form. In addition, any SAE that occurs within 30 days after the last dose of the IP or after study completion due to early termination should be reported only to Grifols Global Pharmacovigilance if the investigator becomes aware of the event and feels that it is related to the use of IP.

Serious adverse events will be reported using the designated SAE Report Form. When the investigator becomes aware of a SAE, she/he must submit a completed, signed and dated SAE Report Form (in English) **within 24 hours** to the sponsor by email/fax. The date of this SAE discovery by the site staff should be documented in the source documents (ie, medical records).

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow-up, and for the outcome, must also be supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the SAE Report Form. In addition, the sponsor or contract research organization may request additional information and/or reports.

All SAE Report Forms must be reported to:

Grifols Global Pharmacovigilance
Email: [redacted]
FAX (back-up only): [redacted] (US/Canada)
[redacted] (International)

When required, and according to local law and regulations, SAEs must be reported to the IRB/EC and regulatory authorities. Copies of the investigator's reports must be sent to the sponsor.

8.3.9.2 Reporting Pregnancy

While pregnancy itself is not a true "AE," pregnancy occurring in a clinical study must be followed, to collect information regarding the experiences of gestation and pregnancy with IP exposure. Any female subject who becomes pregnant during the study will be discontinued from IP treatment. The investigator must report any pregnancy that occurs in a female study subject subsequent to first exposure to the IP until 30 days after the last dose of IP.

A pregnancy will be not considered an AE, unless a relation to the IP is suspected. In any case, a *Pregnancy Report Form* must be completed and sent as soon as possible to the sponsor. A copy of the form should be filed at the study site for follow-up until the end of the pregnancy. Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect observed in the child must be reported as an SAE within 24 hours of the investigator or study personnel's first knowledge.

Please use the email address or fax numbers (back up only) in Section 8.3.9.1 for reporting pregnancy.

8.4 Type and Duration of the Follow-Up of Subjects after Adverse Events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected and the investigator decides that no further follow-up is necessary.

Any SAE that occurs after the end of the clinical study or after study completion due to early termination will not be actively collected. However, if such cases are reported by an investigator as related to the study treatment, they will be considered for expedited purposes.

Pregnancy exposure that results in AE/SAEs should be followed by the investigator until delivery or to the end of pregnancy.

9 STATISTICS

9.1 Statistical Methods

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

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

Data handling and evaluation procedures will be described in the Statistical Analysis Plan (SAP).

9.1.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized separately for treatment-experienced subjects and for treatment-naïve subjects. For quantitative variables, mean, SD, median, minimum, and maximum will be provided. For qualitative variables, the frequency and percentage will be provided.

9.1.2 Pharmacokinetic and Efficacy Analysis

9.1.2.1 Primary Pharmacokinetic Analysis (Treatment-Experienced Subjects)

The primary PK analysis will be based on the PK population. Serial total IgG concentrations will be summarized by treatment group (weekly and biweekly IGSC 20% dosing) and the scheduled/nominal sampling timepoint. Individual, mean, and median total IgG concentration vs. time curves will be plotted. Steady-state PK parameters of total IgG, including AUC, C_{max}, and t_{max} will be determined by noncompartmental PK methods, as data permit. The PK parameters will be determined for weekly dosing following the Week 14 infusion and for biweekly dosing following the Week 30 infusion. PK parameters will be listed and summarized by treatment using descriptive statistics including n, mean, SD, percent coefficient of variation (%CV), median, minimum, and maximum. Geometric mean and 90% confidence interval (CI) for the geometric mean will also be calculated for all PK parameters (except t_{max}).

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

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

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

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

The null hypothesis for the non-inferiority testing is:

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

The alternative hypothesis is:

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

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

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

9.1.2.2 Secondary Analyses

The IgG population will be used for the analyses of trough total IgG concentrations. The analyses of additional PK parameters of total IgG (C_{max} and t_{max}) will be based on the PK population. The Efficacy Evaluable population will be used for the analyses of all other secondary endpoints related to infection.

The secondary variable of steady-state mean trough concentration of total IgG in treatment-experienced subjects will be analyzed as follows. For each treatment period, all pre-infusion total IgG concentrations obtained prior to and at the 12th week of IGSC 20% dosing will be evaluated to determine if an approximate steady-state condition has been achieved by the 12th week of the treatment period. In Treatment Period 1, the steady-state mean trough concentration of total IgG following SC administrated IGSC 20% will be determined as the average value of IgG trough measurements obtained at Weeks 12, 14, and 16 during weekly dosing. In Treatment Period 2, the steady-state mean trough concentration of total IgG following SC administrated IGSC 20% will be determined as the average value of the IgG trough measurements obtained at Weeks 28, 30, and 32 during biweekly dosing. Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG by treatment group. The steady-state mean trough will also be analyzed by a mixed-effect model similar to that for the primary PK analysis (see Section 9.1.2.1).

Descriptive statistics will be used to summarize the following secondary variables related to total IgG: 1) trough concentrations of total IgG at individual time points for treatment-experienced subjects 2) other steady-state PK parameters (C_{max} and t_{max}) of total IgG for treatment-experienced subjects, and 3) mean and individual trough total IgG values for treatment-naïve subjects.

Secondary variables related to infection will be summarized descriptively for all subjects (treatment-experienced and treatment-naïve subjects will be analyzed separately). The number and proportion of subjects having SBIs, infections, days on antibiotics, and hospitalizations due to infection will be calculated and summarized. Furthermore, the total number of events or days and corresponding annualized rate per subject of SBIs, infections, days on antibiotics, and hospitalizations due to infection will be calculated and summarized. Finally, the rate of events or days per person per year will be analyzed using the generalized linear model procedure for Poisson regression.

9.1.3 Exploratory Analysis

Exploratory analyses will be based on the Efficacy Evaluable population.

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

For treatment-naïve subjects, analysis of SF-12/SF-10 will compare the subject's perception of state of health from study entry (pre-SC#1 infusion) to Treatment phase Week 16 and to Treatment phase Week 32.

9.1.4 Safety Analysis

The safety analyses will be based on the safety population.

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

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

9.1.4.1 Adverse Events

Adverse events will be coded and classified using MedDRA terms (system organ class and preferred terms).

When the causal relationship of an AE is classified by the investigator as definitely or possibly related, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definitely related" will be defined as an AR. The sponsor will consider the investigator's causality assessment and also provide its own assessment. If there is any disagreement in the causality assessment between the investigator and the sponsor, a separate summary of suspected ADRs/ARs will be provided.

For summary purposes, AEs will be classified as TEAEs or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of

study treatment. A TEAE will be defined as an AE which occurs between the start of study treatment and the final follow-up visit of the clinical study. A non-TEAE will be defined as an AE which occurs prior to the start of study treatment. Non-TEAEs and TEAEs will be summarized separately.

In addition, TEAEs, suspected ADRs, and ARs will be summarized by treatment group, system organ class, preferred term, causal-relationship, severity, and seriousness (serious vs non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe AE or the AE with the strongest causal relationship. Summaries will also be provided for the total number of events and the rate per infusion. Any suspected ADRs representing sentinel adverse effects such as thromboembolic events may be separately summarized should they occur.

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

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

9.1.4.2 Clinical Laboratory Values

All clinical laboratory data will be listed for each subject and summarized by treatment group. The original value and the change from baseline will be summarized for numeric results and frequency/percentage will be summarized for qualitative results. For laboratory tests with normal ranges, out of normal range values will be flagged and shift tables will be provided.

The investigator will be required to classify out of the normal range laboratory results reported by the laboratory as clinically significant or not according to his/her judgment.

Out of the normal range laboratory results judged by the investigator as clinically significant in the context of the subject's medical history will be considered AEs.

9.1.4.3 Vital Signs

Vital signs (T, RR, HR, SBP, and DBP) will be listed for each subject and summarized by treatment group. The original value and the change from baseline will be summarized for numeric results.

Clinically significant vital signs abnormalities will be presented as AEs. Clinical relevance will be based on the investigator's judgment.

9.1.4.4 Physical Assessment

Physical assessment findings (normal or abnormal) will be listed for each subject and summarized by treatment group. Any clinically significant abnormalities developed by a subject during the clinical study and not already present at baseline will be reported as AEs. Clinical relevance will be based on the investigator's judgement.

9.2 Determination of Sample Size

The planned number of treatment-experienced subjects is 25 subjects dosed with IGSC 20% to ensure at least 20 subjects provide the primary PK endpoint ($AUC_{0-\tau}$) estimates in both treatment periods, assuming a drop-out rate of 20%. This sample size will provide at least 90% power to demonstrate non-inferiority at a 1-sided alpha level of 0.05, assuming the %CV of AUC is no greater than 20% and the true ratio between the 2 treatment groups is 1.0. In addition, this sample size will provide clinical experience with up to 400 weekly infusions (16 infusions × 25 subjects) and 225 biweekly infusions (9 infusions × 25 subjects).

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

9.3 Criteria for Termination of the Study

The sponsor or its representative may terminate the study at any time for scientific or corporate reasons. See Section 4.5.2. for details related to early termination of the treatment - naive cohort from participation in the study.

If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority (ies) when required.

9.4 Procedure for Accounting for Missing, Unused, and Spurious Data

The procedure for accounting for missing, unused, and spurious data (if applicable) will be detailed in the SAP.

9.5 Reporting Deviation(s) from the Statistical Analysis Plan

The detailed statistical analysis methodologies will be documented in the SAP. If there are any deviations from the originally planned analyses in the SAP, they will be fully described and justified in the protocol amendment(s) and/or final CSR.

9.6 Subject Population(s) for Analysis

Safety Population

The safety population will include all subjects (including both treatment-experienced and treatment-naïve subjects) who received any amount of IGSC 20% and will be used for safety analysis.

Efficacy Evaluable Population

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

PK Population

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

IgG Population

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

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data will be recorded and kept current in the subject's source documents and eCRFs by the study site personnel directly responsible for the information and reviewed for completeness by the monitor. Grifols personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the subject's source documents and eCRFs for consistency and to verify adherence to the protocol, and the completeness, consistency, and accuracy of data entered. "Source documentation" includes individual subject files, separate from the eCRFs, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, IP dispensing logs, and other notes as appropriate. The investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with ICH GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, ICH GCP and legal aspects. The on-site verification of the eCRF for completeness and clarity will include cross checking with source documents, and clarification of administrative matters. Query verification of data will be described in the Data Management Plan.

Representatives of regulatory authorities or of Grifols may conduct inspections or audits of the investigator study site. If the investigator is notified of an audit or inspection by a regulatory authority, the investigator agrees to notify the Grifols representative (eg, clinical assessment monitor, program manager, program leader) immediately. The investigator agrees to provide to representatives of a regulatory agency or Grifols access to records, facilities, and personnel for the effective conduct of an inspection or audit.

12 ETHICS

12.1 Institutional Review Board/Ethics Committee

Documented approval from appropriate IRBs/ECs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRBs/ECs approval must be obtained and also forwarded to the sponsor. The IRBs/ECs must supply to the sponsor, upon request, a list of the IRBs/ECs members involved in the vote and a statement to confirm that the IRBs/ECs is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

12.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the sponsor representatives and/or an inspection by regulatory authority representatives at any time. The investigator must agree to the audit or inspection of study-related records by the sponsor representatives and/or regulatory authority representatives, and must allow direct access to source documents to the sponsor and/or regulatory authority representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/EC/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/EC/sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

No medical waivers for protocol inclusion/exclusion criteria will be allowed by the sponsor. If there is a need for a change to the protocol inclusion/exclusion criteria is identified, the protocol will be amended to include such changes. The protocol amendment will be submitted to the regulatory authority and/or IRB/EC as applicable per regulations, which allows implementation of the revised inclusion/exclusion criteria in the study.

12.3 Regulatory Authority Approvals/Authorizations

Regulatory authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

12.4 Subject Information and Consent

Subject information and ICF will be provided to investigator sites. Prior to the beginning of the study, the investigator must have the IRB/EC written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the IRB/EC together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to sponsor by the investigator site.

Written ICF must be obtained before any study specific procedure takes place. Participation in the study and date of ICF given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF will be provided to the subject or subject's authorized representative.

12.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject code number will be recorded in the eCRF, and if the subject's name appears on any other document (eg, pathologist report), it must be redacted before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the sponsor, IRB/EC, or regulatory authorities may inspect their medical records and personal health information to verify the information collected, and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Handling

The study data will be recorded and kept current in the eCRF by the site study personnel directly responsible for the information. Entries made in the eCRF must be verifiable against source documents, or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered the source data. The data in the eCRF will be monitored at the site by Grifols representatives at regular intervals and reviewed for completeness and compared with the source documents. Examples of acceptable source documents include individual subject medical records, prospective information gathered on source documentation worksheets, lab reports and other diagnostics pertinent to this study which are separate from the eCRFs. The listing of types of source documents will be filed in the Trial Master File.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE report form. The SAE form must be kept in site records with a copy provided to the designated person as detailed in the study file.

13.2 Record Retention

At study completion, all study data will be transferred to Grifols according to ICH GCP guidelines, local laws, regulations, and Grifols requirements. The study file and all source data should be retained until notification is given by the sponsor for destruction.

An investigator is required by ICH GCP guidelines to retain the study files. If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (eg, other investigator). Grifols must be notified in writing of the person responsible for record retention and the notification will be retained in the sponsor study file and the investigator site file.

14 FINANCING AND INSURANCE

In the event of subject injury as a direct result of either administration of IP or any non-standard of care study procedure, sponsor will pay for the costs of treatment, provided the subject has followed the instructions given by the study doctor and the illness or injury is not due to the natural progression of any conditions existing before the subject participated in the study. Financial compensation for such things as lost wages, disability, or discomfort due to any research-related injury is not available.

Sponsor shall maintain comprehensive general liability insurance or self-insurance in amounts adequate to cover any damage, demand, claim, loss or liability caused or incurred by sponsor, or as otherwise required by applicable laws and/or regulations.

15 PUBLICATION POLICY

Institution and the investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all

appropriates sites. If such a multi-center publication is not submitted within twelve (12) months after conclusion of the study at all sites or after Grifols confirms there will be no joint, multi-center publication, then institution and/or investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or investigator shall furnish Grifols with a copy of any proposed publication at least thirty (30) days in advance of the date of submission for publication.
- Within said thirty (30) day period, Grifols shall:

  Review such proposed publication for Confidential Information (other than Study results) and for subject information subject to the Health Insurance Portability and Accountability Act of 1996 and other applicable privacy laws;

  Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;

  By written notice to the investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains Confidential Information, protected subject information, or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and

  By written request, Grifols may delay proposed publications up to sixty (60) days to allow Grifols to protect its interests in Grifols Inventions described in such publications.
- Institution and/or investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

16 REFERENCES

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17 APPENDICES

Appendix 1 Schedule of Study Procedures: Treatment-Experienced Subjects

Period	Screen (up to 5 weeks)		Baseline	Treatment Period 1 Clinic Visits Ambulatory Pump: Weekly Dosing All clinic visits must coincide with dosing days unless otherwise specified (eg serial PK sampling)						Treatment Period 2 Clinic Visits Ambulatory Pump: Every 2 Weeks (Biweekly) Dosing All clinic visits must coincide with dosing days unless otherwise specified (eg, serial PK sampling)								
Clinic Visits / **Procedures and Evaluation**	**All Subjects**	**IgG Trough #2[i]**	**Week 0 (Day 1) Pump SC#1[j]**	**Week 1±2 days SC#2 Week 2 Pump SC#3[k]**	**Week 4±2 days**	**Week 8±2 days**	**Week 12±1 day**	**Week 14±1 day**	**Serial PK Sampling Post Wk 14 Days 1, 3, 4, 5, 7 end of infusion**	**Week 16+1 day (Day 113) SC#1l**	**Week 18 SC#2[k]**	**Week 20±2 days SC#3[k]**	**Week 24±2 days**	**Week 28±1 day**	**Week 30±1 day**	**Serial PK Sampling Post Wk 30 Days 1, 3, 4, 7, 11 end of infusion**	**Week 32 +1 day/ Early Termination Visit**	**Week 33 ±1 day Final Follow-up**
Informed consent	X																	
Eligibility criteria	X		X															
Assign subject number	X																	
Medical history including PI type	X																	
Demographics	X																	
Full physical exam[a]	X																	
Abbreviated physical exam[b]						X				X			X				X	X
Vital signs[c]	X		X		X	X	X			X		X	X	X			X	X
Body weight[d]	X		X			X				X			X					
Height	X																	
Predose central laboratory (hematology, chemistry, haptoglobin, urinalysis)[e]	X					X				X			X				X	
Predose central lab DAT and serum/plasma free hemoglobin	X					X				X			X				X	
Pregnancy test[f]	X		X															
Predose IgG trough level[g]	X	X	X		X	X	X	X		X		X	X	X	X		X	

Period	Screen (up to 5 weeks)		Baseline	Treatment Period 1 Clinic Visits Ambulatory Pump: Weekly Dosing All clinic visits must coincide with dosing days unless otherwise specified (eg serial PK sampling)						Treatment Period 2 Clinic Visits Ambulatory Pump: Every 2 Weeks (Biweekly) Dosing All clinic visits must coincide with dosing days unless otherwise specified (eg, serial PK sampling)								
Clinic Visits Procedures and Evaluation	All Subjects	IgG Trough #2[i]	Week 0 (Day 1) Pump SC#1[j]	Week 1±2 days SC#2 Week 2 Pump SC#3[k]	Week 4±2 days	Week 8±2 days	Week 12±1 day	Week 14±1 day	Serial PK Sampling Post Wk 14 Days 1, 3, 4, 5, 7 end of infusion	Week 16+1 day (Day 113) SC#1l	Week 18 SC#2[k]	Week 20±2 days SC#3[k]	Week 24±2 days	Week 28±1 day	Week 30±1 day	Serial PK Sampling Post Wk 30 Days 1, 3, 4, 7, 11 end of infusion	Week 32 +1 day/ Early Termination Visit	Week 33 ±1 day Final Follow-up
LQI, TSQM-9, SF-12 (predose)			Pre-SC#1							X							X	
Observed IGSC 20% dosing *in clinic or by health professional*			X	X	X	X	X	X		X[l]	X	X	X	X	X		X[m]	
Serial PK sampling								X[n]--------- X[n]							X[o]----------X[o]			
SC infusion diary review			X	X	X	X	X	X		X	X	X	X	X	X		X	
AE assessments	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X
Assessments of SBIs and other infections[h]	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X
Concomitant medication	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X

[a] A full physical exam will be performed excluding breast and genitourinary exam.

[b] An abbreviated physical exam will be performed targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and inspection of previous injection sites.

[c] Vital signs (SBP, DBP, HR, T, and RR) will be measured prior to infusion.

[d] Body weight will be measured prior to infusion to determine the SC study drug dose.

[e] Laboratory assessments will be obtained prior to infusion of study drug at all specified visits. Laboratory testing includes Hematology: hemoglobin, hematocrit, platelets, RBC count, WBC count with differential, ARC. Chemistry: sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, TB, indirect bilirubin. Haptoglobin. Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal).

[f] Pregnancy testing will be performed for child-bearing potential females only (serum at Screening and local urine testing at Baseline). Pregnancy testing will be repeated at any time if pregnancy is suspected.

[g] In general trough samples must be drawn within 8 hours prior to dosing, however a shorter timeframe (within 0.5 hours of infusion start [predose]) applies to Serial PK sampling at Week 14 in Treatment Period 1, and Serial PK sampling at Week 30 in Treatment Period 2. Regardless of the clinical visit time window, the trough sample collection MUST precede dosing and occur on the same day.

[h] Record any SBIs, hospitalizations due to infections, and non-serious infections.

[i] Subjects on IVIG or HYQVIA only: An additional pre-baseline blood draw is required for subjects receiving commercial IVIG or HYQVIA in order to obtain 2 true IgG trough levels prior to commencing IGSC 20% treatment and should be drawn within 8 hours prior to the last IVIG or HYQVIA dose (trough sample collection must precede dosing and occur on the same day).

[j] If there are logistical issues for subjects entering the study who are receiving commercial IVIG or HYQVIA due to the schedule adjustment for IGSC 20% administration, the first SC#1 dose may be scheduled 7±2 days after last commercial IVIG or HYQVIA dose.

[k] Subjects demonstrating proficiency with the administration method at the first SC#1 clinic visit as per the investigator's judgment may administer SC#2 and SC#3 of each treatment period at home under the supervision of a healthcare provider (home health aide). Healthcare provider monitoring of SC#2 and SC#3 of each treatment period is required for subjects who were receiving IVIG treatment prior to study entry (naïve to SCIG administration), and is also recommended for subjects receiving SCIG treatment prior to study entry if the method or frequency of administration is different from that of this study. Note that increases in pump infusion rates, eg, stepped escalation in pump infusion rate during an infusion, must be performed at a clinic visit.

[l] First biweekly IGSC 20% dose (transition from weekly IGSC 20% dosing) at Week 16 visit will be after Week 16 predose assessments are complete (for Treatment Period 2 SC Dose #1).

[m] Subjects who receive any amount of IP and discontinue early from the study will be requested to return for the Early Termination Visit prior to starting commercial IgG treatment. The assessments will be the same as those performed at the Week 32 visit and IP dosing for subjects who prematurely discontinue will be at the discretion of the investigator. If IP dosing is administered at the early termination visit, the final dose should be consistent with the dose/frequency of the treatment period in which the subject withdrew (eg, one week after last dose if receiving weekly IP).

[n] Blood sample for Week 14 Serial PK assessments are at the following time points: prior to the Week 14 IGSC 20% infusion (within 0.5 hour of infusion start [predose] and is the same as the Week 14 trough sample); 1 day ± 4 hours post end of Week 14 infusion; 3 days ± 4 hours post end of Week 14 infusion; 4 days ± 4 hours post end of Week 14 infusion; 5 days ± 8 hours post end of Week 14 infusion; 7 days (+1 day) post end of Week 14 infusion (which is equivalent to Week 15 and must be collected prior to Week 15 infusion).

[o] Blood sample for Week 30 Serial PK assessments are at the following time points: prior to the Week 30 IGSC 20% infusion (within 0.5 hour of infusion start [predose] and is the same as the Week 30 trough sample); 1 day ± 4 hours post end of Week 30 infusion; 3 days ± 4 hours post end of Week 30 infusion; 4 days ± 4 hours post end of Week 30 infusion; 7 days (±1 day) post end of Week 30 infusion (which is equivalent to Week 31); 11 days ± 1 day post end of Week 30 infusion; 14 days (+1 day) post end of Week 30 infusion (which corresponds to the last total IgG trough time point for Treatment Period 2, ie Week 32 and must be collected prior to the Week 32 infusion).

Appendix 2 Treatment-Naïve Subjects Only: Schedule of Study Procedures

Period			Treatment Phase Clinic Visits All clinic visits must coincide with dosing days													
Clinic Visit Procedures and Evaluation	Screen	Baseline Week 0 (Day 1) First loading dose SC#1[j]	Week 0 (Days 2-5) SC#2, #3, #4, #5 loading doses[j]	Week 1 (Day 8) First maintenance dose[j]	Week 2 ±2 days	Week 4 ±2 days	Week 6 ±2 days	Week 8 ±2 days	Week 10 ±2 days	Week 12 ±2 days	Week 16 ±2 days	Week 20 ±2 days	Week 24 ±2 days	Week 28 ±2 days	Week 32±2 days/ Early Termination Visit	Week 33 ±1 day Final Follow-up
Informed consent/assent (if applicable)	X															
Eligibility criteria	X	X														
Assign subject number	X															
Medical history including PI type	X															
Demographics	X															
Full physical exam[a]	X															
Abbreviated physical exam[b]								X			X		X		X	X
Vital signs[c]	X	X				X		X		X	X	X	X	X	X	X
Body weight[d]	X	X						X			X		X			
Height	X															
Central laboratory (hematology, chemistry, haptoglobin, urinalysis) (predose when applicable)[e]	X							X			X		X		X	
Central lab DAT and serum/plasma free hemoglobin (predose when applicable)	X							X			X		X		X	
Pregnancy test[f]	X	X														
Trough IgG level[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Review IgG trough value for specific disposition & IGSC 20% dose adjustment criteria[h]					X	X	X	X								

Period	Screen	Baseline	Treatment Phase Clinic Visits All clinic visits must coincide with dosing days													
Clinic Visit		**Week 0 (Day 1) First loading dose SC#1[j]**	**Week 0 (Days 2-5) SC#2, #3, #4, #5 loading doses[j]**	**Week 1 (Day 8) First maintenance dose[j]**	**Week 2 ±2 days**	**Week 4 ±2 days**	**Week 6 ±2 days**	**Week 8 ±2 days**	**Week 10 ±2 days**	**Week 12 ±2 days**	**Week 16 ±2 days**	**Week 20 ±2 days**	**Week 24 ±2 days**	**Week 28 ±2 days**	**Week 32±2 days/ Early Termination Visit**	**Week 33 ±1 day Final Follow-up**
Procedures and Evaluation																
SF-12/SF-10 (predose)		Pre-SC#1									X				X	
Observed IGSC 20% dosing *in clinic*		X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	
SC infusion diary review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments of SBIs and other infections[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] A full physical exam will be performed excluding breast and genitourinary exam.

[b] An abbreviated physical exam will be performed targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and inspection of previous injection sites.

[c] Vital signs (SBP, DBP, HR, T, and RR) will be measured prior to infusion (except at the Screening Visit).

[d] Body weight will be measured prior to infusion (except at the Screening Visit) to determine the SC study drug dose.

[e] Laboratory assessments will be obtained prior to infusion of study drug at all specified visits (except at the Screening Visit). Laboratory testing includes Hematology: hemoglobin, hematocrit, platelets, RBC count, WBC count with differential, ARC. Chemistry: sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, TB, indirect bilirubin. Haptoglobin. Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal).

[f] Pregnancy testing will be performed for child-bearing potential females only (serum at Screening and local urine testing at Baseline). Pregnancy testing will be repeated at any time if pregnancy is suspected.

[g] Trough samples must be drawn within 8 hours prior to dosing (except at the Screening Visit). Regardless of the clinical visit time window, the trough sample collection MUST precede dosing and occur on the same day.

[h] Review IgG trough level from previous visit according to the treatment-naïve algorithms and discontinuation criteria in Sections 4.1.2.1, 4.1.2.2, 5.3.2, and in Appendix 8.

[i] Record any SBIs, hospitalizations due to infections, and non-serious infections.

[j] Treatment-naïve subjects will receive 5 consecutive daily doses of IGSC 20% 150 mg/kg/day (Week 0, Days 1 to 5) followed by weekly maintenance infusions of 150 mg/kg starting Week 1 (Day 8) through Week 32. The 5 consecutive days of loading dose infusions and the first weekly maintenance infusion at Day 8 must be administered in clinic given the medically vulnerable nature of these newly diagnosed subjects. Note that increases in pump infusion rates, eg, stepped escalation in pump infusion rate during an infusion, must be performed at a clinic visit.

[k] Subjects who receive any amount of IP and discontinue early from the study will be requested to return for the Early Termination Visit prior to starting commercial IgG treatment. The assessments will be the same as those performed at the Week 32 visit and IP dosing will be at the discretion of the investigator.

Appendix 3 Quality of Life and Treatment Satisfaction Scales (LQI, TSQM-9, SF-12, SF-10)

LIFE QUALITY INDEX

My current IgG treatments:											
1.	Are convenient	=	7	6	5	4	3	2	1	=	Inconvenient
2.	Are not at all painful	=	7	6	5	4	3	2	1	=	Painful
3.	Have improved my health	=	7	6	5	4	3	2	1	=	Have not improved my health
4.	Do not interfere with my social/family life	=	7	6	5	4	3	2	1	=	Interfere with my social/family life
5.	Do not interfere with my work/school	=	7	6	5	4	3	2	1	=	Interfere with my work/school
6.	Are given in a place where I am comfortable	=	7	6	5	4	3	2	1	=	Given in a place where I am uncomfortable
7.	Do not require too much time waiting beforehand	=	7	6	5	4	3	2	1	=	Require too much time waiting beforehand
8.	Are given in a pleasant atmosphere	=	7	6	5	4	3	2	1	=	Given in an unpleasant atmosphere
9.	In my opinion are worthwhile	=	7	6	5	4	3	2	1	=	In my opinion are a waste of time
10.	Do not make me anxious or nervous	=	7	6	5	4	3	2	1	=	Make me anxious or nervous
11.	Do not seem to me to be too expensive	=	7	6	5	4	3	2	1	=	Seem to me to be too expensive
12.	Do not make me too dependent on others	=	7	6	5	4	3	2	1	=	Make me too dependent on others
13.	Require very little travel time and cost	=	7	6	5	4	3	2	1	=	Require a lot of travel time and cost
14.	Do not limit my freedom to take trips or move	=	7	6	5	4	3	2	1	=	Limit my freedom to take trips or move
15.	Are scheduled according to my convenience	=	7	6	5	4	3	2	1	=	Not scheduled according to my convenience

Source: (39)

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult

☐2 Very Difficult

☐3 Difficult

☐4 Somewhat Easy

☐5 Easy

☐6 Very Easy

☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult

☐2 Very Difficult

☐3 Difficult

☐4 Somewhat Easy

☐5 Easy

☐6 Very Easy

☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient

☐2 Very Inconvenient

☐3 Inconvenient

☐4 Somewhat Convenient

☐5 Convenient

☐6 Very Convenient

☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident

☐2 A Little Confident

☐3 Somewhat Confident

☐4 Very Confident

☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain

☐2 A Little Certain

☐3 Somewhat Certain

☐4 Very Certain

☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

SF-12 Health Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

SF-10™ Health Survey for Children

INSTRUCTIONS

1. This survey asks about your child's health and well-being.
2. There are no right or wrong answers.
3. If you are unsure how to answer an item, please give the best response you can.
4. For each item, please select the response that best describes your answer by marking the appropriate box ☒.
5. Please answer all items.

Thank you for completing this survey.

United States (English) Version

SF-10™ Health Survey for Children

1. **In general, would you say your child's health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **During the past 4 weeks, has your child been limited in any of the following activities due to HEALTH problems?**

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Doing things that take some energy such as riding a bike or skating?	☐1	☐2	☐3	☐4
b. Bending, lifting, or stooping?	☐1	☐2	☐3	☐4

3. **During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of PHYSICAL health problems?**

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
☐1	☐2	☐3	☐4

4. **During the past 4 weeks, has your child been limited in the KIND of schoolwork or activities with friends he/she could do because of EMOTIONAL or BEHAVIORAL problems?**

Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
☐1	☐2	☐3	☐4

5. **During the past 4 weeks, how much bodily pain or discomfort has your child had?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐1	☐2	☐3	☐4	☐5	☐6

6. **During the past 4 weeks, how satisfied do you think your child has felt about his/her friendships?**

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
☐1	☐2	☐3	☐4	☐5

7. **During the past 4 weeks, how satisfied do you think your child has felt about his/her life overall?**

Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
☐1	☐2	☐3	☐4	☐5

United States (English) Version

SF-10™ Health Survey for Children

8. During the <u>past 4 weeks</u>, how much of the time do you think your child acted bothered or upset?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

9. Compared to other children your child's age, in general would you say his/her behavior is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

United States (English) Version

Appendix 4 Diagnostic Criteria for Serious Infection Types

Infection: Bacteremia/sepsis[a]

- *Symptoms:* chills, rigors
- *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mmHg or a reduction of ≥40 mmHg from Baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction
- *Laboratory tests*: **positive blood culture**[b], leukocytosis (white blood cell (WBC) count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis

Infection: Bacterial Meningitis

- *Symptoms*: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures
- *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38°C oral or >39°C rectal
- *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay,** positive blood culture[c], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose

Infection: Osteomyelitis/Septic Arthritis

- *Symptoms*: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults.)
- *Physical findings*: evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal
- *Laboratory tests*: positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture

Imaging studies: **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra**

Note: Items in bold are considered essential diagnostic features.

[a] Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/ >39°C rectal or <36°C oral or <37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or $PaCO_2$ <32 mmHg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms (54). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (55).

[b] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IVIG replacement therapy. For subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. (Multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

[c] A blood culture positive for growth of *S. pneumoniae*, *Neisseria meningitides*, or *H. influenzae*, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (56).

Infection: Bacterial Pneumonia[d]

- *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias
- *Physical findings*: rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or >39°C rectal, or <36°C, hypothermia (temperature <36°C oral or <37°C rectal)
- *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 <60 mmHg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum[e], positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage or protected brush sampling,
- *Imaging studies*: **Pulmonary infiltrate with consolidation on chest X-Ray (CXR)** (new in comparison with Baseline CXR)

Infection: Visceral Abscess

- *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present)
- *Physical findings:* intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice
- *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen,** positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
- *Imaging studies:* **typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan**

Note: Items in bold are considered essential diagnostic features.

[d] For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IVIG, the finding of a new pulmonary infiltrate with consolidation on CXR is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature >38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F). In pediatric patients, elevations of WBC counts >15,000/mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3 may be observed, usually associated with severe infection (57).

[e] We recommend a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture (57).

Appendix 5 Blood Pressure Percentiles for Pediatric Patients

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Appendix 6 Sample IGSC 20% Dose Calculations for Different Frequencies of Administration

For any prior IgG treatment regimen, the initial calculation is to establish the equivalent weekly dose.

This is calculated as follows for prior IgG dosing intervals greater than or equal to 1 week (IVIG, SCIG including HYQVIA):

Equation A:

$$\textbf{\textit{Equivalent Weekly Dose}} = \frac{\textbf{\textit{Previous IVIG or SCIG dose (mg/kg)}}}{\textbf{\textit{Numberof weeks between IVIG or SCIG doses (weeks)}}}$$

This is calculated as follows for prior IgG dosing intervals <1 week (some SCIG regimens):

Equation B:

$$\textbf{\textit{Equivalent Weekly Dose}} = \left(\textbf{\textit{Previous SCIG dose}}\ \left(\frac{mg}{kg}\right)\right) \times (\textbf{\textit{number of times given per week}})$$

Treatment Period 1

- Treatment Period 1: For subjects entering on IVIG, multiply the equivalent weekly dose by the 1.37 dose adjustment factor (DAF) to obtain the mg/kg IGSC 20% dose per week.
- Treatment Period 1: For subjects entering on SCIG, there is no DAF. The dose in mg/kg of IGSC 20% per week is exactly the same as the equivalent weekly dose.

Treatment Period 2

- Treatment Period 2: The dose of IGSC 20% is to be given every 2 weeks (Biweekly).
- Treatment Period 2: Multiply the calculated weekly dose of IGSC 20% by 2.

Dose Calculation Examples

- Example #1: Subject receives 500 mg/kg IVIG every 4 weeks. Equivalent weekly dose is 125 mg/kg (Equation A).
  - Treatment Period 1: Multiply 125 mg/kg by 1.37 (DAF) = 171.25 mg/kg IGSC 20% per week
  - Treatment Period 2: Biweekly dosing (every 2 weeks) is 171.25 mg/kg × 2 (weeks) = 342.5 mg/kg IGSC 20% every 2 weeks.
- Example #2: Subject receives 80 mg/kg SCIG twice per week. Equivalent weekly dose is 160 mg/kg (Equation B)
  - Treatment Period 1: No DAF. 160 mg/kg IGSC 20% per week
  - Treatment Period 2: Biweekly dosing (every 2 weeks) is 160 mg/kg x 2 (weeks) = 320 mg/kg IGSC 20% every 2 weeks.

- Note: Following all dose conversions, the minimum weekly dose of IGSC 20% on study is 100 mg/kg/week. If conversion from the prior IgG replacement regimen yields a value < 100 mg/kg/week, set the dose of IGSC 20% in Treatment Period 1 to 100 mg/kg/week.
- Note: All calculations are in mg/kg. This means that if the subject is taking a certain number of grams of immune globulin at study entry, the grams of immune globulin must be *divided by* the subject's weight in kg.
  - The following division: (grams of IgG)/(kg body weight) provides a dose in g/kg
  - The g/kg figure can be converted to mg/kg by multiplying the result by 1000. (There are 1000 mg in 1 g.)

Appendix 7 Treatment-Naïve Weekly IGSC 20% Dose Adjustment (in mL) Based on Difference From Target IgG Trough Level

The table below is provided for reference purposes. To adjust the dose based on trough levels, calculate the difference (in mg/dL) of the subject's serum IgG trough level from the target IgG trough level. Then find this difference in the table below and the corresponding amount (in mL) by which to increase the weekly dose based on the subject's body weight.

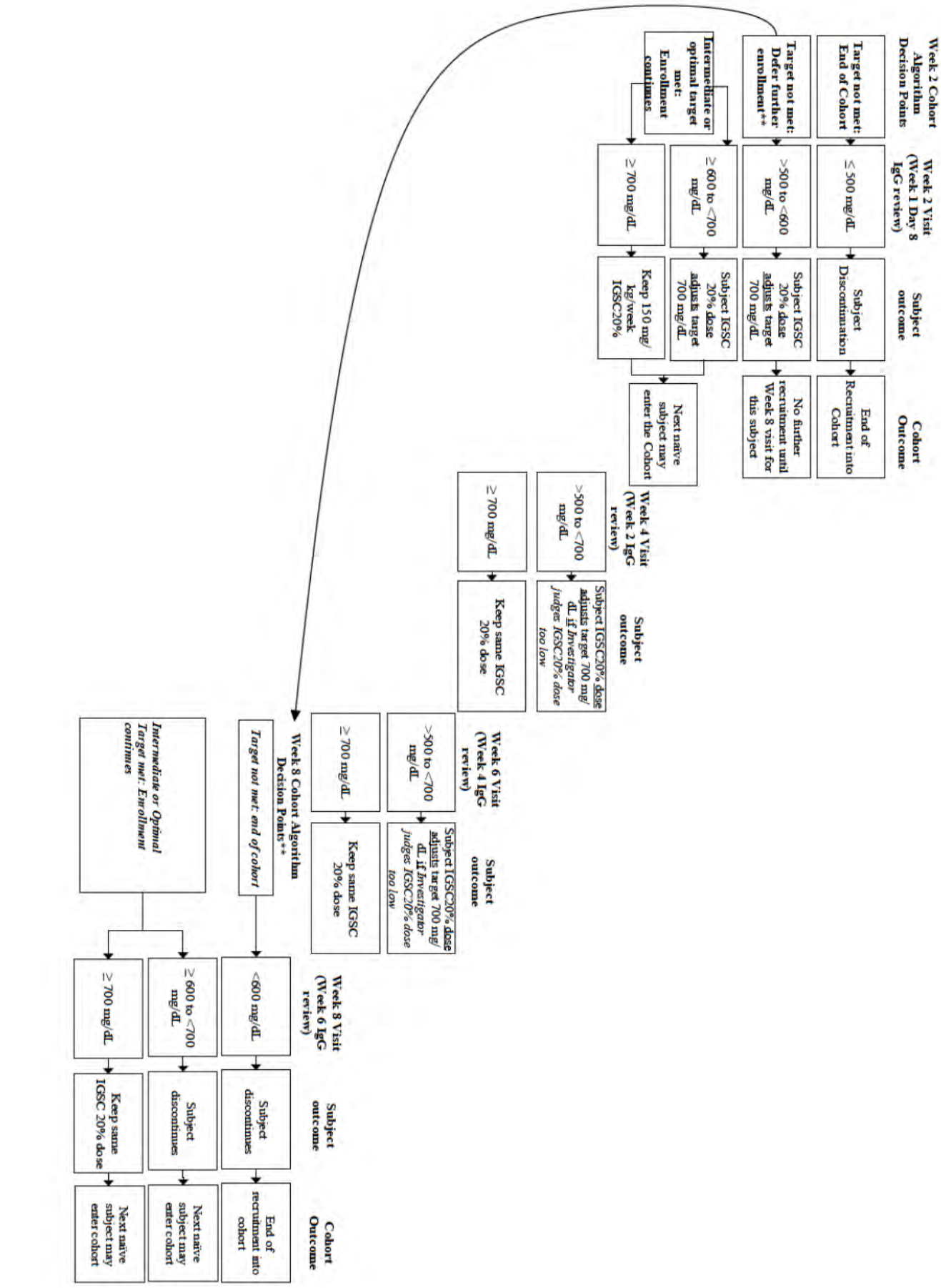
Adjustment (in mL) of the Weekly Subcutaneous Dose for Treatment-Naïve Subjects Based on the Difference (mg/dL) From the Target 700 mg/dL Serum IgG Trough Level

Difference From Target IgG Trough Level (mg/dL)	Body Weight (kg)												
	10	15	20	30	40	50	60	70	80	90	100	110	120
	Dose Adjustment (mL per Week)*												
50	0	1	1	1	2	2	2	3	3	3	4	4	5
100	1	1	2	2	3	4	5	5	6	7	8	8	9
150	1	2	2	3	5	6	7	8	9	10	11	13	14
200	2	2	3	5	6	8	9	11	12	14	15	17	18
250	2	3	4	6	8	9	11	13	15	17	19	21	23
300	2	3	5	7	9	11	14	16	18	20	23	25	27
350	3	4	5	8	11	13	16	19	21	24	27	29	32
400	3	5	6	9	12	15	18	21	24	27	30	33	36
450	3	5	7	10	14	17	20	24	27	31	34	38	41
500	4	6	8	11	15	19	23	27	30	34	38	42	45

* Dose adjustment in mL is based on the slope of the serum IgG trough level response to subcutaneous administration of IGSC 20% dose increments (about 6.6 mg/dL per increment of 1 mg/kg per week).

For example, if a subject with a body weight of 70 kg has an actual IgG trough level of 600 mg/dL and the target level is 700 mg/dL, this results in a difference of 100 mg/dL. Therefore, the increase in the weekly subcutaneous dose would be 5 mL + current volume IGSC 20% according to the table.

Appendix 8 Treatment-Naïve Individual IGSC 20% Dosing and Cohort Recruitment Algorithm Based on IgG Trough Levels


Week 2 Cohort Algorithm Decision Points
Week 2 Visit (Week 1 Day 8 IgG review)
Subject outcome
Cohort Outcome
Target not met: End of Cohort
≤ 500 mg/dL
Subject Discontinuation
End of Recruitment into Cohort
Target not met: Defer further enrollment**
>500 to <600 mg/dL
Subject IGSC 20% dose adjusts target 700 mg/dL
No further recruitment until Week 8 visit for this subject
Intermediate or optimal target met: Enrollment continues
≥ 600 to <700 mg/dL
Subject IGSC 20% dose adjusts target 700 mg/dL
≥ 700 mg/dL
Keep 150 mg/kg/week IGSC20%
Next naïve subject may enter the Cohort
Week 4 Visit (Week 2 IgG review)
Subject outcome
>500 to <700 mg/dL
Subject IGSC20% dose adjusts target 700 mg/dL if Investigator judges IGSC20% dose too low
≥ 700 mg/dL
Keep same IGSC 20% dose
Week 6 Visit (Week 4 IgG review)
Subject outcome
>500 to <700 mg/dL
Subject IGSC20% dose adjusts target 700 mg/dL if Investigator judges IGSC20% dose too low
≥ 700 mg/dL
Keep same IGSC 20% dose
Week 8 Cohort Algorithm Decision Points**
Target not met: end of cohort
Intermediate or Optimal Target met: Enrollment continues
Week 8 Visit (Week 6 IgG review)
Subject outcome
Cohort Outcome
<600 mg/dL
Subject discontinues
End of recruitment into cohort
≥ 600 to <700 mg/dL
Subject discontinues
Next naïve subject may enter cohort
≥ 700 mg/dL
Keep same IGSC 20% dose
Next naïve subject may enter cohort