Official Title:	**A Phase 3, Multicenter, Open-label, Single-sequence, Cross-over, Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of IVIG-PEG compared to Gamunex-C in Subjects with Primary Humoral Immunodeficiency**
NCT Number:	NCT04561115
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Completion of the signature block below signifies the review and approval of this document.

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Clinical Study Protocol

Protocol Title:	A Phase 3, Multicenter, Open-label, Single-sequence, Cross-over, Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of IVIG-PEG compared to Gamunex-C in Subjects with Primary Humoral Immunodeficiency
Test Product:	Immune Globulin (Human) 10% (Gamunex-C) PEG process (IVIG-PEG)
Sponsor's Name and Address:	Grifols Therapeutics LLC 79 TW Alexander Dr Research Triangle Park, North Carolina 27709 USA
Additional Identifier	IVIG-PEG PI Bioequivalence Study
Study Number:	GC1902
IND Number:	19431
Development Phase:	3
Sponsor Signatories:	[redacted], MD, CPT, MSc, BSc [redacted] Grifols Bioscience Industrial Group Email address: [redacted] Telephone number: [redacted] [redacted] Grifols Bioscience Industrial Group Email address: [redacted] Telephone number: [redacted] See Sponsor signatures on the cover page of the protocol

Summary of Changes for Amendment 3

Protocol Version	Date of Approval/Effective Date
4.0 Amendment 3 + Integrated Protocol	See left margin
3.0 Amendment 2 + Integrated Protocol	29 Jul 2020
2.0 Amendment 1 + Integrated Protocol	04 Mar 2020
1.0 Original	25 Sep 2019

Amendment 3

The protocol for GC1902 (Version 3.0, dated 29 July 2020) has been amended as Protocol Amendment 3,Version 4.0. See Appendix 5 for a summary of changes for Protocol Amendment 3.

PROTOCOL SYNOPSIS

Title of Study: A Phase 3, Multicenter, Open-label, Single-sequence, Cross-over, Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of IVIG-PEG compared to Gamunex-C in Subjects with Primary Humoral Immunodeficiency

Study Number: GC1902

Phase: 3

Study Objectives:

Primary Pharmacokinetic Objective

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

Other Pharmacokinetic Objectives

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

Secondary Efficacy Objectives

- To evaluate the rate of serious bacterial infection (SBI)
- To evaluate all infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed per subject year due to infections and their treatment

Exploratory Objectives

- To evaluate trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- To evaluate antibody levels for *Streptococcus pneumoniae (S. pneumoniae)*, *Haemophilus influenzae (H. influenzae)*, and tetanus (*Clostridium tetani* [*C. tetani*])

- To evaluate validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- Trough measles antibody titers (functional assay) is an exploratory variable for informational purposes

Safety Objective

The safety objective is to evaluate the safety and tolerability of IVIG-PEG as replacement therapy in subjects with PI.

Overall Study Design and Description:

This is a clinical Phase 3, multicenter, open-label, single-sequence, cross-over, bioequivalence study to assess the steady-state PK, safety, and tolerability of IVIG-PEG compared with Gamunex-C in adult subjects with PI. A total of approximately 35 adult subjects will be enrolled in order to have 20 evaluable subjects for PK analysis.

The study will include the following phases:

- Screening Phase of approximately 28 days
- Gamunex-C Run-in Phase (IV administration of Gamunex-C) of up to 4.5 months (if applicable)
- Gamunex-C PK Phase of 3 or 4 weeks
- IVIG-PEG Treatment Phase of up to 4.5 months
- IVIG-PEG PK Phase of 3 or 4 weeks
- Final Visit/Early Termination visit

Prior to enrollment into the study, subjects with PI currently receiving IVIG replacement treatment will be screened during the Screening Phase. Subjects must meet all the inclusion criteria and meet none of the exclusion criteria to be enrolled in this study.

Depending on their current IVIG treatment regimen, eligible subjects may enter directly into the Gamunex-C PK Phase (those who are on a stable Gamunex-C treatment) or may be required to enter the Gamunex-C Run-in Phase. Eligible subjects not on stable Gamunex-C treatment will be required to enter the Gamunex-C Run-in Phase to receive Gamunex-C treatment (Sponsor provided) to achieve an approximate steady-state condition prior to entering the Gamunex-C PK Phase. Subjects meeting the following conditions are required to enter the Run-in Phase:

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

After reaching a stable dose and approximate steady-state (i.e., administration of 5 consecutive doses of Gamunex-C for subjects on every 4 weeks dosing regimen and 6 consecutive doses of Gamunex-C for subjects on every 3 weeks dosing regimen), the subjects will then enter the Gamunex-C PK Phase to determine the total IgG AUC profile of IV

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

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

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

Trough IgG levels will be obtained prior to all infusions in the Screening, Gamunex-C Run-in, and IVIG-PEG Treatment phases.

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

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

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

Some treatment visits for the IVIG-PEG Treatment Phase may also be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site.

Number of Subjects Planned:

Approximately 35 adult subjects are planned to be enrolled, in which a minimum number of 6 subjects are planned to be enrolled in each dosing interval (i.e., 3-weeks dosing interval vs 4-weeks dosing interval).

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A subject must meet all the following inclusion criteria to be eligible for participation in this study.

1. Male or female between 18 and 75 years of age (inclusive) at Screening
2. Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IV IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria
3. IgG trough level ≥500 mg/dL at Screening Visit

   Note: Patients entering Group 1 must additionally have trough levels ≥500 mg/dL documented within the previous year. For patients entering Group 2, if Screening trough levels are not ≥500 mg/dL, the subject will be a Screen Failure, but may be rescreened following dose adjustment of their original IV IgG replacement therapy regimen and recording an IgG trough level ≥500 mg/dL
4. Has not had an SBI within the last 6 months prior to Screening or during the Screening Phase
5. Medical records are available to document diagnosis, previous infections, and treatment
6. Willing to comply with all aspects of the study protocol, including blood sampling, for the duration of the study
7. Signed and dated a written informed consent form confirming his or her willingness to participate in Study GC1902

Exclusion Criteria

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

1. Has 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 (HIV) infection/acquired immune deficiency syndrome (AIDS)
2. Has 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 primary humoral immunodeficiency which have decreased IgA in addition to decreased IgG requiring IgG replacement)
3. Has isolated IgG subclass deficiency or an isolated specific antibody deficiency disorder, or transient hypogammaglobulinemia of infancy
4. The subject has had a known serious adverse reaction to immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product

5. Has a history of thrombotic complications following IVIG therapy
6. Has a history of or current diagnosis of deep venous thrombosis (DVT) or thromboembolism (e.g., myocardial infarction, cerebrovascular accident or transient ischemic attack); history refers to an incident in the year prior to the Screening Visit or 2 episodes over lifetime or has thrombosis risk factors (e.g., prolonged immobilization, use of estrogens, indwelling central vascular catheters)
7. Has a known hyperviscosity syndrome or hypercoagulable states
8. Has liver enzyme levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gammaglutamyl transferase [GGT], or lactate dehydrogenase [LDH]) greater than 2.5 times the upper limit of normal (ULN) at the Screening Visit as defined by the testing laboratory
9. Has pre-existing renal impairment (defined by serum creatinine greater than 1.5 times the ULN or blood urea nitrogen [BUN] greater than 2.5 times the ULN, or any subject who is on dialysis) at the Screening Visit or any history of acute renal injury
10. Has clinically significant history of drug or alcohol abuse or dependence in the opinion of the Investigator (must be within the past 12 months and noted in the subject's medical records or documented at Screening)
11. Clinical evidence of any significant acute or chronic medical condition (e.g., renal disease or predisposing conditions for renal disease, coronary artery disease, or protein losing state) that, in the opinion of the Investigator, may interfere with the conduct of the study or may place the subject at undue medical risk
12. Females of childbearing potential who are pregnant, have a positive pregnancy test at Screening (human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (e.g., oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], 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 [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception)
13. 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 not exceeding >1mg of prednisone equivalent/kg/day for >30 days would not exclude the subject. Inhaled or topical corticosteroids are allowed
14. Has uncontrolled arterial hypertension (systolic blood pressure [SBP] >160 mm Hg and/or diastolic blood pressure [DBP] >100 mm Hg)
15. Has hemoglobin <11 g/dL at the Screening Visit
16. Unable or unwilling to provide a storage serum sample at the Screening Visit

Note: a pre-treatment serum sample to be stored at -94°F (-70ºC) for possible future testing is required

17. Received any live virus vaccine within 5 months prior to the Screening Visit and not willing to postpone receiving any live virus vaccines until 6 months after completing study treatment
18. Has a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
19. Has participated in another clinical trial within 30 days prior to Screening or has received any investigational product, with the exception of other IgG products, within the previous 3 months prior to the Screening Visit

Test Product, Dose, and Mode of Administration

IVIG-PEG will be investigated in this study.

The IVIG-PEG dose and dosing interval will be individualized based on the previous Gamunex-C treatment the subject was receiving for PI either at the Screening Visit or at the end of the Run-in Phase (for subjects not directly entering the Gamunex-C Treatment Phase).

Subjects will receive IVIG-PEG by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. IVIG-PEG will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.

Duration of Treatment:

The duration of Gamunex-C treatment will include the Gamunex-C PK Phase (up to 4 weeks) plus the additional Gamunex-C Run-in Phase (up to 4.5 months) for subjects not receiving Gamunex-C or not on a stable dose of Gamunex-C upon entering the trial. The approximate maximum duration is up to 6 months.

The duration of IVIG-PEG treatment will include the IVIG-PEG Treatment Phase (up to 4.5 months) and the IVIG-PEG PK Phase (up to 4 weeks), for an approximate maximum of up to 6 months.

Reference Therapy, Dose and Mode of Administration

Gamunex-C will be evaluated in this study as a comparator to IVIG-PEG.

The Gamunex-C dose and dosing interval will be individualized based on the previous IVIG treatment the subject was receiving for PI during the Screening Visit.

Subjects will receive Gamunex-C by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. The subject's usual mg/kg dose (given on either a 3 or 4 week repeating schedule) will be the same mg/kg dose and schedule that the subject was receiving prior to entering screening. This mg/kg dose and schedule will be used throughout the study duration. Note that the weight of the subject will be measured at each visit and if the subject's weight changes, the actual weight at each visit will be used to calculate amount of drug (mg) to be

administered. Gamunex-C will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.

Key Study Variables:

Primary Pharmacokinetic Variables:

The primary PK variables are steady-state AUC of total IgG over a regular dosing interval (τ), either every 3 weeks or every 4 weeks (i.e., $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively) and C_{max} in subjects with PI

Other Pharmacokinetic Variables:

- Mean steady-state trough concentration of total IgG following IV administration of Gamunex-C and following IV administration of IVIG-PEG
- T_{max}
- Cl
- V_d

Key Secondary Efficacy Variables:

- Rate of SBIs
- All infections of any kind as determined by the Investigator
- Number of days on antibiotics

Key Exploratory Variables:

- Antibody levels for *S. pneumonia*, *H. influenzae*, and *C. tetani*
- Validated infections

Safety Variables:

- Adverse events including serious adverse events (SAEs) and suspected adverse drug reactions (ADRs) (i.e., potentially drug-related AEs)
- Clinical laboratory panels: hematology, clinical chemistry, and urinalysis
- Physical assessments
- Vital signs (temperature [T], heart rate [HR], respiratory rate [RR], SBP, and DBP)
- Thromboembolic and hemolytic risk assessments

Key Assessments and Procedures:

Complete schedules of study procedures and events are located in Appendix 1, Table A (for subjects on an every 3 weeks dosing regimen) and Table B (for subjects on an every 4 weeks dosing regimen).

Assessments for the Primary Pharmacokinetic Objective:

Total IgG concentration will be assessed throughout the study, with total IgG trough PK samples taken within 1 hour prior to each IP infusion during the Gamunex-C Run-in and the IVIG-PEG Treatment phases. During the Gamunex-C and IVIG-PEG PK phases, total IgG PK samples will be taken within 30 minutes prior to the start of the IP infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, 6, 24, and 48 hours; and 4, 7, 14, 21, and 28 days (the PK sample drawn at 28 days applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion. A PK sample will also be taken at the last visit (Final/Early Termination Visit) of any subjects discontinuing from the study early.

Statistical Methods:

Unless otherwise specified, descriptive statistics will include the number of non-missing 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.

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

Primary Pharmacokinetic Analyses

Total IgG concentrations will be summarized for IVIG-PEG and Gamunex-C by each time point. Individual and mean total IgG concentrations versus time curves will be plotted. PK parameters of total IgG will be determined by noncompartmental PK methods using WinNonlin. Steady-state PK parameters to be calculated, as appropriate, or as permitted by data, will include AUC, C_{max}, t_{max}, Cl and V_d. All PK parameters will be calculated separately for IVIG-PEG and Gamunex-C administration and will be tabulated and summarized descriptively. The mean and the lower and upper bounds of the 90% confidence interval (CI) will be calculated on ln-transformed AUC parameters. These mean and lower and upper bounds will be back-transformed (exponentiated) to provide the geometric mean and 90% CI on the original scale.

Pharmacokinetic analyses will be performed on the PK population. The Primary PK endpoints are the steady-state AUC over a dosing interval defined as $AUC_{0-\tau}$ (i.e., the AUC over a regular dosing interval (τ) at an approximate steady-state condition, either every 3 weeks or every 4 weeks, i.e., $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively) and C_{max}. The hypothesis to be tested is that the IV dose of IVIG-PEG will achieve an approximate steady-state $AUC_{0-\tau}$ and C_{max} of total IgG that is bioequivalent to that achieved by the IV dose of Gamunex-C. Bioequivalence of steady-state IgG AUC and C_{max} between IVIG-PEG and Gamunex-C will be tested based on established regulatory guidelines for bioequivalence testing. Analysis of covariance (ANCOVA) with a mixed-effect model will be used with study PK phase as a fixed effect, the exact administered dose and dose frequency during the PK phase as covariates, and subject as a random effect. The 90% CI of the geometric least-squares mean (LSM) AUC and C_{max} ratio of IVIG-PEG to Gamunex-C will be calculated. IVIG-PEG is considered to be bioequivalent to Gamunex-C if the 90% CI for the geometric

LSM AUC and C_{max} ratio of IVIG-PEG to Gamunex-C is within (0.80, 1.25) based on log-transformed data.

Depending on the number of subjects being dosed at 3- or 4-week dosing intervals, subgroup analyses may be performed to evaluate PK variables by IV dosing interval. Subgroup analyses will additionally include age, sex, race, and/or other factors as appropriate.

Other Pharmacokinetic Analyses

Other PK parameters will be listed and summarized for IVIG-PEG and Gamunex-C using arithmetic as well as geometric means and SD, percentage coefficient of variation (CV), median, and minimum/maximum, as appropriate.

Other PK parameters include steady-state mean trough concentration of total IgG, T_{max}, Cl, and V_d. The steady-state mean trough concentrations of total IgG will be determined as the average value of trough concentration measurements obtained at the PK visit and at 21 or 28 days after the PK infusion (depending on dosing interval). Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG and for the t_{max}, Cl, and V_d.

Secondary Efficacy and Exploratory variables

Secondary efficacy and exploratory parameters will be summarized descriptively. The generalized linear model procedure for Poisson regression with log link will be used to estimate the SBI rate and its one-sided 99% upper confidence bound.

Safety Analysis

The safety analyses will be addressed by listing and tabulation of AEs (includes suspected ADRs [i.e., potentially related AEs]), vital signs, physical assessments and clinical laboratory tests. Data will be described using descriptive analyses. The safety analyses are based on the safety population.

Determination of Sample Size

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

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GLOSSARY AND ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	anterior-posterior
AR	adverse reaction
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the plasma and/or serum concentration time curve during the defined interval
B19V	Parvovirus B19
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
Cl	clearance
cGMP	current Good Manufacturing Practice
C_{max}	maximum concentration in a dosing interval
CRO	Contract Research Organization
CV	coefficient of variation
CVID	common variable immunodeficiency
DAT	direct antiglobulin test
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DVT	deep venous thrombosis
eCRF	case report form/electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GGT	gammaglutamyl transferase
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
IB	Investigator's Brochure
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IG	immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	intramuscular
IP	investigational product
IRB/EC	Institutional Review Board/Ethics Committee
ITP	primary immune thrombocytopenia
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IVIG	intravenous immunoglobulin
IVIG-C	Immune Globulin (Human), 10% Caprylate/Chromatography Purified OR Gamunex-C
IVIG-PEG	Immune Globulin (Human) 10% (Gamunex-C) PEG process
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NAT	nucleic acid amplification technology
NSAID	nonsteroidal anti-inflammatory drug

OPK	opsonophagocytic killing
PA	posterior-anterior
PI	primary humoral immunodeficiency
PK	pharmacokinetic(s)
PRN	as needed
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBI	serious bacterial infection
SBP	systolic blood pressure
SC	subcutaneous
SCIG	subcutaneous immunoglobulin
SD	standard deviation
SRC	Safety Review Committee
T	temperature
TBL	total bilirubin
TE	thromboembolic
TEAE	treatment-emergent adverse event
T_{max}	time of maximum observed plasm/serum concentration
TRALI	transfusion related acute lung injury
ULN	upper limit of normal
US	United States
V_d	volume of distribution
WBC	white blood cell
XLA	X-linked agammaglobulinemia

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

A modified Gamunex-C manufacturing process has been developed by Grifols to produce Immune Globulin (Human) 10% (Gamunex-C) PEG process (IVIG-PEG). Upon agreement with the United States (US) Food and Drug Administration (FDA), a clinical, bioequivalence study to compare the pharmacokinetics (PK), safety, and tolerability of IVIG-PEG with those of Gamunex-C in adult subjects with primary humoral immunodeficiency (PI) has been developed. The manufacturing process for Gamunex-C has been revised to produce the test product, IVIG-PEG, that contains the same product characteristics as Gamunex-C.

In addition to the information provided below, please refer to the Investigator's Brochure (IB) and any additional data supplied by the sponsor (1).

2.1 Name and Description of the Investigational Products

IVIG-PEG is a sterile, liquid, highly purified, unmodified, human immunoglobulin (primarily immunoglobulin G [IgG]) product intended for intravenous (IV) administration. IVIG-PEG is made from large pools of human plasma via modifications of the Immune Globulin (Human), 10% Caprylate/Chromatography Purified Gamunex-C (IVIG-C) manufacturing process.

Gamunex-C, used as a comparator (reference therapy) to IVIG-PEG in this study, is a ready-to-use sterile solution of human IgG indicated in the United States (US) for IV administration in subjects with PI, primary immune thrombocytopenia (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP). Gamunex-C consists of 9 to 11% IgG in 0.16 to 0.24 M glycine.

See Section 4.4 Study Treatments for detail.

2.2 Relevant Findings from Nonclinical and Clinical Trials

The nonclinical efficacy, PK, safety and toxicity profile of IVIG-PEG is similar to Gamunex-C, as assessed in multiple nonclinical studies:

- *In vitro* efficacy studies of opsonophagocytic killing (OPK) or serum bactericidal killing (SBA) of select bacteria IVIG-PEG demonstrate functional activity comparable to

Gamunex-C. Two virulent pathogens of clinical significance were included: *Streptococcus pneumoniae (S. pneumoniae)* and *Haemophilus influenzae (H. influenzae) type b.*

- In a safety pharmacology study in cynomolgus monkeys with IVIG-PEG doses up to 2000 mg/kg, no clinically relevant changes were observed in cardiovascular, respiratory, and neurological function.
- In New Zealand White rabbits, PK parameters of human IgG were similar between IVIG-PEG and Gamunex-C comparator following single administration by either IV or subcutaneous (SC) routes at both low and high dose levels. The IV to SC dose adjustment factor of 1.37×was confirmed using area under the curve concentration (AUC) analysis.
- Safety of IVIG-PEG was demonstrated in a repeated dose toxicology study in Sprague-Dawley rats. IVIG-PEG was administered using either IV or SC routes of delivery at doses up to 1000 mg/kg/day for 5 consecutive days; these doses were well-tolerated. Based on the long half-life of human IgG, these doses were essentially cumulative. No differences between IVIG-PEG and Gamunex-C were noted in hematology, coagulation, clinical chemistry, or urinalysis parameters. Any findings were limited to repeated exposure to human xenogenic proteins.
- A repeated dose toxicology study in New Zealand White rabbits was confounded by species-specific adverse effects observed with both IVIG-PEG and Gamunex-C. Nonetheless, no differences between IVIG-PEG and Gamunex-C in hematology, coagulation, clinical chemistry, or urinalysis parameters were noted in this study.

2.3 Known and Potential Risks and Benefits to Human Subjects

The PI diseases are a heterogeneous group of disorders in which there is an intrinsic defect in the tissues, cells, and/or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinemia and/or defective antibody production and, and as a consequence, increased susceptibility to infection (2). Administration of polyclonal IG preparations of human origin, including intravenous immunoglobulin (IVIG), have long been used as replacement therapy in patients with PI (3).

Administered intravenously, Gamunex-C is indicated as a replacement therapy for patients with PI to prevent infection. It is approved in 57 countries worldwide under different trade names and for several indications. Gamunex-C was initially approved in 2003 in the United States (US). This IG preparation has been extensively prescribed and confirmed to be safe, well-tolerated, and effective. Its safety profile is well established with a total number of 8,159,628 estimated infusions (4).

IVIG-PEG results from an improved purification process for Gamunex-C, which allows a process simplification as well as an improvement of final product purity by reducing the levels of isoagglutinins (anti-A/anti-B). The manufacturing process developed by Grifols is based on the implementation of an initial PEG precipitation step in the Gamunex-C manufacturing process as a replacement for the caprylate precipitation step.

The PEG precipitation step has been used in the manufacturing process of another Grifols product, Flebogamma® DIF (Instituto Grifols, S.A. Parets del Vallès, Barcelona, Spain) for many years. Flebogamma DIF is another IVIG product manufactured by Grifols that was first authorized for marketing in the US in 2007 (5). This change in the manufacturing process of Gamunex-C is not expected to change either the structure of the IG, its activity, or the safety of the product.

With the administration of any IG preparation, there is the potential for acute adverse reactions to occur. Symptoms observed with the infusion of immunoglobulins include transfusion related acute lung injury (TRALI), pyrexia, rigors, cyanosis, hypoxia, bronchospasm, hepatic dysfunction, leukopenia, pancytopenia, tremor, erythema multiforme, epidermolysis, pulmonary edema, seizures, hypotension, thrombosis, warmth, flushing, urticaria, eczema, back pain, headache, fever, chills, anxiety, malaise, faintness, dizziness, nausea, vomiting, muscle and joint pain, abdominal pain, chest pain, chest tightness, isolated cases of hemolysis/hemolytic anemia, dyspnea, wheezing, tachycardia, pruritus and rash.

Intravenous IG administration may result in mild hemolytic reactions, usually due to the presence of anti-A or anti-B isoagglutinins or, less commonly, anti-D or anti-K antibodies. These blood group antibodies often result in a slight degree of hemolysis, mild hyperbilirubinemia, and a positive direct Coombs' test. These events are usually subclinical (6). The PEG precipitation step in IVIG-PEG manufacturing is aimed to reduce the levels of isoagglutinins.

True anaphylactic reactions to IVIG may occur in recipients with documented prior histories of severe allergic reactions to immunoglobulins. Very rarely an anaphylactoid reaction may occur in subjects with no prior history of severe allergic reactions to IG administration. Gamunex-C is contraindicated in individuals with known anaphylactic or severe systemic response to Immune Globulin (Human) and in IgA deficient subjects with antibodies against IgA and history of hypersensitivity.

Intravenous IG products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death (7). Subjects predisposed to acute renal failure include subjects with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or subjects receiving known nephrotoxic drugs. In subjects with a predisposition to renal insufficiency, IVIG products should be administered at the minimum concentration available and at the minimum rate of infusion. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIG products, those products containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Gamunex-C does not contain sucrose but contains glycine, a natural amino acid, as a stabilizer. In addition, proper hydration will be ensured in this study and IVIG will be discontinued if signs/symptoms of renal insufficiency develop.

Both IVIG-PEG and Gamunex-C are prepared from human plasma obtained from healthy donors. For products of biological origin, the presence of infectious agents cannot be totally excluded. However, in the case of products prepared from human plasma, the risk is reduced by: (1) epidemiological controls on the donor population and selection of individual donors

by a medical interview, (2) screening of individual donations and plasma pools for viral infection markers, and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

Grifols has designed a clinical program to acquire clinical data in support of an application to the regulatory authorities on biologics for marketing authorization for IVIG-PEG.

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

2.4.1 Administration of Investigational Products

IVIG-PEG and Gamunex-C will be administered intravenously (peripheral or central vein) through a separate infusion line. Mixing and administration of any other drug (including normal saline) with the supplied product is strictly prohibited. It is recommended that the investigational products (IPs) should initially be infused at a rate of 0.01 mL/kg/min (1 mg/kg/min) for the first 30 minutes. If well-tolerated, the rate may be gradually increased to a maximum of 0.08 mL/kg per minute (8 mg/kg/min). If AEs occur, the rate may be reduced or the infusion interrupted until symptoms subside. Lack of tolerance at any given rate must be recorded as an adverse event (AE) at that rate. The infusion may then be resumed at the rate that is tolerable for the subject.

2.4.2 Justification for Selection of Doses/Timing of Investigational Products

Gamunex-C is approved in a number of countries for IV administration for a number of immune disorders. In general, the recommended IV dosing regimen for PI varies from country to country from as low as 100 mg/kg to up to 800 mg/kg per local labeling.

The dose of Gamunex-C and IVIG-PEG for subjects with PI is between 200 and 800 mg/kg body weight (2 mL/kg to 8 mL/kg) administered every 3 to 4 weeks and will be individualized based on each subject's current IgG regimen, which is assumed to be an effective dose. Subjects are required to have been clinically stable at a dose of between 200 and 800 mg/kg Gamunex-C administered every 3 or 4 weeks, for at least 6 or 5 consecutive doses respectively, prior to the first dose of IVIG-PEG. Dosing is based on current Gamunex-C labeling (8,9).

The dosing schedule has been designed to maintain IgG trough levels ≥500 mg/dL, which are considered to be protective as a replacement therapy in PI subjects (8,9).

The recommended initial infusion rate is 0.01 mL/kg/min (1 mg/kg/min). If the infusion is well-tolerated, the rate may be gradually increased to a maximum of 0.08 mL/kg/min (8 mg/kg/min). For subjects judged to be at risk for renal dysfunction or thrombosis, IP infusion should be at the minimum infusion rate practicable.

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 subjects who are between 18 and 75 years of age (inclusive) and have a diagnosis of PI requiring IV IgG replacement therapy.

Subjects who initially fail to meet the eligibility criteria may be rescreened once. Subjects who fail to meet eligibility criteria upon rescreening 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 Humoral Immunodeficiency

Primary humoral 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 (2). 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 (10). Worldwide upper estimates suggest that 6 million people (638,000 in Europe alone) may be living with a PI, although only a fraction of these patients have been identified in registries (11). 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 therapy in the treatment of these disorders has been well established (12,13) since 1952 when the use of serum globulin fraction was reported to reduce the frequency of infections in a patient with agammaglobulinemia (14).

Although PI was the first US FDA-approved indication for IG therapy, it is becoming increasingly recognized for the treatment of other immunodeficiency diseases for which B-cell function and antibody production are implicated in the immunodeficiency, but for which the role is not clearly identified. Although the prevalence of subjects with immunodeficiencies is very low, IG therapy is vital for minimizing potentially fatal infections and improving quality of life and overall clinical outcomes (15).

2.7.2 Primary Humoral Immunodeficiency Treatment

Immune globulin therapy is the mainstay of treatment for a variety of PI states, and it is indicated for most PI diseases in accordance with recommendations from expert guidelines (3,20,21). A systematic literature review performed by the American Academy of Allergy, Asthma & Immunology designated IVIG and subcutaneous immunoglobulin (SCIG) as definitely beneficial therapies across several PI diseases with an evidence category IIb and strength of recommendation B (3).

The therapeutic management of PI has been carried out via intramuscular (IM), IV, and SC injections of various IG preparations (16,17). Patients with mild PI were historically treated

with IG administered via the IM route up to a maximum dose of 25 mg/kg/wk, limiting the dose administration in subjects with more severe forms of deficiency who required higher doses. Intravenous preparations allowed for the treatment of subjects with severe PI disease (i.e., X-linked agammaglobulinemia [XLA], and common variable immunodeficiency [CVID]) with higher doses of IG (18); however, the efficacy of IVIG for treatment of IgG subclass deficiency, with or without IgA deficiency, is uncertain. Subcutaneous infusion of IG is considered an effective alternative to IV therapy, with the convenience of at home dosing (19).

2.7.3 Isoagglutinins and Hemolytic Adverse Events

Antibody-mediated hemolysis is a rare AE of IVIG products. Clinically significant hemolytic reactions reported after IVIG infusion have been attributed to isoagglutinins, antibodies present in IVIG products that react with red blood cell (RBC) antigens of the Rh and ABO blood group systems (e.g., anti-Rh(D), anti-A, anti-B).The hemolytic reactions range from mild cases in which there may be a positive direct antiglobulin test (DAT, Coombs' test) to acute severe cases in which intravascular hemolysis can cause hemoglobinemia (excess of hemoglobin in the plasma), hemoglobinuria, and renal damage/dysfunction (22-31).

An investigation of 1000 patients receiving IVIG identified 16 cases of hemolysis (1.6 percent) in which females, non-O blood type subjects, and subjects receiving high-dose IVIG infusions (e.g., >100 grams) were at the greatest risk for hemolysis (23,32,33). The onset of hemolysis ranged from 12 hours to 10 days with a mean decrease in hemoglobin of 3.2 g/dL and over half of the patients presented with these risk factors.

In addition, it has been reported that dividing the total IVIG dose into 4 or 5 doses administered on consecutive days may minimize the occurrence of hemolysis (34).

The purpose of the IVIG-PEG manufacturing change is to reduce the levels of isoagglutinins in the final product in order to reduce the chance of antibody mediated hemolysis occurring post-administration. The process changes are focused on the replacement of the caprylate precipitation step by a PEG precipitation step. To date, consistency of the IVIG-PEG process has been evaluated with 3 different processes at clinical scale (approximately 3500 L plasma equivalent) that demonstrate that the proposed process changes consistently result in a 10% IVIG product with reduced levels of isoagglutinins while maintaining the current product characteristics and safety profile.

A detailed study of the isoagglutinin reduction capacity of the process has been conducted. For this purpose, a new method for Anti A/B isoagglutinins determination by flow cytometry has been developed, allowing an increased sensitivity. The process has also been followed with a DAT. The results confirmed the capacity of the process to reduce isoagglutinins, reaching lower levels than are currently present in Gamunex-C. In addition, a full characterization study has been conducted including purity, functionality, process, and product related carry over constituents, antibodies titers, and procoagulant activity. The results of these studies do not show significant variations due to the IVIG-PEG process.

Decreasing the presence of isoagglutinins in IVIG products through manufacturing changes has been recommended to decrease in the incidence of hemolysis associated with IVIG administration (35). The PEG precipitation step in the IVIG-PEG manufacturing process can further reduce isoagglutinin levels in the final product compared to Gamunex-C, which in turn may have an effect on the incidence of hemolytic AEs. Events of hemolysis in this study will therefore be treated as events of special interest.

3 STUDY OBJECTIVES AND PURPOSE

3.1 Pharmacokinetic Objectives

3.1.1 Primary Pharmacokinetic Objective

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

3.1.2 Other Pharmacokinetic Objectives

Other PK objectives include:

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

3.1.3 Secondary Efficacy Objectives

- To evaluate the rate of serious bacterial infections (SBIs)
- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed per subject year due to infections and their treatment

3.1.4 Exploratory Objectives

- To evaluate trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- To evaluate antibody levels for *S. pneumoniae*, *H. influenzae*, and tetanus (*Clostridium tetani* [*C. tetani*])
- To evaluate validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- Trough measles antibody titers (functional assay) is an exploratory variable for informational purposes

3.2 Safety Objectives

The safety objective is to evaluate the safety and tolerability of IVIG-PEG as replacement therapy in subjects with PI.

4 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Pharmacokinetic Endpoints

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

- AUC_{0-21}: the AUC over a regular dosing interval of every 3 weeks at an approximate steady-state condition following the regular IV infusion
- AUC_{0-28}: the AUC over a regular dosing interval of every 4 weeks at an approximate steady-state condition following the regular IV infusion

4.1.2 Other Pharmacokinetic Endpoints

The other PK endpoints include:

- Mean steady-state trough concentration of total IgG following Gamunex-C administration and following IVIG-PEG administration
- T_{max}
- Cl
- V_d

4.1.3 Secondary Efficacy Endpoints

- Rate of SBIs

- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed per subject year due to infections and their treatment

4.1.4 Exploratory Endpoints

The exploratory endpoints include:

- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *S. pneumoniae*, *H. influenzae*, and tetanus (*C. tetani*)
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- Trough measles antibody titers (functional assay) is an exploratory variable for informational purposes

4.1.5 Safety Endpoints

Safety endpoints include AEs, SAEs, suspected adverse drug reactions ([ADRs], i.e., potentially related AEs), ARs, clinical safety laboratory tests, vital signs, and physical assessments.

4.2 Study Design and Plan

This is a Phase 3, multicenter, open-label, single-sequence, cross-over, bioequivalence clinical study to assess the steady-state PK, safety, and tolerability of IVIG-PEG compared with Gamunex-C in adult subjects with PI. A total of approximately 35 adult subjects in which a minimum of 6 subjects are planned to be enrolled in each dosing interval (i.e., 3-week dosing interval vs 4-week dosing interval) will be enrolled in order to have 20 evaluable subjects for PK analysis.

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

Prior to enrollment into the study, subjects with PI currently receiving IVIG replacement treatment will be screened during the Screening Phase. Subjects must meet all the specific

inclusion criteria and meet none of the exclusion criteria described in Section 5.1 and Section 5.2, respectively to be enrolled in this study.

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

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

After reaching a stable dose and approximate steady-state (i.e., administration of 5 consecutive doses of Gamunex-C for subjects on every 4 weeks dosing regimen and 6 consecutive doses of Gamunex-C for subjects on every 3 weeks dosing regimen), the subjects will then enter the Gamunex-C PK Phase to determine the AUC profile of IV infusions of Gamunex-C.

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

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

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

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

At the conclusion of the IVIG-PEG Treatment Phase (i.e., after 5 or 6 infusions of IVIG-PEG depending on the individual dosing interval), subjects will enter into the IVIG-PEG PK Phase lasting 3 or 4 weeks in duration depending on the individual dosing interval. Pharmacokinetic samples will be drawn 30 minutes prior to the start of the IVIG-PEG infusion in the PK Phase, immediately upon the completion of the PK Phase IVIG-PEG infusion (within 10

minutes of infusion completion), and at 1, 3, 6, 24, and 48 hours; and 4, 7, 14, 21, and 28 days (the PK sample drawn at 28 days applies only for subjects on every 4 weeks dosing regimen) after the end of the PK Phase IVIG-PEG infusion.

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

Safety variables will be assessed at all study visits.

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

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

Some treatment visits for the IVIG-PEG Treatment Phase may also be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site.

4.2.1 Screening Phase

At Screening, subjects will be categorized into 2 groups: 1) those subjects who can directly enter the Gamunex-C PK Phase of the study, and 2) those subjects who will require a 4-month or 4.5-month Run-in Phase (corresponding to administration of 5 or 6 consecutive doses of Gamunex-C depending on previous dosing regimen) (Table 4-1 and Figure 4-1). The Screening Phase lasts up to 28 days.

Table 4-1 Subject Entry Criteria

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

4.2.2 Gamunex-C Phase

4.2.2.1 Run-in Phase

Subjects will be evaluated during the Screening Visit and placed into 1 of 2 groups based on their previous IVIG regimen as follows:

Group 1 - Subjects are eligible for direct entry into the Gamunex-C PK Phase:

Subjects who are currently receiving a stable dose of Gamunex-C between 200 and 800 mg/kg per infusion every 3 or 4 weeks and have trough levels equal to or greater than 500 mg/dL within the previous year and documented at the Screening Visit are not required to enter the Run-in Phase and may proceed directly to the Gamunex-C PK Phase.

Group 2 – Subjects required to enter the Gamunex-C Run-in Phase:

Those subjects who are receiving an IVIG therapy other than Gamunex-C prior to Screening (i.e., a different commercially available IVIG), and those subjects who are currently receiving Gamunex-C, but either have not been on a stable dose for the 5 months prior to Screening, the dose is not between 200 and 800 mg/kg, or the dosing frequency is not every 3 or 4 weeks, will be required to enter the Run-in Phase and receive 5 or 6 consecutive doses of IV Gamunex-C (at a dose between 200 and 800 mg/kg and a dosing interval as in their previous IVIG therapy [i.e., 5 consecutive doses for subjects on the every 4 weeks dosing regimen and 6 consecutive doses for subjects on every 3 weeks dosing regimen]). Subjects that are receiving an IVIG therapy other than Gamunex-C prior to Screening will be required to switch their normal immunoglobulin product dose to a proportional dose of intravenous Gamunex-C (between 200 to 800 mg/kg every 3 or 4 weeks) to ensure that they receive the same IVIG dose during the Run-in Phase as with their previous immunoglobulin product.

Furthermore, any subject whose prior dosing frequency was not every 3 to 4 weeks will be adjusted to one of these two frequency options by their physician during the Run-in Phase also to ensure that they receive the same dose as with their previous immunoglobulin product.

During the Run-in Phase, subjects will receive an individualized dose of Gamunex-C between 200 to 800 mg/kg that treating physicians consider appropriate compared to their previous IVIG treatment regimen. The subject's usual mg/kg dose (given on either a 3 or 4 week repeating schedule) will be the same mg/kg dose and schedule that the subject was receiving prior to entering screening. This mg/kg dose and schedule will be used throughout the study duration. Note that the weight of the subject will be measured at each visit and if the subject's weight changes, the actual weight at each visit will be used to calculate amount of drug (mg) to be administered. The first 3 consecutive doses of Gamunex-C during the Run-in Phase (visits #1, #2, and #3) can be adjusted as needed by treating physicians to achieve a stable dose for subjects, and then such stable dose should be maintained throughout the remainder of the Run-in Phase (visits #4, #5, and #6). Doses during visits #4, #5, and #6 cannot vary from each other or from the dose given during visit #3 by more than 20%. Subjects who cannot achieve a stable dose of Gamunex-C during the Run-in Phase may not continue to the Gamunex-C PK Phase and will be withdrawn from the study (see Section 5.3.2).

Trough levels will be measured within 1 hour prior to the start of each infusion of Gamunex-C.

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

4.2.2.2 Gamunex-C PK Phase

After Screening (for subjects in Group 1) or after the Run-in Phase (for subjects in Group 2), subjects will enter the Gamunex-C PK Phase and receive 1 additional dose of Gamunex-C. Pharmacokinetic samples will be collected within 30 minutes prior to the start of the last of Gamunex-C infusion, immediately upon the completion of the last Gamunex-C infusion (within 10 minutes of infusion completion), and at 1, 3, 6, 24, and 48 hours and 4, 7, 14, 21, and 28 days (the PK sample drawn at 28 days applies only for subjects on every 4 weeks dosing regimen) after the end of the last the Gamunex-C infusion for determination of a PK curve.

Visits for the Gamunex-C PK Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

4.2.3 IVIG-PEG Phase

4.2.3.1 IVIG-PEG Treatment Phase

At the end of the Gamunex-C PK Phase, all subjects will enter the IVIG-PEG Treatment Phase. During the IVIG-PEG Treatment Phase, all subjects will receive 6 or 5 doses of IVIG-PEG at either 3-week or 4-week intervals. The dose and frequency of IVIG-PEG administered during this phase will be the same as the subject's dose and frequency during the Gamunex-C PK Phase.

Trough IgG levels will be measured within 1 hour prior to each infusion.

Some treatment visits for the IVIG-PEG Treatment Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site. If there are extenuating circumstances that prevent the subject from returning to the study site for these visits, the PI or designee is to discuss the situation with the sponsor. Sponsor approval may be granted to conduct the visit(s) at an alternate location under the care and supervision of trained healthcare personnel.

4.2.3.2 IVIG-PEG PK Phase

Subjects will enter the IVIG-PEG PK Phase at the conclusion of the IVIG-PEG Treatment Phase and will receive 1 additional dose of IVIG-PEG. Pharmacokinetic samples will be collected within 30 minutes prior to the start of the last IVIG-PEG infusion, immediately upon the completion of the last IVIG-PEG infusion (within 10 minutes of infusion completion), and at 1, 3, 6, 24, and 48 hours and 4, 7, 14, 21 and 28 days (the PK sample drawn at 28 days applies only for subjects on every 4 weeks dosing regimen) after the end of the last the IVIG-PEG infusion for determination of a PK curve.

Visits for the IVIG-PEG PK Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

4.2.4 Final Visit/Early Termination Visit

After the completion of the IVIG-PEG PK Phase, subjects will complete the Final Visit/Early Termination Visit.

The Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

The overall study diagram is depicted in Figure 4-1 and Figure 4-2 below.

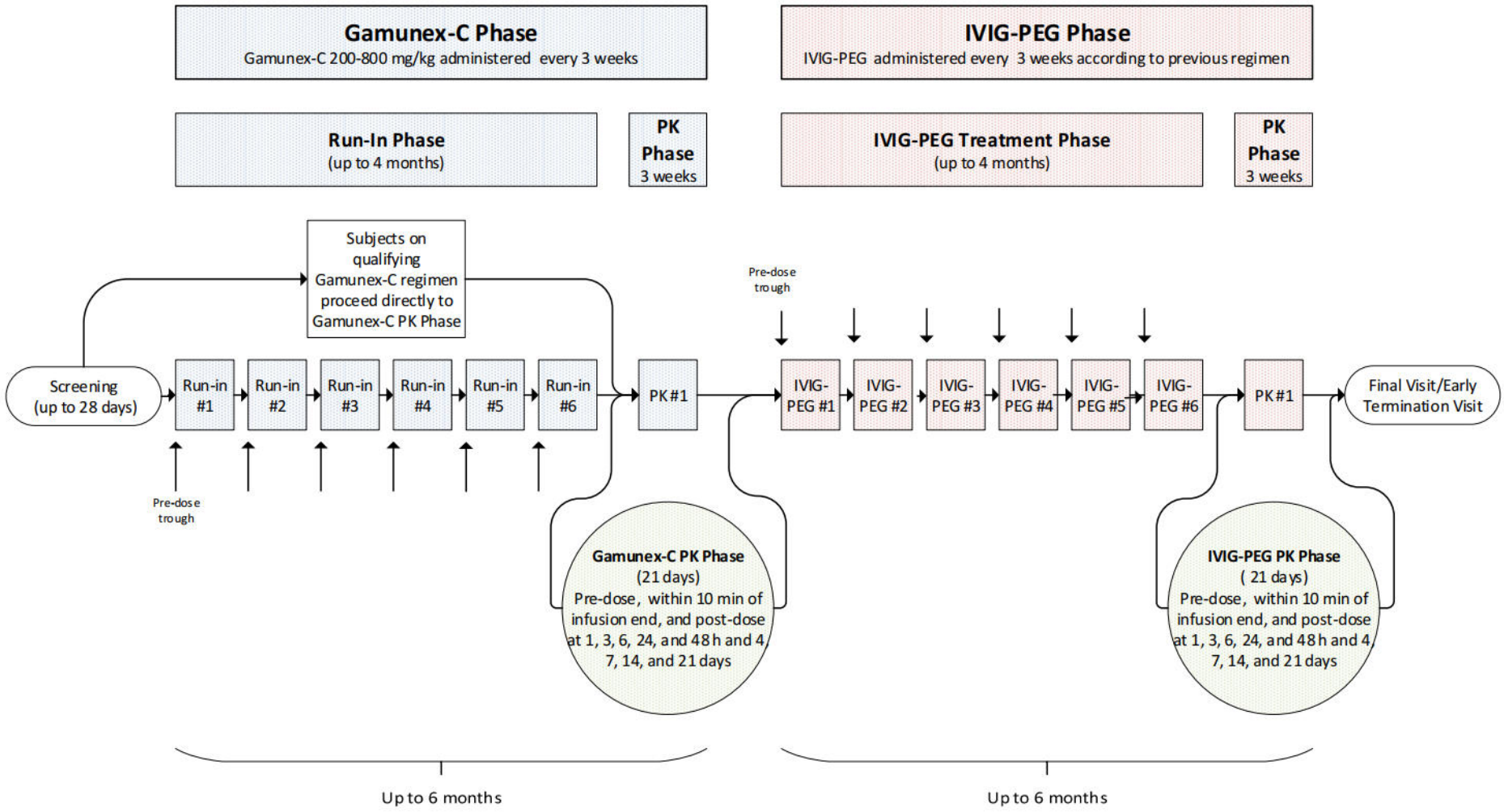

Figure 4-1 Overall Study Schema – Subjects on Every 3-Week Dosing Regimen

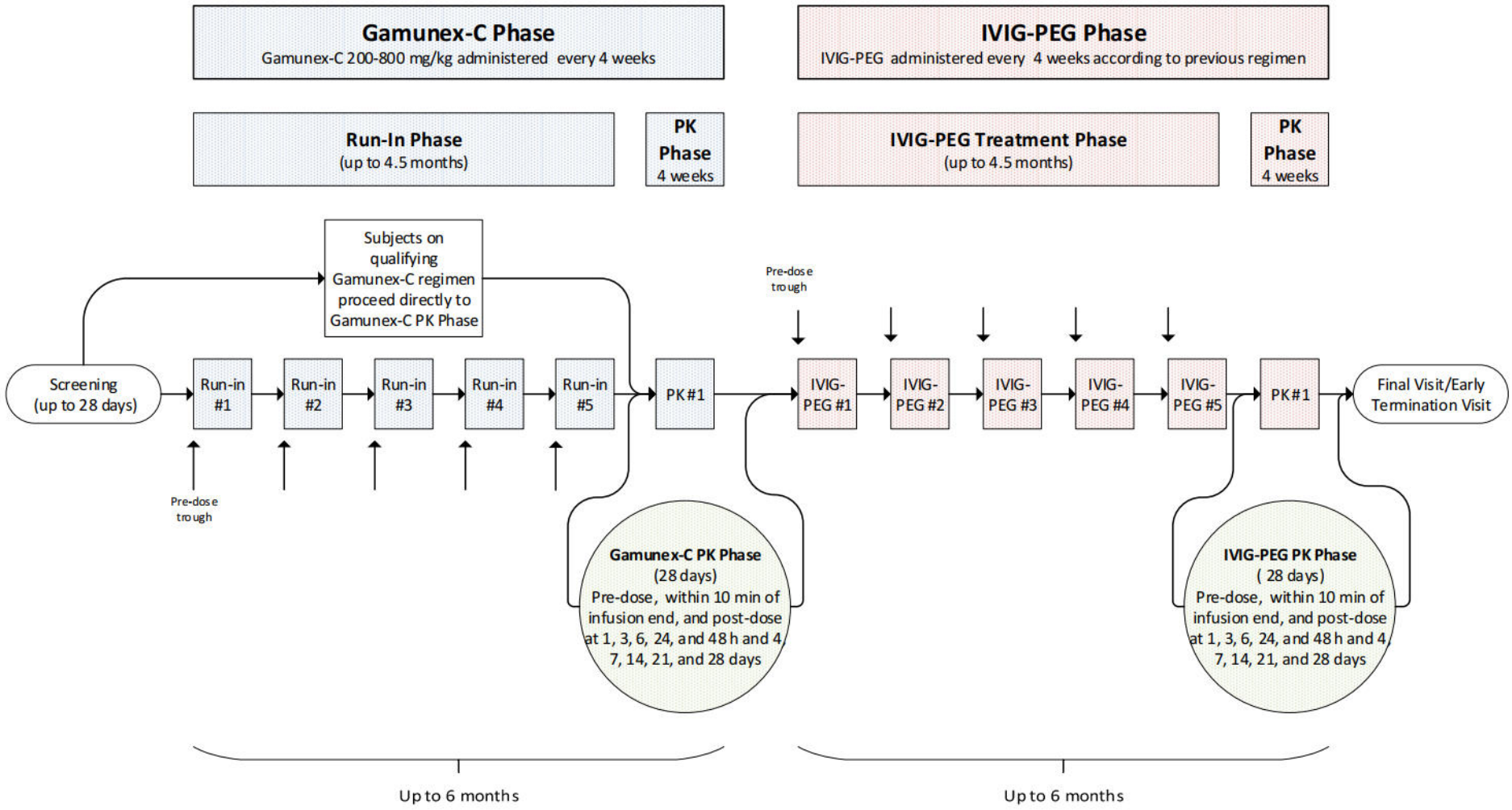

Figure 4-2 Overall Study Schema – Subjects on Every 4-Week Dosing Regimen

4.3 Measures Taken to Minimize/Avoid Bias

4.3.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (3 digits, assigned by the sponsor) followed consecutively with a unique number for each subject (4 digits, including leading zeros). For example, if the Investigators' center number is 301, subject number will be 3010001, 3010002, 3010003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

4.3.2 Randomization

This is an open-label, single-sequence, cross-over study design, therefore randomization is not applicable.

4.3.3 Blinding

Blinding is not applicable for this study.

4.4 Study Treatments

4.4.1 Treatments to Be Administered

IVIG-PEG and Gamunex-C (reference therapy) will be administered during this study.

4.4.1.1 IVIG-PEG

IVIG-PEG is a 10% solution of purified human IgG made from large pools of human plasma via modifications of the Gamunex-C manufacturing process. IVIG-PEG is a sterile, liquid, highly purified, unmodified human IgG product intended for IV administration. In this study, administration of IVIG-PEG will be via the IV route only.

IVIG-PEG consists of 9 to 11% IgG in 0.16 to 0.24 M glycine. IVIG-PEG 10% may be supplied in vial sizes of 10, 25, 50, 100, 200 and 400 mL. For this study, IVIG-PEG will be supplied in 100 mL vials.

4.4.1.2 Gamunex-C

Gamunex-C is a ready-to-use sterile solution of human IgG protein for IV or SC administration. Gamunex-C is a licensed product. Gamunex-C vials may be supplied in the vial sizes of 10, 25, 50, 100, and 200 mL. In this study, administration of Gamunex-C will be via the IV route only.

Gamunex-C consists of 9 to 11% IgG in 0.16 to 0.24 M glycine. The buffering capacity of Gamunex-C is 35.0 mEq/L (0.35 mEq/g protein). A dose of 1 g/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45 to 50 mEq/L of blood, or 3.6 mEq/kg body weight. Thus,

the acid load delivered with a dose of 1 g/kg of Gamunex-C would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously (4).

4.4.2 Labeling of Investigational Products

Investigational products will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed Grifols' procedures and a copy of the labels will be made available to each individual study site.

4.4.3 Packaging of Investigational Products

The sponsor will be responsible for ensuring that the IP is manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

4.4.4 Storage of Investigational Products

IVIG-PEG and Gamunex-C 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 IPs.

IVIG-PEG and Gamunex-C may be stored for up to 36 months from the date of manufacture at 2 to 8°C (36 to 46°F). The products may be stored at temperatures not exceeding 25°C (77°F) for up to 6 months any time during the shelf life from date of manufacture, after which the product must be used immediately or discarded. Do not freeze. All partially used vials should be discarded as no preservative is present. Do not use after expiration date. Investigators, or designees, are responsible for maintaining storage temperature logs and for immediately reporting deviations in temperature to the monitor.

Details for the storage are located in the pharmacy manual provided to each study site.

4.5 Expected Duration of Subject Participation in the Study

The study consists of a Screening Phase (up to 28 days), a Gamunex-C Run-in Phase (up to 4.5 months) for subjects not currently receiving Gamunex-C or not on a stable dose of Gamunex-C, a Gamunex-C PK Phase (up to 4 weeks), an IVIG-PEG Treatment Phase (up to 4.5 months), an IVIG-PEG PK Phase (up to 4 weeks), and a Final Visit/Early Termination Visit. The expected duration of a subject's participation in this study will be up to 54 weeks depending on dosing frequency and Run-in Phase requirement.

4.6 Discontinuation Criteria for Individual Subjects and Study

4.6.1 Discontinuation Criteria for Individual Subjects

See Section 5.3 Subject Withdrawal Criteria

4.6.2 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 reasons:

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

4.6.2.1 Study Stopping Rules

As a conservative measure, if 5 subjects on IVIG-PEG develop a serious adverse event (SAE) of exactly the same type (i.e., the same MedDRA [Medical Dictionary for Regulatory Activities] preferred term) which is not an infection or manifestation of an underlying disorder documented in medical history, then this would constitute an unanticipated clustering which could signal a potential safety concern. If this situation were to arise, the Sponsor will constitute a Safety Review Committee (SRC) whose members (from Grifols) will be impartial and independent of the clinical trial team. In cases where there is a clear medical plausibility supporting an uncommon clustering of SAEs of the same type (not including infections), and these sentinel SAEs are designated as ‘definitely related’, ‘probably related’, or ‘possibly related’ by both the Investigator and the SRC, consideration would be given to possibly discontinuing the study.

Furthermore, if any of the two following situations occur for subjects on IVIG-PEG:

- Three or more subjects develop at least a 50% decrease in trough IgG level from Screening or initiation of the first infusion, whichever is lower, and IVIG-PEG is correctly dosed in terms of mg/kg dosage and treatment interval in all cases.
- Study subjects develop a total of 6 independent and temporally distinct SBIs while on IVIG-PEG given at the correct dose and treatment time interval.

All subsequent infusions of IVIG-PEG will be temporarily suspended in all study subjects and the SRC convene to consider whether to discontinue the study or not in agreement with the PI.

If the SRC and Investigator decision is to discontinue the study due to any of the circumstances described above, all subjects will complete a Final Visit/Early Termination Visit before initiation of treatment with a licensed IVIG.

4.7 Accountability Procedures for Investigational Products

IVIG-PEG and Gamunex-C are to be used only for the study in accordance with the directions given in this protocol and pharmacy/study manual. The Investigator, or designee such as the study pharmacist, is responsible for the distribution of the IPs in accordance with directions given in the protocol and pharmacy manual.

The Investigator, or designee such as the study pharmacist, is responsible for maintaining accurate records of the IVIG-PEG and Gamunex-C 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 inventory must be made available for inspection by the monitor. IVIG-PEG and Gamunex-C supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to the return or destruction of IVIG-PEG and Gamunex-C. 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.

An IP accountability record for both the IPs must be kept current by the clinical site and must contain:

- Subject number
- Initials of the staff person dispensing the product
- Dates and quantities of IP received
- Dates and quantities of IP dispensed
- Dates and quantities of IP returned

4.8 Maintenance of Treatment Randomization Codes

This is an open-label, single-sequence, cross-over study design; therefore, randomization is not applicable.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

This study will be carried out in adult subjects previously diagnosed with PI currently receiving stable replacement therapy with IVIG (either on a 3-week or 4-week treatment schedule) whose disease process is expected to be stable for the duration of the study.

Subjects who initially fail to meet certain eligibility criteria may be rescreened once upon consultation with the sponsor. Subjects who fail to meet eligibility criteria upon rescreening will be considered screen failures and will not be eligible to participate in the study.

5.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for enrollment in this study:

1. Male or female between 18 and 75 years of age (inclusive) at Screening
2. Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IV IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Section 5.2 Exclusion Criteria
3. IgG trough level ≥500 mg/dL at Screening Visit

   Note: Patients entering Group 1 must additionally have trough levels ≥500 mg/dL documented within the previous year. For patients entering Group 2, if Screening trough levels are not ≥500 mg/dL, the subject will be a Screen Failure, but may be rescreened following dose adjustment of their original IV IgG replacement therapy regimen and recording an IgG trough level ≥500 mg/dL
4. Has not had an SBI within the last 6 months prior to Screening or during the Screening
5. Medical records are available to document diagnosis, previous infections, and treatment.
6. Willing to comply with all aspects of the study protocol, including blood sampling, for the duration of the study
7. Signed and dated a written informed consent form (ICF) confirming his or her willingness to participate in study GC1902 (See Section 12.4)

5.2 Exclusion Criteria

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

1. Has 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 (HIV) infection/acquired immune deficiency syndrome (AIDS)
2. Has 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 primary humoral immunodeficiency which have decreased IgA in addition to decreased IgG requiring IgG replacement)
3. Has isolated IgG subclass deficiency or an isolated specific antibody deficiency disorder, or transient hypogammaglobulinemia of infancy
4. The subject has had a known serious adverse reaction to immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product
5. Has a history of thrombotic complications following IVIG therapy
6. Has a history of or current diagnosis of deep venous thrombosis (DVT) or thromboembolism (e.g., myocardial infarction, cerebrovascular accident or transient ischemic attack); history refers to an incident in the year prior to the Screening Visit or 2 episodes over lifetime or has thrombosis risk factors (e.g., prolonged immobilization, use of estrogens, indwelling central vascular catheters)

7. Has a known hyperviscosity syndrome or hypercoagulable states
8. Has liver enzyme levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gammaglutamyl transferase [GGT], or lactate dehydrogenase [LDH]) greater than 2.5 times the upper limit of normal (ULN) at the Screening Visit as defined by the testing laboratory
9. Has pre-existing renal impairment (defined by serum creatinine greater than 1.5 times the ULN or blood urea nitrogen [BUN] greater than 2.5 times the ULN, or any subject who is on dialysis) at the Screening Visit or any history of acute renal injury
10. Has clinically significant history of drug or alcohol abuse or dependence in the opinion of the Investigator (must be within the past 12 months and noted in the subject's medical records or documented at Screening)
11. Clinical evidence of any significant acute or chronic medical condition (e.g., renal disease or predisposing conditions for renal disease, coronary artery disease, or protein losing state) that, in the opinion of the Investigator, may interfere with the conduct of the study or may place the subject at undue medical risk
12. Females of childbearing potential who are pregnant, have a positive pregnancy test at Screening (human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (e.g., oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], 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 [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception)
13. 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 not exceeding >1mg of prednisone equivalent/kg/day for >30 days would not exclude the subject. Inhaled or topical corticosteroids are allowed
14. Has uncontrolled arterial hypertension (systolic blood pressure [SBP] >160 mm Hg and/or diastolic blood pressure [DBP] >100 mm Hg)
15. Has hemoglobin <11 g/dL at the Screening Visit
16. Unable or unwilling to provide a storage serum sample at the Screening Visit

    Note: A pre-treatment serum sample to be stored at -94°F (-70ºC) for possible future testing is required
17. Received any live virus vaccine within 5 months prior to the Screening Visit and not willing to postpone receiving any live virus vaccines until 6 months after completing study treatment
18. Has a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus (HBV) or hepatitis C virus (HCV) infection

19. Has participated in another clinical trial within 30 days prior to Screening or has received any investigational product, with the exception of other IgG products, within the previous 3 months prior to the Screening Visit

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 upon consultation with the sponsor. Subjects who fail to meet the eligibility criteria upon rescreening will be considered screen failures and will not be allowed to participate in the study.

5.3.2 Removal of Subjects

Subjects may withdraw or be withdrawn from the study for the following reasons:

- 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 from IP or the study for the following reasons:

- The subject is uncooperative and noncompliant (defined as 2 consecutive or 3 overall missed study visits) with respect to provisions of the protocol
- The subject develops infection with HBV, HCV, or HIV as determined by the appropriate combination of nucleic acid testing (NAT) and serological tests for each virus
- The subject has a serious AE while participating in the study that, at the discretion of the site Investigator, should lead to discontinuation
- Subjects who develop two SBIs while participating in the study
- The subject becomes pregnant while participating in the study
- The subject requires treatment with any of the medications listed under exclusion criteria
- A subject entering through the Run-in Phase cannot achieve a stable dose of Gamunex-C during the Run-in Phase, i.e., doses during Run-in visits #4, #5, and #6 vary from each other or from the dose given during visit #3 by more than 20%.

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's records.

Subjects who have completed the study and subjects who have withdrawn from the study cannot participate in the study for a second time.

5.3.3 Subject Replacement

Subjects who are withdrawn from the study will not 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 Final Visit/Early Termination Visit procedures as close as practical to 30 days after their last administration of IP, provided that the subjects do not withdraw their consent to participate in this study.

6 TREATMENT OF SUBJECTS

See Section 4.4 for the treatments to be administered, including the names of all the products, the doses, the dosing schedules, the route/modes of administration.

6.1 Administration and Timing of Investigational Products for Each Subject

The Gamunex-C dose and dosing interval during the Run-in Phase or Gamunex-C PK Phase will be individualized based on the previous IVIG treatment the subject was receiving for PI during the Screening Phase. During the IVIG-PEG phases, the IVIG-PEG dose and dosing interval will be individualized based on the previous Gamunex-C treatment the subject was receiving for PI either during the Screening Phase or at the end of the Gamunex-C Run-in Phase (for subjects not directly entering the Gamunex-C PK Phase).

Subjects will receive IVIG-PEG and Gamunex-C by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. The subject's usual mg/kg dose (given on either a 3 or 4 week repeating schedule) will be the same mg/kg dose and schedule that the subject was receiving prior to entering screening. This mg/kg dose and schedule will be used throughout the study duration. Note that the weight of the subject will be measured at each visit and if the subject's weight changes, the actual weight at each visit will be used to calculate amount of drug (mg) to be administered. IVIG-PEG and Gamunex-C will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.

Subjects currently on stable Gamunex-C (for administration of at least 5 consecutive doses) will directly enter the Gamunex-C PK Phase, followed by the IVIG-PEG Treatment Phase in which they will receive 5 or 6 consecutive doses of IVIG-PEG according to their previous dosing regimen (every 4 weeks or every 3 weeks, respectively) and IVIG-PEG PK Phase. Subjects currently on IVIG therapy other than Gamunex-C or on Gamunex-C treatment but not at a stable dose of 200 to 800 mg/kg per infusion or not at every 3- or 4-week intervals will receive Gamunex-C for approximately 4.5 months during the Run-in Phase, prior to the Gamunex-C PK Phase, IVIG-PEG Treatment Phase, and IVIG-PEG PK Phase.

All infusions for both study drugs will be administered using a standard (e.g., polyvinyl chloride) administration kit prepared by qualified personnel, working to local standard operating procedures and under aseptic conditions.

IVIG-PEG and Gamunex-C will be brought to room temperature before each infusion. The nurse performing the infusion should verify by touch that the temperature of product is approximately room temperature. Heating devices should not be used to bring product to room temperature.

6.2 Prior and Concomitant Therapy

Concomitant medications must be recorded in the subject's source documents and eCRF, including the trade and generic names of the medication, the dose, the route of administration, and the duration of the medication (frequency).

Use of prophylactic antibiotics must be recorded as appropriate in the subject's medical records and eCRF to distinguish between prophylactic use and use for treatment of an episode of infection.

6.2.1 Prohibited Medications Prior to Study Participation

Use of the following medications excludes a subject from participating in this study:

- Received any investigational product, with the exception of other IgG products, within the previous 3 months prior to the Screening Visit
- At the time of Screening, receiving systemic corticosteroids (i.e., long-term daily doses >1 mg of prednisone equivalent/kg/day for >30 days; intermittent courses not exceeding 1mg of prednisone equivalent/kg/day for >30 days would not exclude the subject)
  Note: Inhaled or topical corticosteroids are allowed
- At the time of Screening, receiving immunosuppressants including chemotherapeutic agents or immunomodulators
- Clinically significant drug or alcohol abuse or dependence in the opinion of the Investigator (must be within the past 12 months and noted in the subject's medical records or documented at Screening) excludes a subject from participating in this study

6.2.2 Prohibited Concomitant Medications during the Study

All concomitant medications used and therapies received by subjects will be recorded on the appropriate subject's medical records and eCRF page. Use of the following medications is prohibited during study participation:

- Any IgG replacement therapy other than IVIG-PEG or Gamunex-C provided in this study with the exception of the screening visit, when subjects will receive their usual IVIG treatment
- Investigational products not included in this study

- Corticosteroids in excess of stipulations delineated in Section 6.2.1
- Immunosuppressants including chemotherapeutic agents or immunomodulators

6.2.3 Restricted Concomitant Medications during the Study

This section describes medications that are restricted, but not prohibited during study participation. Subjects cannot receive routine premedication during this study. Adequate hydration will be administered to all subjects prior to initiation of infusion with IVIG-PEG. If a subject who previously required premedication is to be enrolled, they must start this study without routine premedication. The previous use of premedication as well as the AE for which the premedication was used must be recorded on the subject's medical records and Screening eCRF page. If an AE which may be prevented by the use of a premedication occurs 2 or 3 times, the AE must be documented on the subject's medical records and appropriate eCRF page, and use of the premedication may be resumed for the remaining study infusions of the same product (i.e., subjects who required premedication in the Gamunex-C Run-in period should start the IVIG-PEG period without using premedication).

The medications listed below are not allowed during the study as premedication (unless after 2 or 3 times occurrence as explained above) to an infusion; however, these medications are allowed during the study for general use (e.g., to treat an AE):

- Acetaminophen
- Antihistamines
- NSAIDs
- Steroids (provided dosing is as outlined in Section 6.2.1)

When premedication is needed, it is recommended that premedication is started using acetaminophen or/and antihistamines, and that NSAIDS as well as steroids are used only if the symptoms are not controlled appropriately with acetaminophen or/and antihistamines.

Note: When premedication is administered, the medication will need to be entered into the eCRF each time that it is administered. The premedication should not be entered into the eCRF only once with the frequency of as needed (PRN).

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 (35). Subjects may not have received any live virus vaccine within the 5 months prior to the Screening Visit (as per exclusion criterion 17). Passive transfer of antibodies from IVIG-PEG or Gamunex-C 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.

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 eCRF and in the subject's medical records.

7 ASSESSMENT OF PHARMACOKINETIC AND OTHER STUDY PARAMETERS

7.1 Pharmacokinetic, Secondary Efficacy, and Exploratory Variables

7.1.1 Primary Pharmacokinetic Variables

The primary PK variables are steady-state AUC of total IgG over a regular dosing interval (τ), defined as $AUC_{0-\tau}$, either every 3 weeks or every 4 weeks (i.e., $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively) and C_{max} in subjects with PI.

7.1.1.1 Other Pharmacokinetic Variables

The other PK variables include:

- Mean steady-state trough concentration of total IgG following IV administration of Gamunex-C and following IV administration of IVIG-PEG
- T_{max}
- Cl
- V_d

7.1.2 Secondary Efficacy Variables

- Rate of SBIs
- All infections of any kind (serious/nonserious including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc.) as determined by the Investigator
- Number of days on antibiotics (including oral, parenteral, oral plus parenteral, prophylactic and therapeutic). Use of prophylactic antibiotics will be distinguished from antibiotics for treatment of acute infection
- Number of hospitalizations due to infection
- Number of days of work/school/daily activities missed per subject year due to infections and their treatment

7.1.3 Exploratory Variables

Exploratory variables include:

- Trough levels of IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Antibody levels for *S. pneumoniae*, *H. influenzae*, and tetanus (*C. tetani*)
- Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen detection test)
- Trough measles antibody titers (functional assay) are an exploratory variable for informational purposes

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

The study phases are described in Section 4.2. The study consists of 4 phases, a Screening Phase (up to 28 days), a Gamunex-C Phase consisting of a Run-in Phase (up to 4.5 months) for subjects not eligible for direct entry into the Gamunex-C PK Phase and a Gamunex-C PK Phase (up to 4 weeks), an IVIG-PEG Phase consisting of an IVIG-PEG Treatment Phase (up to 4.5 months) and an IVIG-PEG PK Phase (up to 4 weeks), and a Final Visit/Early Termination Visit. The total duration of study participation may be up to 54 weeks.

7.2.1 Observations and Measurements

The following sections describe the procedures/assessments to take place at each study visit. See the Schedules of Study Procedures and Events in Appendix 1 for a summary of study visits and the procedures to be conducted at each visit.

7.2.1.1 Screening Phase

Subjects who initially fail to meet eligibility criteria may be rescreened once upon consultation with the sponsor. Subjects who fail to meet eligibility criteria upon rescreening will be considered screen failures and will not be eligible to participate in the study. The duration of the Screening Phase is approximately 28 days.

The Screening Phase will include the following:

- Obtain written informed consent prior to initiation of any Screening procedures
- Assess inclusion and exclusion criteria to determine subject eligibility
- Assign and record subject number
- Record medical history
- Record demographics: year of birth, age at screening (years), gender (if female, fertility status), race, and ethnic origin
- Record specific diagnosis of type of PI, date of diagnosis, and name, start/stop date and dose of current IgG replacement regimen
- Record available IgG trough levels within previous year period

- Record prior medication history
- Perform full physical exam (excluding breast and genitourinary exam)
- Perform chest X-ray (if chest X-ray or CT have not been performed within past 6 months prior to Screening) Note: at least one radiographic view (anterior-posterior [AP] or posterior-anterior [PA]) is required)
- Vital signs: SBP and DBP, heart rate (HR), temperature (T), respiratory rate (RR) after 5 minutes at rest
- Measure body weight and height
- Administration of the subject's usual IVIG treatment
- Blood and/or urine sample for: (see Table 7-1).
  - Hematology: Hb, hct, platelets, RBC count including morphology, white blood cell (WBC) count with differential; absolute reticulocyte count (ARC)
  - Clinical chemistry: sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, GGT, alkaline phosphatase (ALP), glucose, total bilirubin (TBL), indirect and direct bilirubin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), specific gravity
  - Serum pregnancy test (females of child-bearing potential only see Section 5.2)
  - Total IgG trough level determination: participants are required to have a documented total IgG level of ≥500 mg/dL to enroll
  - D-dimer (collected only once during this visit, before their standard of care infusion)
  - Virus safety retains
- Wells Scoring
- Evaluation of clinical signs and symptoms of thromboembolic (TE) events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion (Appendix 3)
- Record AEs (including infusion reactions and prophylactic treatment, if applicable) and history of SBIs up to 1 year

Subjects who are eligible for the clinical trial will enter into the Gamunex-C Run-in Phase or directly into the Gamunex-C PK Phase with the next visit scheduled to coincide with the date for their next IV infusion.

7.2.1.2 Gamunex-C Phase

The duration of the Gamunex-C Phase is approximately 6 months including a Run-in Phase of up to 4.5 months depending on the subject's dosing frequency (every 3 or every 4 weeks) and a Gamunex-C PK Phase of up to 4 weeks (those subjects already receiving stable doses of Gamunex-C can enter directly the Gamunex-C PK Phase and skip the Run-in Phase).

7.2.1.2.1 RUN-IN PHASE –RUN-IN #1, RUN-IN #3, AND RUN-IN #5/#6 VISITS

The following procedures and tests will be completed at the Run-in #1, Run-in #3, and Run-in #5/#6 visits (for the every 4 weeks and every 3 weeks dosing regimens, respectively) during the Run-in Phase for those subjects who are required to enter the Run-in Phase (see Section 4.2.2.1).

- Pre-dose abbreviated physical examination
- Pre-dose vital signs (pre-infusion: SBP and DBP, HR, T, RR) measured within 30 ± 10 minutes before the beginning of each infusion
- Pre-dose body weight
- Pre-dose blood and urine samples for: (see Table 7-1).
  - Hematology: Hb, Hct, platelets, RBC count including morphology, WBC count with differential; ARC
  - Clinical chemistry: sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, GGT, ALP, glucose, TBL, indirect and direct bilirubin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), specific gravity
  - Urine pregnancy test (Run-in #1 Visit only and for females of child-bearing potential only see Section 5.2)
  - Hemolysis detection: plasma free Hb, haptoglobin, DAT, blood smear, urine sediment, measuring of hemoglobinuria, and hematuria
  - Pre-dose blood draw for trough total IgG prior to IV infusion (within 1 hour prior to the start of infusion)
  - Pre-dose blood draw for IgG subclass levels and antibody titer
  - Pre-dose virus safety retains
- D-dimer (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)
- IV Gamunex-C infusion
- Post-dose vital signs (SBP, DBP, HR, T, and RR) measured within 30 ± 10 minutes post-completion of each infusion
- Wells scoring (post-infusion)
- Evaluation of clinical signs and symptoms of TE events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion
  (Appendix 3)
- Evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the

infusion visit (pre-infusion and post-infusion) and by a phone call at 10 days (±2 days) after each infusion (Appendix 4).

- Record AEs including SBIs (subjects who develop two SBIs during the study will be discontinued and requested to complete a Final Visit either 21 or 28 days after the last infusion of IP [depending on the subject's dosing schedule]). Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 7.2.4. (*The site is to record non-serious infections [by category], which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this 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, e.g., bacterial, viral, fungal, or protozoal pathogens [for instance, rapid streptococcal antigen test]. The specific evaluations performed to validate infections must be recorded in the medical records and the eCRF.)
  - Note: If a subject develops an SBI, a serum IgG level should be obtained.
- Record concomitant medications
- Record days lost from work/school/daily activities due to infections and treatment

Gamunex-C Run-in #1, Run-in #3, and Run-in #5/#6 visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

7.2.1.2.2 RUN-IN PHASE –RUN-IN #2, RUN-IN #4, AND RUN-IN #5 VISITS

The following procedures and tests will be completed at the Run-in #2 and #4 visits for all subjects in the Run-in Phase, and at the Run-in #5 visit for subjects on the 3 weeks dosing regimen only (see Section 4.2.2.1).

- Pre-dose abbreviated physical examination
- Pre-dose vital signs (pre-infusion: SBP and DBP, HR, T, RR) measured within 30 ± 10 minutes before the beginning of each infusion
- Pre-dose body weight
- Hemolysis detection (pre-infusion)
  - Blood: whole blood Hb, RBC, hematocrit, plasma free Hb, haptoglobin, LDH, DAT, ARC, TBL, indirect and direct bilirubin, and blood smear
  - Urine: urine sediment, measuring of hemoglobinuria, and hematuria
- Pre-dose blood draw for trough total IgG prior to IV infusion (within 1 hour prior to the start of infusion)

- D-dimer (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)
- IV Gamunex-C infusion
- Post-dose vital signs (SBP, DBP, HR, T, and RR) measured within 30 ± 10 minutes post-completion of each infusion
- Wells scoring (post-infusion)
- Evaluation of clinical signs and symptoms of TE events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion
  (Appendix 3)
- Evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post-infusion) and by a phone call at 10 days (±2 days) after each infusion (Appendix 4)
- Record AEs including SBIs (subjects who develop two SBIs during the study will be discontinued and requested to complete a Final Visit either 21 or 28 days after the last infusion of IP [depending on the subject's dosing schedule]). Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 7.2.4. (*The site is to record non-serious infections [by category], which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this 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, e.g., bacterial, viral, fungal, or protozoal pathogens [for instance, rapid streptococcal antigen test]. The specific evaluations performed to validate infections must be recorded in the subject's medical records and eCRF.)
  - Note: If a subject develops an SBI, a serum IgG level should be obtained.
- Record concomitant medications
- Record days lost from work/school/daily activities due to infections and treatment

Gamunex-C Run-in #2, Run-in #4, and Run-in #5 visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

7.2.1.2.3 GAMUNEX-C PK PHASE

The duration of the Gamunex-C PK Phase is up to 4 weeks (depending on the subject's dosing frequency). For subjects receiving infusions every 3 weeks, the Gamunex-C PK #1 infusion will correspond to the seventh infusion; for subjects receiving infusions every 4

weeks, the Gamunex-C PK #1 infusion will correspond to the sixth infusion. The following procedures and tests will be completed during the Gamunex-C PK Phase.

- Pre-dose abbreviated physical examination
- Pre-dose vital signs (pre-infusion: SBP and DBP, HR, T, RR) measured within 30 ± 10 minutes before the beginning of each infusion
- Pre-dose body weight
- Hemolysis detection (pre-infusion)
  - Blood: whole blood Hb, RBC, hematocrit, plasma free Hb, haptoglobin, LDH, DAT, ARC, TBL, indirect and direct bilirubin, and blood smear
  - Urine: urine sediment, measuring of hemoglobinuria, and hematuria
- Pre-dose blood draw for trough total IgG prior to IV infusion (within 30 min prior to the start of infusion)
- Pre-dose blood draw for IgG subclass levels and antibody titer
- Urine pregnancy test (only for females of child-bearing potential skipping the Run-in Phase who enter directly into the Gamunex-C PK Phase [see Section 4.2.1])
- Pre-dose virus safety retain samples (only for subjects skipping the Run-in Phase who enter directly into the Gamunex-C PK Phase [see Section 4.2.1]).
- D-dimer (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)
- IV Gamunex-C infusion
- Post-dose vital signs (SBP, DBP, HR, T, and RR) measured within 30 ± 10 minutes post-completion of each infusion
- Wells scoring (post-infusion)
- Evaluation of clinical signs and symptoms of TE events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion
  (Appendix 3)
- Evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post-infusion) and by a phone call at 10 days (±2 days) after each infusion (Appendix 4)
- Serial PK blood sample collection immediately upon the completion of the last Gamunex-C infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day sample applies only for subjects on every 4 weeks dose regimen) after the end of the Gamunex-C infusion.
- Record concomitant medications

- Record AEs including SBIs (subjects who develop two SBIs during the study will be discontinued and requested to complete a Final Visit either 21 or 28 days after the last infusion of IP [depending on the subject's dosing schedule]). Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 7.2.4. (*The site is to record non-serious infections [by category], which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this 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, e.g., bacterial, viral, fungal, or protozoal pathogens [for instance, rapid streptococcal antigen test]. The specific evaluations performed to validate infections must be recorded in the subject's medical records and eCRF.)
  - Note: If a subject develops an SBI, a serum IgG level should be obtained.

Gamunex-C PK Visits may be performed at the study site or, if deemed appropriate, at alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

7.2.1.3 IVIG-PEG Phase

The duration of the IVIG-PEG Phase is up to 6 months, including an IVIG-PEG Treatment Phase of up to 4.5 months depending on the subject's dosing frequency (every 3 or every 4 weeks) and an IVIG-PEG PK Phase of up to 4 weeks.

7.2.1.3.1 IVIG-PEG TREATMENT PHASE – IVIG-PEG #1, IVIG-PEG #3, AND IVIG-PEG #5/#6 VISITS

The following procedures and tests will be completed at IVIG-PEG #1, IVIG-PEG #3, and IVIG-PEG #5/#6 (for every 4 weeks and every 3 weeks dosing regimens, respectively) Visits during the IVIG-PEG Treatment Phase.

- Pre-dose abbreviated physical examination
- Pre-dose vital signs (pre-infusion: SBP and DBP, HR, T, RR) measured within 30 ± 10 minutes before the beginning of each infusion
- Pre-dose body weight
- Pre-dose blood and urine samples for: (see Table 7-1).
  - Hematology: Hb, Hct, platelets, RBC count including morphology, WBC count with differential; ARC
  - Clinical chemistry: sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, GGT, ALP, glucose, TBL, indirect and direct bilirubin

- Hemolysis detection: plasma free Hb, haptoglobin, DAT, blood smear, urine sediment, measuring of hemoglobinuria, and hematuria
- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), specific gravity
- Urine pregnancy test (for females of child-bearing potential only see Section 5.2)
- Pre-dose blood draw for trough total IgG prior to IV infusion (within 1 hour prior to the start of infusion).
- Pre-dose blood draw for IgG subclass levels and antibody titer
- Pre-dose virus safety retains

- D-dimer (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)
- IVIG-PEG infusion
- Post-dose vital signs (SBP, DBP, HR, T, and RR) measured within 30 ± 10 minutes post-completion of each infusion
- Wells scoring (post-infusion)
- Evaluation of clinical signs and symptoms of TE events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion
(Appendix 3)
- Evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post-infusion) and by a phone call at 10 days (±2 days) after each infusion (Appendix 4)
- Record AEs including SBIs (subjects who develop two SBIs during the study will be discontinued and requested to complete a Final Visit either 21 or 28 days after the last infusion of IP [depending on the subject's dosing schedule]). Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 7.2.4. (*The site is to record non-serious infections [by category], which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this 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, e.g., bacterial, viral, fungal, or protozoal pathogens [for instance, rapid streptococcal antigen test]. The specific evaluations performed to validate infections must be recorded in the subject's medical records and eCRF.)
  - Note: If a subject develops an SBI, a serum IgG level should be obtained.
- Record concomitant medications

- Record days lost from work/school/daily activities due to infections and treatment

IVIG-PEG #3 and IVIG-PEG #5/#6 visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. The IVIG-PEG #1 treatment visit is to be performed at the study site. If there are extenuating circumstances that prevent the subject from returning to the study site for these visits, the PI or designee is to discuss the situation with the sponsor. Sponsor approval may be granted to conduct the visit(s) at an alternate location under the care and supervision of trained healthcare personnel.

7.2.1.3.2 IVIG-PEG TREATMENT PHASE – IVIG-PEG #2, IVIG-PEG #4, AND IVIG-PEG #5 VISITS

The following procedures and tests will be completed at the IVIG-PEG #2 and #4 visits for all subjects, and at the IVIG-PEG #5 visit for subjects on the 3 weeks dosing regimen only, during the IVIG-PEG Treatment Phase:

- Pre-dose abbreviated physical examination
- Pre-dose vital signs (pre-infusion: SBP and DBP, HR, T, RR) measured within 30 ± 10 minutes before the beginning of each infusion
- Pre-dose body weight
- Hemolysis detection (pre-infusion)
  - Blood: whole blood Hb, RBC, hematocrit, plasma free Hb, haptoglobin, LDH, DAT, ARC, TBL, indirect and direct bilirubin, and blood smear
  - Urine: urine sediment, measuring of hemoglobinuria, and hematuria
- Pre-dose blood draw for trough total IgG prior to IV infusion (within 1 hour prior to the start of infusion).
- D-dimer (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)
- Pre-dose urine pregnancy test (for females of child-bearing potential only see Section 5.2)
- IVIG-PEG infusion
- Post-dose vital signs (SBP, DBP, HR, T, and RR) measured within 30 ± 10 minutes post-completion of each infusion
- Wells scoring (post-infusion)
- Evaluation of clinical signs and symptoms of TE events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion
  (Appendix 3)

- Evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post-infusion) and by a phone call at 10 days (±2 days) after each infusion (Appendix 4)
- Record AEs including SBIs (subjects who develop two SBIs during the study will be discontinued and requested to complete a Final Visit either 21 or 28 days after the last infusion of IP [depending on the subject's dosing schedule]). Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 7.2.4. (*The site is to record non-serious infections [by category], which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this 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, e.g., bacterial, viral, fungal, or protozoal pathogens [for instance, rapid streptococcal antigen test]. The specific evaluations performed to validate infections must be recorded in the subject's medical records and eCRF.)
  - Note: If a subject develops an SBI, a serum IgG level should be obtained.
- Record concomitant medications
- Record days lost from work/school/daily activities due to infections and treatment

IVIG-PEG #4 and IVIG-PEG #5 visits (as applicable) may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. The IVIG-PEG #2 treatment visit is to be performed at the study site. If there are extenuating circumstances that prevent the subject from returning to the study site for these visits, the PI or designee is to discuss the situation with the sponsor. Sponsor approval may be granted to conduct the visit(s) at an alternate location under the care and supervision of trained healthcare personnel.

7.2.1.3.3 IVIG-PEG PK PHASE

The duration of the IVIG-PEG PK Phase is up to 4 weeks (depending on the subject's dosing frequency). For subjects receiving infusions every 3 weeks, the IVIG-PEG PK #1 infusion will correspond to the seventh infusion; for subjects receiving infusions every 4 weeks, the IVIG-PEG PK #1 infusion will correspond to the sixth infusion. The following procedures and tests will be completed during the IVIG-PEG PK Phase.

- Pre-dose abbreviated physical examination
- Pre-dose vital signs (pre-infusion: SBP and DBP, HR, T, RR) measured within 30 ± 10 minutes before the beginning of each infusion

- Pre-dose body weight
- Hemolysis detection (pre-infusion)
  - Blood: whole blood Hb, RBC, hematocrit, plasma free Hb, haptoglobin, LDH, DAT, ARC, TBL, indirect and direct bilirubin, and blood smear
  - Urine: urine sediment, measuring of hemoglobinuria, and hematuria
- Pre-dose blood draw for trough total IgG prior to IV infusion (within 30 min prior to the start of infusion)
- Pre-dose blood draw for IgG subclass levels and antibody titer
- D-dimer (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)
- Pre-dose urine pregnancy test (for females of child-bearing potential only see Section 5.2)
- IVIG-PEG infusion
- Post-dose vital signs (SBP, DBP, HR, T, and RR) measured within 30 ± 10 minutes post-completion of each infusion
- Wells scoring (post-infusion)
- Evaluation of clinical signs and symptoms of TE events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of the infusion (Appendix 3)
- Evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post-infusion) and by a phone call at 10 days (±2 days) after each infusion (Appendix 4)
- Serial PK blood sample immediately upon the completion of the last IVIG-PEG infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day sample applies only for subjects on every 4 weeks dose regimen) after the end of the infusion.
- Record concomitant medications
- Record AEs including SBIs (subjects who develop two SBIs during the study will be discontinued and requested to complete a Final Visit either 21 or 28 days after the last infusion of IP [depending on the subject's dosing schedule]). Note: Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category*) as detailed in Section 7.2.4. (*The site is to record non-serious infections [by category], which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this 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, e.g., bacterial, viral, fungal, or

protozoal pathogens [for instance, rapid streptococcal antigen test]. The specific evaluations performed to validate infections must be recorded in the subject's medical records and eCRF.)

- Note: If a subject develops an SBI, a serum IgG level should be obtained.

IVIG-PEG PK Visits may be performed at the study site or, if deemed appropriate, at alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

7.2.1.4 Final Visit/Early Termination Visit

The Final Visit will be scheduled either 21 or 28 days after the last infusion of IP (depending on the subject's dosing schedule). If a subject discontinues at any point during the study after the first visit, the subject will be requested to return to the study site for an Early Termination Visit. The assessments at this visit will be the same as the Final Visit, with the exception of an added PK sample for subjects who prematurely discontinue the study during the PK curves sampling periods (i.e., Gamunex-C PK Phase and IVIG-PEG PK Phase) and a sample for total IgG concentration for safety purposes for subjects prematurely discontinuing the study at any point.

The following procedures and tests (see Appendix 1) will be completed at the Final Visit/Early Termination Visit (note that no study-related infusion will be scheduled):

- Full physical exam (excluding breast and genitourinary exam)
- Vital signs (SBP, DBP, HR, T, RR)
- Blood and urine samples for clinical laboratory assessments (e.g., hematology, clinical chemistry, special tests, urinalysis, and pregnancy testing) (see Table 7-1).
  - Hematology: Hb, Hct, platelets, RBC count including morphology, WBC count with differential; ARC
  - Clinical chemistry: sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, GGT, ALP, glucose, TBL, indirect and direct bilirubin
  - Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), specific gravity
  - Urine pregnancy test (for females of child-bearing potential only see Section 5.2)
  - Blood draw for total IgG concentration for safety purposes (only for subjects prematurely discontinuing the study)
  - Pre-dose virus safety retain samples
- Record concomitant medications
- Record AEs including SBIs

- Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category) as detailed in Section 7.2.4.
- Note: If a subject develops an SBI, a serum IgG level should be obtained.

- Record days lost from work/school/daily activities due to infections and treatment

The Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.

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. Under extraordinary circumstances, some of the laboratory tests can be performed at the site's local laboratory if testing is unable to be performed by the central laboratory. When feasible and time permits, the site should discuss the extraordinary circumstances in advance with the sponsor and/or Contract Research Organization (CRO).

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

Test Panel	Description	Location
Hematology[a]	Hemoglobin, hematocrit, platelets, RBC count including RBC morphology, WBC count with differential; ARC	Central
Hemolysis detection[a,b]	Blood: whole blood Hb, RBC, hematocrit, plasma free Hb, haptoglobin, LDH, DAT, ARC, TBL, indirect and direct bilirubin, and blood smear Urine: urine sediment, measuring of hemoglobinuria, and hematuria	Central (central DAT if feasible)
Thromboembolic events risk[a,b]	D-Dimer	Central
Chemistry[a]	Sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, GGT, glucose, TBL, indirect and direct bilirubin	Central
IgG levels[a]	Total IgG levels will consist of trough (pre-dose) measurements in all subjects, and for PK profiling of IVIG-PEG and a total IgG concentration for safety purposes for subjects prematurely discontinuing the study	Central
IgG subclass levels and antibody titers[a]	Measurement of IgG subclasses (IgG1, IgG2, IgG3, IgG4). Measurement of levels of selected specific antibodies against *H. influenzae,* anti-pneumococcal polysaccharide (*S. pneumoniae*), tetanus *(C. tetani)*, and measles	Specialty
Serum pregnancy test[a]	Quantitative serum β-HCG for females of child-bearing potential will be performed at Screening	Central

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

Test Panel	Description	Location
Urine pregnancy test	Qualitative urine pregnancy test for females of child-bearing potential will be performed prior to the first dose received for each IP as well as prior to each IVIG-PEG infusion, and at the Final Visit/Early Termination Visit	Local
Viral NAT testing[a,c]	Collect retain samples for hepatitis A virus (HAV) RNA, HBV DNA, HCV RNA, HIV RNA, and parvovirus B19 (B19V) DNA testing	Central
Viral serology testing[a,c]	Collect retain samples for hepatitis A antibody differential (IgM/IgG), hepatitis B core antibody differential (IgM/IgG), hepatitis C antibody, HIV-1/-2 + Group O antibody, and B19V antibody differential (IgM/IgG) testing	Central
Urinalysis[a]	Microscopic evaluation is done only with cause. pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of the urine if abnormal), specific gravity, and urine sediment	Central

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

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

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

7.2.3 Immunoglobulin G Assessments

All subjects will have trough (pre-dose) total IgG measurements performed at Screening and prior to every infusion to ensure that adequate IgG concentration levels are maintained (not less than 500 mg/dL) to avoid serious infections. Furthermore, if a subject develops an SBI, a serum IgG level should be obtained. Additionally, IgG subclass antibody levels (IgG1, IgG2, IgG3, and IgG4) will be measured prior to the Gamunex-C PK infusion, prior to Infusions 1, 3, and 5 or 6 (for subjects on every 4- or 3-weeks dosing regimen, respectively) during the Gamunex-C Run-in Phase and IVIG-PEG Treatment Phase, and prior to the IVIG-PEG PK infusion.

Specific antibody levels to the following pathogens will also be measured prior to the Gamunex-C PK infusion, prior to Infusions 1, 3, and 5 or 6 (for subjects on every 4- or 3-weeks dosing regimen, respectively) during the Gamunex-C Run-in Phase and IVIG-PEG Treatment Phase, and prior to the IVIG-PEG PK infusion: *H. influenzae*, anti-pneumococcal polysaccharide (*S. pneumoniae*), tetanus (*C. tetani*), and measles.

Samples will be retained until all analyses in support of the study specified in Section 7.2.1 are complete.

Total IgG PK profiling will be performed as described in Section 7.2. Samples will be obtained within 30 minutes prior to the start of the last Gamunex-C and IVIG-PEG infusion and at the following post-infusion time points:

- Immediately upon the completion of the infusion (within 10 minutes of infusion completion)
- 1 hour ±10 min after completion of infusion
- 3 hours ±10 min after completion of the infusion
- 6 hours ±10 min after the completion of the infusion
- 24 hours ±2 hours after the completion of the infusion
- 48 hours ±2 hours after the completion of the infusion
- 4 days ±2 hours after the completion of the infusion
- 7 days ±1 day after the completion of the infusion
- 14 days ±1 day after the completion of the infusion
- 21 days ±2 days after the completion of the infusion (last sample for subjects on a 3-week dosing schedule)
- 28 days ±2 days after the completion of the infusion (only for subjects on a 4-week dosing schedule)

7.2.4 Assessment and Recording of Infections

The site is to record non-serious infections (by category), which include infections of any kind including, for example, acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, pneumonia, acute bronchitis, infectious diarrhea, etc., which will be recorded as an AE with the Investigator answering the following question affirmatively in the subject's medical records and eCRF: "Is this an infection?" (verbatim term delineating nature of infection). Validated infections documented by positive radiograph, fever (>38°C oral or >39°C rectal), culture, or diagnostic testing for microorganisms, e.g., bacterial, viral, fungal, or protozoal pathogens (for instance, rapid streptococcal antigen test) will be recorded in the subject's source documents and eCRF. The specific evaluations performed to validate infections must be recorded in the subject's medical records and eCRF.

7.2.5 Virus Safety Testing

Virus safety (viral NAT and viral serology) retain samples will be collected prior to the first infusions of Gamunex-C, and IVIG-PEG and at the Final/Early Termination Visit and will only be tested if the subject exhibits clinical signs and symptoms consistent with hepatitis A virus (HAV), HBV, HCV, HIV, or parvovirus B19 (B19V) infection while participating in the study. Virus safety samples will be retained until all analyses in support of the study are complete. Additional blood samples for viral NAT and viral serology testing may be

collected and tested during the study only if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V infection while participating in the study.

If samples collected for laboratory analyses are non-analyzable due to various factors (i.e., lost, quantity not sufficient/useful, laboratory error), they will be recollected by contacting the subject and arranging for resampling.

8 ASSESSMENT OF SAFETY

8.1 Safety Parameters

Safety of IVIG-PEG and Gamunex-C will be evaluated in this study.

The following safety variables will be assessed:

- Adverse events, suspected ADRs (i.e., potentially related AEs), adverse reactions (ARs), SAEs, and discontinuations due to AEs and SAEs
- Criteria for events of special interest (See Section 8.2.5)
- Vital signs during clinic visits (SBP, DBP, HR, T, RR)
- Physical assessments
- Laboratory assessments including chemistry, hematology, special tests, and urinalysis.

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

See Section 7.2.1 and Appendix 1 for a full accounting of PK and safety assessments by study phase and visit.

8.2.1 Adverse Events

Adverse events (including ARs) occurring at any time between signing of the subject's ICF and the last day of the subject's participation in the study will be reported and recorded in the subject's source documentation and on the appropriate eCRF page.

It is the 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

Clinical laboratory data for hematology, chemistry, and urinalysis will be collected as detailed in Appendix 1. All clinical laboratory data for hematology, chemistry, and urinalysis will be listed for each study subject.

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 criteria.

Laboratory results out of the normal range judged by the Investigator as clinically significant will be considered AEs.

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. The following vital signs will be assessed:

- Temperature
- Blood pressure (SBP and DBP)
- Heart rate
- Respiratory rate

Vital signs will be routinely monitored by the study staff as detailed in Appendix 1. The Investigator will be required to classify vital signs abnormalities as clinically significant or not according to his/her criteria. Results will be recorded in source documents and on the subject eCRF. Vital signs abnormalities judged by the Investigator as clinically significant will be considered AEs.

8.2.4 Physical Examinations

A medically certified individual will conduct either a full or abbreviated physical examination (excluding breast and genitourinary examination) as indicated in Appendix 1.

8.2.5 Monitoring of Events of Special interest

8.2.5.1 Monitoring of Thrombotic Events

Subjects will be monitored by the Investigator and/or study staff for signs and symptoms of arterial and venous TE events at Screening and occurring between the first infusion (either the first infusion of Gamunex-C during the Run-in Phase or the first infusion of IVIG-PEG during the IVIG-PEG Treatment Phase) and the Final Visit/Early Termination Visit.

In addition, the Grifols Medical Monitor will routinely review reported AEs for possible TE events. Arterial and venous TE events will be identified according to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Such TE events include, but are not limited to, DVT, PE, acute myocardial infarction, cerebrovascular accident, acute coronary syndrome, limb thrombosis, sagittal sinus thrombosis, and portal vein or mesenteric artery thrombosis. All TE events will be recorded as AEs and reported accordingly.

At Screening and during all infusion visits, TE events risk will be assessed using:

1. D-dimer blood levels (within 8 hours prior to the study IP infusion and 30 ±10 minutes after the completion of the infusion)

Note: The sample for the D-dimer blood level is only collected before the subject's standard-of-care infusion at the Screening Visit.

2. The Wells prediction score for DVT and for PE (after the completion of the infusion)
3. Evaluation of clinical signs and symptoms of TE events (such as, dyspnea, pain, swelling, tenderness and discoloration [paleness or redness] in lower extremities) after the completion of the infusion

After getting results from (1) to (3) and prior to the next study infusion visit, a medical doctor will assess the risk of TE events considering algorithms provided in Appendix 3 from the first Gamunex-C to the last IVIG-PEG study infusions.

Active medical monitoring of thromboembolic AEs of special interest is described in a detailed manner in Appendix 3.

8.2.5.2 Monitoring of Hemolysis

Subjects will be monitored for signs and symptoms of hemolysis occurring between the first infusion (either the first infusion of Gamunex-C during the Run-in Phase or the first infusion of IVIG-PEG during the IVIG PEG Treatment Phase) and the Final Visit/Early Termination Visit.

In addition, the Grifols Medical Monitor will routinely review reported AEs for possible hemolysis. Hemolysis will be recorded as an AE and reported accordingly.

During all infusion visits, hemolysis detection will be evaluated using:

1. Blood assessments including whole blood hemoglobin, plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, total and indirect and direct bilirubin, and blood smear within 8 hours prior to the infusion
2. Urinalysis including urinary sediment, hematuria, and hemoglobinuria within 8 hours prior to the infusion
3. Clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) will be evaluated at each infusion visit (pre-infusion and post infusion) and by a phone call at 10 days (±2 days) after each infusion

After getting results from (1) to (3) and prior to the next study infusion visit, a medical doctor will assess the hemolysis considering algorithm provided in Appendix 4from the first Gamunex-C to the last IVIG-PEG study infusions.

Active medical monitoring of hemolysis AEs of special interest is described in detail in Appendix 4.

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 IVIG-PEG refer to the IB.

8.3.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs and symptoms. 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.

Infusional AEs (i.e., AEs temporally associated with an infusion of IP) will be defined and reported. Any AE occurred during infusion or within 72 hours after completion of infusion will be considered temporally associated with the infusion and labelled as infusional AEs.

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 (i.e., potentially related AE). 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.

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 Sponsor will consider the Investigator's causality assessment and also provide its own assessment.

Causal relationship to the IPs will be established according to medical judgment on whether there is a **reasonable possibility of a causal relationship between the AE and 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 of 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 "definitively related" or "possibly 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 visit of the study will be considered treatment-emergent AEs (TEAEs).

8.3.5 Severity of Adverse Event or Suspected Adverse Drug Reaction

Adverse events and suspected ADRs (i.e., potentially related AEs) 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 event and suspected ADR (i.e., potentially related AE) 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 study, 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 (i.e., potentially related AE) 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 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 (i.e., potentially related AE) 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 study protocol, or as part of a routine procedure followed by the center.
- Admissions not associated with an AE (e.g., 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 (e.g., 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 Visit (i.e., end of study)** must be fully recorded in the subject's source documentation and eCRF, and in the SAE form (if serious) as well as in the medical record. If no AE has occurred during the study phase, 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 AE CRF/eCRF and the subject's source documents:

- 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 sequelae (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 (if applicable), 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 and the subject's source document.

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, e.g., 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 Visit (i.e., 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 medical records and the CRF/eCRF and SAE Report Form.

In addition, any SAE that occurs in a subject after their last study visit 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.

SAEs will be reported using the designated paper SAE Report Form. When the Investigator becomes aware of an 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 (i.e., medical records).

Each SAE reported 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 CRO may request additional information and/or reports.

All SAE Report Forms must be reported to Grifols by email 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.

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. The Investigator must report any pregnancy that occurs in a study subject subsequent to informed consent until 28 days after the last dose of IP.

A pregnancy will not be 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.

Pregnancy exposures that result in AEs/SAEs should be followed by the Investigator until delivery or to the end of pregnancy.

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

Insofar as is possible, all individuals will be followed up until the AE or suspected ADR (i.e., potentially related AE) 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 study or after study completion due to early termination will not be actively collected. However, if such cases are reported by the Investigator as related to the study treatment, they will be considered for expedited reporting purposes.

9 STATISTICS

9.1 Statistical Methods

Unless otherwise specified, descriptive statistics will include the number of non-missing 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.

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. For quantitative variables, mean, SD, median, and minimum/maximum will be provided. For qualitative variables, the frequency and percentage will be provided.

9.1.2 Pharmacokinetic Analysis

Total IgG concentrations will be summarized for IVIG-PEG and Gamunex-C by each time point. Individual and mean total IgG concentrations versus time curves will be plotted. Pharmacokinetic parameters of total IgG will be determined by noncompartmental PK methods using WinNonlin. Steady-state PK parameters to be calculated, as appropriate, or as permitted by data, will include AUC, C_{max}, t_{max}, Cl, and V_d. All PK parameters will be calculated separately for IVIG-PEG and Gamunex-C administration and will be tabulated and summarized descriptively. The mean and the lower and upper bounds of the 90% CI will be calculated on natural log-transformed AUC parameters. These mean and lower and upper bounds will be back-transformed (exponentiated) to provide the geometric mean and 90% CI on the original scale.

Pharmacokinetic analyses will be performed on the PK population. The Primary PK endpoints are the steady-state AUC over a dosing interval defined as $AUC_{0-\tau}$ (i.e., the AUC over a regular dosing interval (τ) at an approximate steady-state condition, either every 3 weeks or every 4 weeks, i.e., $AUC_{0\text{-}21\ days}$ or $AUC_{0\text{-}28\ days}$, respectively) and C_{max}. The hypothesis to be tested is that the IV dose of IVIG-PEG will achieve an approximate steady-state $AUC_{0-\tau}$ and C_{max} of total IgG that is bioequivalent to that achieved by the IV dose of Gamunex-C. Bioequivalence of steady-state IgG AUC and C_{max} between IVIG-PEG and Gamunex-C will be tested based on established regulatory guidelines for bioequivalence testing. Analysis of covariance (ANCOVA) with a mixed-effect model will be used with study PK phase as a fixed effect, the exact administered dose and dose frequency during the PK phase as covariates, and subject as a random effect. The 90% CI of the geometric least-squares mean (LSM) AUC and C_{max} ratio of IVIG-PEG to Gamunex-C will be calculated. IVIG-PEG is considered to be bioequivalent to Gamunex-C if the 90% CI for the geometric LSM AUC and C_{max} ratio of IVIG-PEG to Gamunex-C is within (0.80, 1.25) based on log-transformed data.

Other PK parameters will be listed and summarized for IVIG-PEG and Gamunex-C using arithmetic as well as geometric means and SD, percentage coefficient of variation (CV), median, and minimum/maximum, as appropriate.

Other PK parameters include steady-state mean trough concentration of total IgG, T_{max}, Cl, and V_d. The steady-state mean trough concentrations of total IgG will be determined as the average value of trough concentration measurements obtained at the PK visit and at 21 or 28 days after the PK infusion (depending on dosing interval). Descriptive statistics will be calculated for the steady-state mean trough concentration of total IgG and for the T_{max}, Cl, and V_d.

Depending on the number of subjects being dosed at 3- or 4-week dosing intervals, subgroup analyses may be performed to evaluate PK variables by IV dosing interval. Subgroup analyses will additionally include age, sex, race, and/or other factors as appropriate.

Furthermore, baseline corrected PK parameters (i.e., AUC and C_{max}) will be calculated and analyzed as a sensitivity analysis similar to the primary PK endpoints.

9.1.3 Secondary Efficacy and Exploratory Analyses

Summaries will be provided for trough concentration of total IgG and each of its subclasses for IVIG-PEG and Gamunex-C. Summaries of trough level concentration of antibody titers against *H. influenzae*, anti-pneumococcal polysaccharide (*S. pneumoniae*), and tetanus (*C. tetani*) will also be provided. Trough measles antibody titers (functional assay) will be summarized as an exploratory variable for informational purposes.

The number of SBIs and percentage of subjects with SBIs will be summarized for IVIG-PEG and Gamunex-C. The generalized linear model procedure for Poisson regression with log link will be used to estimate the SBI rate and its one-sided 99% upper confidence bound. Person-year will be calculated for each subject and will be used in the generalized linear model as offset variable. No covariates but the intercept term are included in the model. The estimated intercept term and the upper limit of its confidence interval (CI) will be transformed by using the natural exponential function.

The other variables of all infections, validated infusions, days missed of work/school/daily activities, days on antibiotics, and hospitalizations will be summarized descriptively for the number and percentage of subjects with the events, the total number of events or days, the annualized rate of events or days for individual subjects, and the rate of events or days per person per year for IVIG-PEG and Gamunex-C. Annualized rate of all infections, validated infusions, days missed of work/school/daily activities, days on antibiotics, and hospitalizations will be calculated.

9.1.4 Safety Analysis

The safety analyses will be addressed by listing and tabulation of AEs (including suspected ADRs [i.e., potentially related AEs]), vital signs, physical assessments and clinical laboratory tests. Data will be described using descriptive analyses. The safety analyses are based on the safety population.

9.1.4.1 Adverse Events

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

Adverse events will be classified as treatment-emergent AEs (TEAEs) or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment with the IP. A TEAE will be defined as an AE which occurs between the beginning of the first infusion of IP and the final visit of the 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.

All AEs, suspected ADRs (i.e., potentially related AEs), ARs, SAEs, and discontinuations due to AEs and SAEs will be summarized by presenting subject incidences and percentages and will also be listed by system organ class and preferred terms.

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

Infusional AEs will be defined as any AE that occurred during infusion or within 24 and 72 hours after completion of infusion. Infusional AEs within 24 and 72 hours after completion of the infusion will be separately summarized. Also, the infusional AE rate per infusion and the proportion of infusions with one or more infusional AEs will be summarized.

Subjects with deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed and presented in a narrative form.

9.1.4.2 Clinical Laboratory Values

All clinical laboratory data collected will be listed for each subject.

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 criteria.

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.

For all laboratory tests, 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.

9.1.4.3 Vital Signs

Vital signs (T, RR, HR, SBP and DBP) will be listed for each study subject. In case a subject presents a clinically significant abnormality of vital signs during an infusion, the event will be flagged and reported as an AE temporally associated to the infusion.

Clinical relevance will be based on the Investigator's criteria. For each subject and for each infusion, every vital sign will be considered.

For all vital signs, the original value and the change from Baseline will be summarized for numeric results.

9.1.4.4 Physical Assessment

Physical findings (normal and abnormal) will be listed for each study subject. Any clinically significant abnormality developed by an individual subject during the study and not already present at baseline will be reported as AE.

9.2 Determination of Sample Size

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

9.3 Level of Significance to Be Used

The relative alpha level for statistical significance to be used is 0.1 (alpha=0.05 for one-sided test), or a 90% CI is to be used for the bioequivalence test.

9.4 Criteria for Termination of the Study

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

A study center can be closed for the following reasons:

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

Additional details on study stopping rules can be found in Section 4.6.2.1.

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

Handling of missing, unused, and spurious data will be described in the SAP. All available PK and safety data will be included in data listings.

9.6 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 Clinical Study Report.

9.7 Subject Populations for Analysis

9.7.1 Safety Population

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

9.7.2 Pharmacokinetic Population

The PK population will consist of all subjects who received study drug and have sufficient and valid total IgG concentration versus time data for either the IVIG-PEG PK Phase or Gamunex-C PK Phase to allow calculation of $AUC_{0-\tau}$ (the primary PK endpoint).

The validity of total IgG concentrations will be reviewed and determined before database lock based on consideration of treatment compliance and blood sampling/testing issues (such as collection problem). Any invalid total IgG concentrations will be flagged with the reason for invalidity in the subject listing.

9.7.3 Immunoglobulin G Population

The IgG population will consist of all subjects who receive study drugs and have any total IgG concentration data. The summary of total IgG concentration data, mean trough, IgG subclasses, and antibody titers will be based on the IgG Population.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data will be recorded and kept current in the subject's medical records and the 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 CRF/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 audits or 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 (e.g., Clinical Assessment Monitor [CAM], Project Manager [PM], Project Lead [PL]) immediately. The Investigator agrees to provide to representatives of a regulatory authority or Grifols access to records, facilities, and personnel for the effective conduct of an audit or inspection.

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 are organized and operate 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 a need for changes 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 competent 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 written approval/favorable opinion of the written ICF by the IRB/EC 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 the 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 signed 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 (e.g., 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 subject's medical records and 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 which will be defined in the source data agreement will be filed in TMF.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE 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 (e.g., 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, the 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.

The 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 the 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 ("HIPAA") 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.

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17 APPENDICES

Appendix 1 Schedule of Procedures and Events

Table A. Every 3 Weeks Dosing Regimen

Study Phase / Visit / Procedure	Screening Visit (up to 28 days)	Run-in Phase (Gamunex-C every 3 weeks)						Gamunex-C PK Phase	Treatment Phase (IVIG-PEG every 3 weeks)						IVIG-PEG PK Phase	Final Visit/Early Termination
		Run-in #1	Run-in #2	Run-in #3	Run-in #4	Run-in #5	Run-in #6	Gamunex-C PK#1	IVIG-PEG #1	IVIG-PEG #2	IVIG-PEG #3	IVIG-PEG #4	IVIG-PEG #5	IVIG-PEG #6	IVIG-PEG PK#1	
Informed consent	X															
Inclusion/exclusion criteria	X															
Medical history & demographics	X															
Prior medication history	X															
Full physical exam[a]	X								X							X
Abbreviated physical exam[b]		X	X	X	X	X	X	X		X	X	X	X	X	X	
Chest X-ray[c]	X															
Vital signs	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X
Height	X															
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[f]	X															
Urine pregnancy test[f]		X						X[u]	X	X	X	X	X	X	X	X
Laboratory assessments (hematology, chemistry, urinalysis)[g,h,i,s]	X	X[s]		X[s]			X[s]		X[s]		X[s]			X[s]		X
Thromboembolism evaluation[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hemolysis detection[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Total IgG trough level	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Sample for IgG subclass levels and Ab titer[l,m]		X		X			X	X	X		X			X	X	
Virus safety retain[n,]	X	X		X			X	X[u]	X		X			X		X
Gamunex-C infusion[o]		X	X	X	X	X	X	X								
IVIG-PEG infusion[o]									X	X	X	X	X	X	X	
Serial PK samples[p]								X							X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessments including infections[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record days lost from work/school/daily activities		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor signs and symptoms of hemolysis[r]		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] Pre-dose abbreviated physical exam (targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and inspection of previous injection sites.)

[c] Only if chest X-ray or CT have not been performed in the 6 months prior to the Screening Visit.

[d] Vital signs (SBP, DBP, HR, T, and RR) will be measured within 30 ± 10 minutes before the beginning of each infusion and within 30 ± 10 minutes post-completion of each infusion.

[e] Body weight will be measured prior to the infusion to determine the IP dose.

[f] Females of child-bearing potential only; results must be negative to participate in the study or continue on IP. Quantitative serum β-HCG will be performed at the Screening Visit. A qualitative urine pregnancy test will be performed prior to the first dose received for each IP as well as prior to each IVIG-PEG infusion, and at the Final Visit/Early Termination Visit. Pregnancy testing will be repeated at any time if pregnancy is suspected.

[g] Hematology will include: hemoglobin, hematocrit, platelets, RBC count including RBC morphology, WBC count with differential, and ARC.

[h] Chemistry will include: sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, GGT, glucose, TBL, indirect and direct bilirubin.

[i] Urinalysis will include: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), and specific gravity.

[j] During study IP infusion visits, D-dimer testing is to be performed within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion. At the Screening Visit, blood for the D-dimer level will only be collected prior to the subject's standard of care infusion. Wells scoring is to be performed post-infusion. Section 7.2 describes at each visit evaluation of clinical signs and symptoms of thromboembolic events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of infusion (Appendix 3)

[k] Laboratory samples must be taken prior to IP infusion (within 8 hours prior to the infusion) and analyzed as described for monitoring hemolytic AEs in Appendix 4; specific laboratory parameters include the following: blood specimens (*DAT, blood smear, hematocrit, RBC count, ARC, Hb, plasma free-Hb, haptoglobin, LDH, total indirect and direct bilirubin*); and urine specimens (*urinary sediment, hemoglobinuria, and hematuria*).

[l] IgG subclasses IgG1, IgG2, IgG3, IgG4 measured prior to the start of the infusion.

[m] Antibody levels for *S. pneumoniae*, *H. influenzae*, *C. tetani* (tetanus), and measles are measured prior to the start of the infusion.

[n] Collect virus safety retain samples prior to the infusion but test only if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V infection while participating in the study. See Section 7.2.5 and Table 7-1 for details.

[o] IP infusion intervals will be either every 3 weeks (21 days) or 4 weeks (28 days) depending on the subject's previous IVIG dosing interval. Any subject who's prior dosing frequency was not every 3 to 4 weeks will be adjusted to one of these two frequency options by their physician during the Run-in Phase.

[p] PK samples will be obtained as follows: within 30 minutes prior to the start of the intravenous infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day PK sample applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion. An added PK sample will be requested for subjects who prematurely discontinue the study during the PK curves sampling periods (i.e., Gamunex-C PK Phase and IVIG-PEG PK Phase).

[q] Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category). If a subject develops an SBI, a serum IgG level should be obtained.

[r] Clinical evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post infusion) and by a phone call by the Investigator or appropriate study staff (medical doctor) at 10 days (±2 days) after each infusion.(Appendix 4).

[s] Pre-dose sample.

[t] PK samples will only be taken at a subject's final visit if they discontinue the study prematurely. A sample for total IgG concentration for safety purposes will be taken from subjects prematurely discontinuing the study.

[u] Only for subjects skipping the Run-in Phase who entered directly into the Gamunex-C PK Phase (see Section 4.2.1).

Table B. Every 4 Weeks Dosing Regimen

Study Phase / Visit / Procedure	Screening Visit (up to 28 days)	Run-in Phase (Gamunex-C every 4 weeks)					Gamunex-C PK Phase	Treatment Phase (IVIG-PEG every 4 weeks)					IVIG-PEG PK Phase	Final Visit/Early Termination
		Run-in-#1	Run-in-#2	Run-in-#3	Run-in-#4	Run-in #5	Gamunex-C PK#1	IVIG-PEG-#1	IVIG-PEG -#2	IVIG-PEG -#3	IVIG-PEG -#4	IVIG-PEG -#5	IVIG-PEG PK#1	
Informed consent	X													
Inclusion/exclusion criteria	X													
Medical history & demographics	X													
Prior medication history	X													
Full physical exam[a]	X							X						X
Abbreviated physical exam[b]		X	X	X	X	X	X		X	X	X	X	X	
Chest X-ray[c]	X													
Vital signs	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X
Height	X													
Body weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[f]	X													
Urine pregnancy test[f]		X					X[u]	X	X	X	X	X	X	X
Laboratory assessments (hematology, chemistry, urinalysis)[g,h,i,s]	X	X[s]		X[s]		X[s]		X[s]		X[s]		X[s]		X
Thromboembolism evaluation[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hemolysis detection[k]		X	X	X	X	X	X	X	X	X	X	X	X	
Total IgG trough level	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Sample for IgG subclass levels and Ab titer[l,m]		X		X		X	X	X		X		X	X	
Virus safety retain[n]	X	X		X		X	X[u]	X		X		X		X
Gamunex-C infusion[o]		X	X	X	X	X	X							
IVIG-PEG infusion[o]								X	X	X	X	X	X	
Serial PK samples[p]							X						X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessments including infections[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record days lost from work/school/daily activities		X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor signs and symptoms of hemolysis[r]		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] Pre-dose abbreviated physical exam (targeted to symptoms and to include examination of heart, lungs, ears/nose/throat, and inspection of previous injection sites).
[c] Only if chest X-ray or CT have not been performed in the 6 months prior to the Screening Visit.
[d] Vital signs (SBP, DBP, HR, T, and RR) will be measured within 30 ± 10 minutes before the beginning of each infusion and within 30 ± 10 minutes post-completion of each infusion.
[e] Body weight will be measured prior to the infusion to determine the IP dose.
[f] Females of child-bearing potential only; results must be negative to participate in the study or continue on IP. Quantitative serum β-HCG will be performed at the Screening Visit. A qualitative urine pregnancy test will be performed prior to the first dose received for each IP as well as prior to each IVIG-PEG infusion, and at the Final Visit/Early Termination Visit. Pregnancy testing will be repeated at any time if pregnancy is suspected.
[g] Hematology will include: hemoglobin, hematocrit, platelets, RBC count including RBC morphology, WBC count with differential, and ARC.
[h] Chemistry will include: sodium, potassium, creatinine, chloride, calcium, BUN, bicarbonate, albumin, LDH, AST, ALT, ALP, GGT, glucose, TBL, indirect and direct bilirubin.
[i] Urinalysis will include: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), and specific gravity.
[j] During study IP infusion visits, D-dimer testing is to be performed within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion. At the Screening Visit, blood for the D-dimer level will only be collected prior to the subject's standard of care infusion. Wells scoring is to be performed post-infusion. Section 7.2 describes at each visit evaluation of clinical signs and symptoms of thromboembolic events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of infusion (Appendix 3).
[k] Laboratory samples must be taken prior to IP infusion (within 8 hours prior to the infusion) and analyzed as described for monitoring hemolytic AEs in Appendix 4; specific laboratory parameters include the following: blood specimens (*DAT, blood smear, hematocrit, RBC, ARC, Hb, plasma free-Hb, haptoglobin, LDH, total, indirect and direct bilirubin*); and urine specimens (*urinary sediment, hemoglobinuria, and hematuria*).
[l] IgG subclasses IgG1, IgG2, IgG3, IgG4 measured prior to the start of the infusion.
[m] Antibody levels for *S. pneumoniae*, *H. influenzae*, *C. tetani* (tetanus), and measles are measured prior to the start of the infusion.
[n] Collect virus safety retain samples prior to the infusion but test only if the subject exhibits clinical signs and symptoms consistent with HAV, HBV, HCV, HIV, or B19V infection while participating in the study. See Section 7.2.5 and Table 7-1 for details.
[o] IP infusion intervals will be either every 3 weeks (21 days) or 4 weeks (28 days) depending on the subject's previous IVIG dosing interval. Any subject who's prior dosing frequency was not every 3 to 4 weeks will be adjusted to one of these two frequency options by their physician during the Run-in Phase.
[p] PK samples will be obtained as follows: within 30 minutes prior to the start of the intravenous infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day PK sample applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion. An added PK sample will be requested for subjects who prematurely discontinue the study during the PK curves sampling periods (i.e., Gamunex-C PK Phase and IVIG-PEG PK Phase).
[q] Record any SBIs (defined in Appendix 2), hospitalizations due to infections, and non-serious infections (by category). If a subject develops an SBI, a serum IgG level should be obtained.
[r] Clinical evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post infusion) and by a phone call by the Investigator or study staff (medical doctor) at 10 days (±2 days) after each infusion (Appendix 4).
[s] Pre-dose sample.

[t] PK samples will only be taken at a subject's final visit if they discontinue the study prematurely. A sample for total IgG concentration for safety purposes will be taken from subjects prematurely discontinuing the study.

[u] Only for subjects skipping the Run-in Phase who entered directly into the Gamunex-C PK Phase (see Section 4.2.1).

Appendix 2 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, oliguria, 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, 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 (36). 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 (38).

[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 (39).

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 (PaO2 <60 mm Hg 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, MRun-in 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 (40).

[e] We recommend a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10 to 20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10× low power magnification to determine suitability of sputum culture (40).

Appendix 3 Monitoring of Thromboembolic Events Risk

At Screening and during all the infusion visits, subjects will be actively monitored for signs and symptoms of arterial and venous thromboembolic (TE) events. Arterial and venous TE events will be identified according to definitions in the International Classification of Diseases (ICD) [41]. Such events include, but are not limited to, deep vein thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction, cerebral infarction, acute ischaemic heart disease, embolism or thrombosis of arteries of lower extremities, sagittal sinus thrombosis, portal vein thrombosis and injury of mesenteric artery.

All TE events will be recorded as adverse events (AEs) and reported accordingly. Any TE event fulfilling any of the criteria for "serious" will be reported as a serious adverse event (SAE).

The Sponsor's Medical Monitor (or designee) will routinely review reported AEs for possible TE events.

In addition, TE events risk will be evaluated using the following assessments, schedule (Table 1) and algorithms (Figure 1 and 2):

1. Measurement of D-dimer blood levels (42);
2. The Wells Score (43) will be utilized to assess the clinical characteristics indicative of possible DVT or PE (Table 2);
3. Evaluation of clinical signs and symptoms of arterial and venous TE (such as, dyspnea, pain, swelling, tenderness and discoloration [paleness or redness] in lower extremities).

After getting results from (1) to (3) and prior to the next study infusion visit, a medical doctor will assess the risk of TE events considering algorithms (provided in Figure 1 and Figure 2 below) from the first Gamunex-C to the last IVIG-PEG study infusions.

Table 1. Schedule of Monitoring of Thromboembolic Events Risk

Study Visit	D-dimer[a]	Wells Score[b]	Clinical Assessment TE[c]
Screening Visit	Once during Screening Visit, prior to IVIG infusion	During Screening Visit	During Screening Visit
Run-in #1	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
Run-in #2	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
Run-in #3	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
Run-in #4	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
Run-in #5	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion

Study Visit	D-dimer[a]	Wells Score[b]	Clinical Assessment TE[c]
Run-in #6[d]	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
Gamunex-C PK#1	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG #1	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG #2	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG #3	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG #4	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG #5	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG #6[d]	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
IVIG-PEG PK#1	Pre-infusion and Post-Infusion	Post-infusion	Post-infusion
Final Visit/Early Termination	Not performed	Not performed	Not performed

a. A blood sample for D-dimer testing will be collected within 8 hours pre-infusion and 30 ±10 minutes post-completion of infusion. At the Screening Visit, blood for the D-dimer level will only be collected prior to the subject's standard of care infusion.
b. Wells score completed after the infusion by the Investigator or appropriate study staff (medical doctor, study nurse, or study coordinator).
c. Evaluation of clinical signs and symptoms of arterial and venous TE is performed after the infusion by the Investigator or designee medical doctor or study nurse.
d. These visits only apply to subjects on the every 3 weeks dosing regimen.

Table 2: Wells Prediction Score

DEEP VEIN THROMBOSIS	
Clinical Characteristic	**Score**
Active cancer (treatment ongoing, within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within previous 12 weeks requiring general or regional anesthesia	1
Previously documented DVT	1
Localized tenderness along distribution of deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis at least as likely as DVT	-2
Total Score:	

PULMONARY EMBOLISM	
Clinical Characteristic	**Score**
Previous DVT or PE	1.5
Surgery or bedridden for 3 days during past 4 weeks	1.5
Active cancer (treatment within 6 months or palliative)	1
Hemoptysis	1
Heart rate >100 beats/min	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Total Score:	

After getting results from D-dimer levels, Wells Score, and evaluation of signs and symptoms of TE, and prior to the next study visit, the Investigator or designee medical doctor will assess the risk of DVT and PE considering the following algorithms adapted from Wells [43] (Figure 1 and Figure 2):

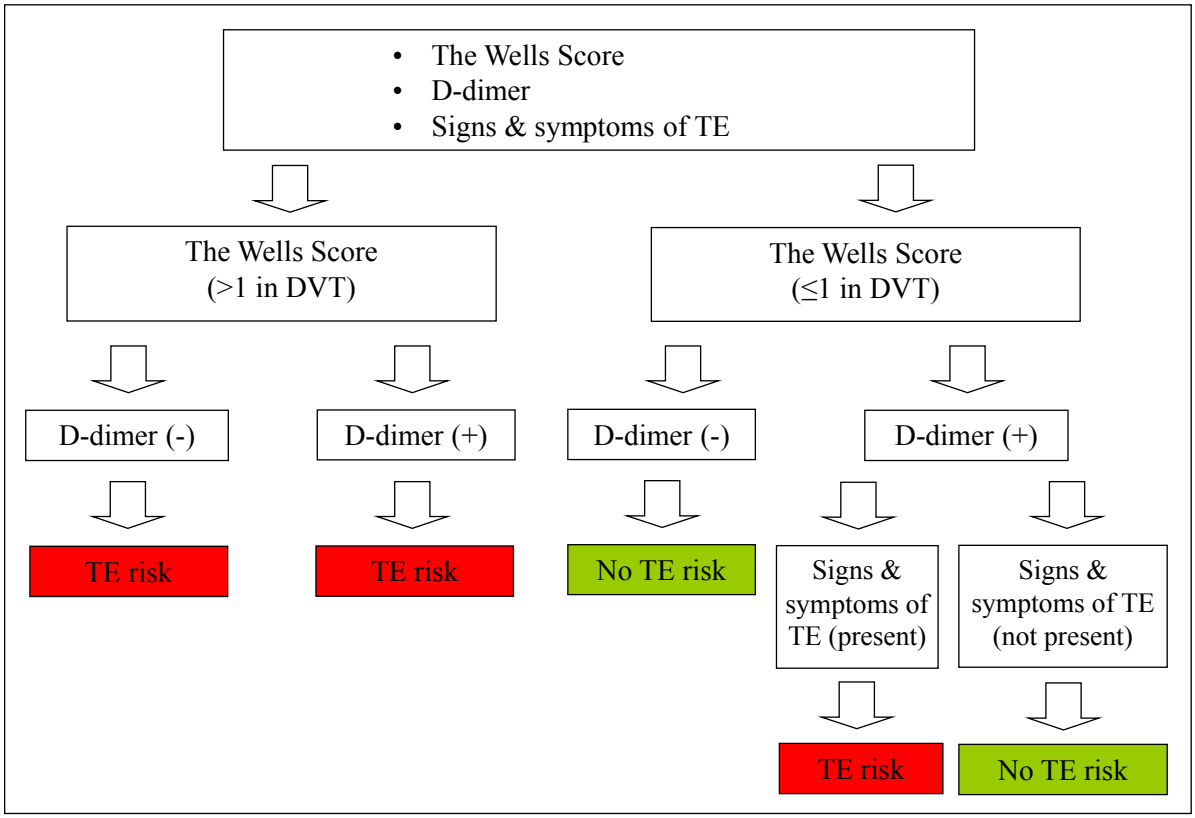

Figure 1. Algorithm to assess thromboembolic events risk for DVT

Any subject with a total Wells prediction score >1 for DVT assessment should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 1).

Any subject with a total Wells prediction score ≤1 for DVT assessment and a positive D-dimer value (i.e., above baseline and out of normal range of the reporting laboratory) in combination with clinical signs or symptoms of a TE event (as per AEs assessment and such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 1). For this purpose, "baseline" refers to the first study infusion (Run-In #1 or Gamunex-C PK visit).

If the subject experiences a confirmed TE event, the study treatment must be discontinued and if necessary standard therapy started.

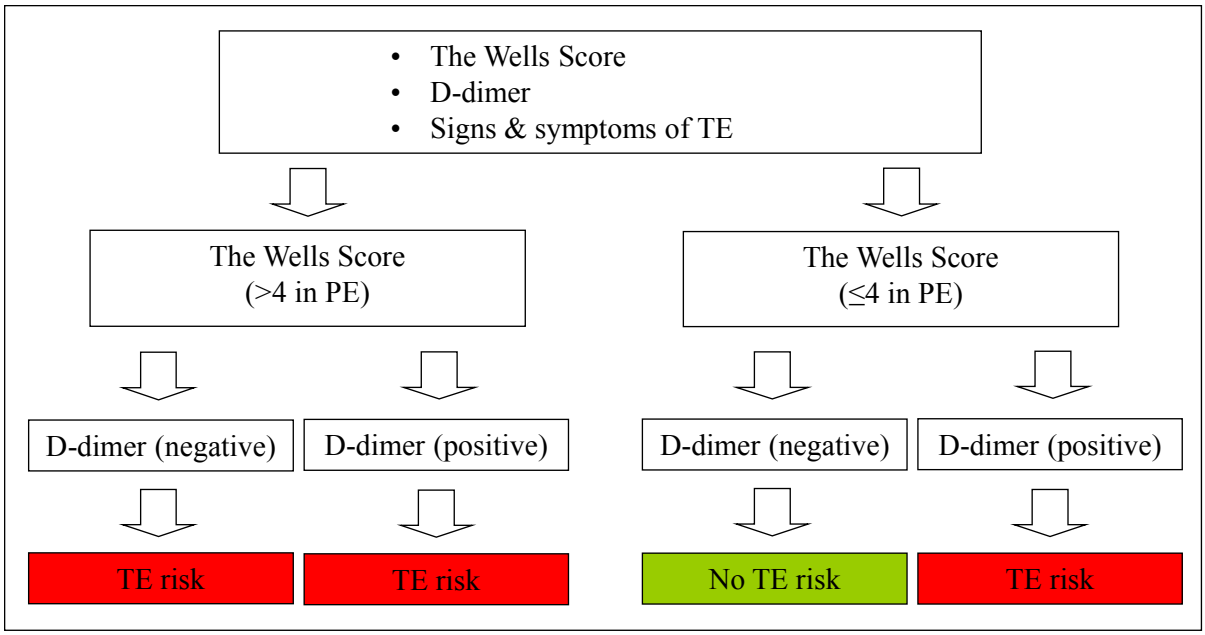

Figure 2. Algorithm to assess thromboembolic events risk for PE

Any subject with a total Wells prediction score >4 for PE assessment should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 2).

Any subject with a total Wells prediction score ≤4 for PE assessment and a positive D-dimer value (i.e., above baseline and out of normal range of the reporting laboratory) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 2). For this purpose, "baseline" refers to the first study infusion (Run-In #1 or Gamunex-C PK visit).

If the subject experiences a confirmed TE event, the study treatment must be discontinued and if necessary standard therapy started.

Appendix 4 Detection of Hemolysis

During all the infusion visits, subjects will be monitored for signs of hemolysis associated with the administration of the IP.

All hemolytic events will be recorded as adverse events (AEs) and reported accordingly. Any hemolytic event fulfilling any of the criteria for "serious" will be reported as a serious adverse event (SAE).

The Sponsor's Medical Monitor (or designee) will routinely review reported AEs for possible hemolytic events.

Hemolysis will be monitored using the following assessments and schedule (Table 1):

1. Blood testing: whole blood hemoglobin, plasma free hemoglobin, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), red blood count (RBC), hematocrit, total and indirect and direct bilirubin, and blood smear.
2. Urine testing: urinary sediment, and hemoglobinuria.
3. Evaluation of clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) evaluated by the Investigator or appropriate study staff (medical doctor) at any time on the day of infusion before the infusion and after the completion of the infusion, and via a phone call 10 days (±2 days) after the initiation of the infusion by the Investigator or appropriate study staff (medical doctor).

Table 1. Schedule of Detection of Hemolysis

Study Visit	Blood Testing[a]	Urine Testing[a]	Clinical Parameters[b]
Screening Visit	Not performed	Not performed	Not performed
Run-in #1	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Run-in #2	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Run-in #3	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Run-in #4	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Run-in #5	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Run-in #6[d]	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Gamunex-C PK#1	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG #1	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG #2	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG #3	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG #4	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG #5	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG #6[d]	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
IVIG-PEG PK#1	Pre-infusion	Pre-infusion	Pre-infusion, Post-Infusion, and 10±2 days after
Final Visit/Early Termination	Not performed	Not performed	Not performed

a. Blood and urine testing must be performed within 8 hours prior to the infusion at each study visit. If the Investigator or designee medical doctor performing the Day 10 (±2 days) phone call considers that the subject is at risk of suffering from a hemolytic event, additional testing may be also requested.
b. The clinical assessment at Day 10 (±2 days) after each infusion to be performed via phone call by the Investigator or appropriate study staff (medical doctor).

During the phone call, the following questions may be asked to the subject in addition to questions that the Investigator or designee medical doctor will consider necessary to monitor the potential risk of hemolysis associated with the use of IP:

- Are you more tired since the last infusion of the study drug?
- Do you feel an increase in your heart rate since the last infusion of the study drug?
- Do you have yellow eyes since the last infusion of the study drug?
- Is your urine dark since the last infusion of the study drug?
- Do you have pale face or hands?

Important note:

If the Investigator or designee medical doctor detect any evidence of risk of hemolysis during the assessment of clinical parameters of hemolysis after each infusion or by the phone call (at Day 10, ±2 days following each infusion), additional blood and urine testing will also be performed. In case the risk of hemolysis is identified during the phone call, the subject will be asked to go to the investigational site to have a blood draw and to provide urine sample.

Definition of hemolysis associated with the administration of IP:

In this study, a hemolytic reaction is one in which there is evidence of a new hemolytic process within 10 days (±2 days) of each IP administration (31).

The following laboratory signs must be present:

1. Drop in whole blood hemoglobin of ≥1 g/dL[1]; and
2. Positive result of DAT[2]; and
3. At least 2 of the following:

- Increased ARC[1]
- Increased LDH level[1]
- Low haptoglobin level[1]
- Unconjugated hyperbilirubinemia[2]
- Hemoglobinemia (excess of hemoglobin in the plasma)[2]
- Hemoglobinuria[2]
- Presence of significant spherocytosis[2]

[1] Changes from baseline values (For this purpose, "baseline" refers to the first study infusion [Run-In #1 or Gamunex-C PK visit].)

[2] Results from blood and urine testing performed after infusion and/or at Day 10 after infusion of the IP.

Subjects from this study may be severely ill and may have anemia for a number of reasons. Therefore, it is important to exclude the underlying condition and concomitant medications as a cause of anemia. The exclusions are:

- History or examination consistent with an alternative cause of anemia including blood loss (e.g., frequent phlebotomy is highly associated with changes in hemoglobin and

hematocrit levels for patients admitted to an internal medicine service [44,45]), iron-deficiency anemia and other drug-induced hemolytic anemia).

- Negative DAT.
- Absence of evidence of hemolysis.

If the subject has confirmed hemolysis due to the administration of IP, the study treatment must be discontinued and, if necessary, standard therapy started.

Appendix 5 Summary of Changes

(Note: Administrative changes including minor administrative corrections are not included in Protocol Summary of Changes.)

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Synopsis, Study Objectives	Gamunex-C	Gamunex-C (IVIG-C)	Clarification about which agent is referred to by providing the generic abbreviation as well as the trade name
Synopsis, (Overall Study Design and Description) 4.2	A total of approximately ~~25~~ adult subjects will be enrolled in order to have 20 evaluable subjects for PK analysis.	A total of approximately 35 adult subjects will be enrolled in order to have 20 evaluable subjects for PK analysis.	Increased sample size to ensure a minimum of 20 evaluable subjects for PK analysis
Synopsis, Overall Study Design and Description		Treatment visits for the Gamunex-C Run-In Phase, Gamunex-C PK Phase, IVIG-PEG PK Phase, and the Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. Some treatment visits for the IVIG-PEG Treatment Phase may also be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site.	Addition of clarifying new paragraphs to further explain where treatment visits may be conducted

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Synopsis, (Number of Subjects Planned)	Approximately ~~25~~ adult subjects are planned to be enrolled, in which a minimum number of 6 subjects are planned to be enrolled in each dosing interval (i.e., 3-weeks dosing interval vs 4-weeks dosing interval).	Approximately 35 adult subjects are planned to be enrolled, in which a minimum number of 6 subjects are planned to be enrolled in each dosing interval (i.e., 3-weeks dosing interval vs 4-weeks dosing interval).	Increased sample size to ensure a minimum of 20 evaluable subjects for PK analysis
Synopsis, Inclusion Criteria	2. 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 (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria	2. Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IV IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria	Clarification that eligible previous IgG replacement therapy must be intravenous
	3. IgG trough level ≥500 mg/dL at Screening Visit Note: Patients entering Group 1 must additionally have trough levels ≥500 mg/dL documented within the previous year. For patients entering Group 2, if Screening trough levels are not ≥500 mg/dL, the subject will be a Screen Failure, but may be rescreened following dose adjustment of their original IgG replacement therapy regimen and recording an IgG trough level ≥500 mg/dL	3. IgG trough level ≥500 mg/dL at Screening Visit Note: Patients entering Group 1 must additionally have trough levels ≥500 mg/dL documented within the previous year. For patients entering Group 2, if Screening trough levels are not ≥500 mg/dL, the subject will be a Screen Failure, but may be rescreened following dose adjustment of their original IV IgG replacement therapy regimen and recording an IgG trough level ≥500 mg/dL	Clarification that eligible previous IgG replacement therapy must be intravenous
Synopsis, Duration of Treatment	~~IGIV-C~~	Gamunex-C	Consistent replacement of IGIV-C with Gamunex-C

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Synopsis, Reference Therapy, Dose and Mode of Administration	Subjects will receive Gamunex-C by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. Gamunex-C will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.	Subjects will receive Gamunex-C by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. The subject's usual mg/kg dose (given on either a 3 or 4 week repeating schedule) will be the same mg/kg dose and schedule that the subject was receiving prior to entering screening. This mg/kg dose and schedule will be used throughout the study duration. Note that the weight of the subject will be measured at each visit and if the subject's weight changes, the actual weight at each visit will be used to calculate amount of drug (mg) to be administered. Gamunex-C will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.	Clarification of dosing by weight procedure
Glossary and Abbreviations		CRO Contract Research Organization	Addition of new abbreviation that appears more than once in the text
	~~IGIV-C~~	IVIG-C	Correction of acronym
	Immune Globulin (Human), 10% Caprylate/Chromatography Purified	Immune Globulin (Human), 10% Caprylate/Chromatography Purified OR Gamunex-C	Clarification that the product described is Gamunex-C
Section 2.1	(IGIV-C or Gamunex-C)	Gamunex-C (IVIG-C)	Clarification of wording to specify that Gamunex-C is IVIG-C
Section 2.2	~~IGIV-C~~	Gamunex-C	Correction of IVIG-C/IGIV-C acronym and consistent replacement of IGIV-C with Gamunex-C

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 2.6	Eligible participants for this study include male or female subjects who are between 18 and 75 years of age (inclusive) and have a diagnosis of PI requiring IgG replacement therapy.	Eligible participants for this study include male or female subjects who are between 18 and 75 years of age (inclusive) and have a diagnosis of PI requiring IV IgG replacement therapy.	Clarification that eligible previous IgG replacement therapy must be intravenous
Section 4.2		Treatment visits for the Gamunex-C Run-In Phase, Gamunex-C PK Phase, IVIG-PEG PK Phase and the Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. Some treatment visits for the IVIG-PEG Treatment Phase may also be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site.	Addition of clarifying new paragraphs to further explain where treatment visits may be conducted

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 4.2.2.1	During the Run-in Phase, subjects will receive an individualized dose of Gamunex-C between 200 to 800 mg/kg that treating physicians consider appropriate compared to their previous IVIG treatment regimen. The first 3 consecutive doses of Gamunex-C during the Run-in Phase (visits #1, #2, and #3) can be adjusted as needed by treating physicians to achieve a stable dose for subjects, and then such stable dose should be maintained throughout the remainder of the Run-in Phase (visits #4, #5, and #6). Doses during visits #4, #5, and #6 cannot vary from each other or from the dose given during visit #3 by more than 20%. Subjects who cannot achieve a stable dose of Gamunex-C during the Run-in Phase may not continue to the Gamunex-C PK Phase and will be withdrawn from the study (see Section 5.3.2).	During the Run-in Phase, subjects will receive an individualized dose of Gamunex-C between 200 to 800 mg/kg that treating physicians consider appropriate compared to their previous IVIG treatment regimen. The subject's usual mg/kg dose (given on either a 3 or 4 week repeating schedule) will be the same mg/kg dose and schedule that the subject was receiving prior to entering screening. This mg/kg dose and schedule will be used throughout the study duration. Note that the weight of the subject will be measured at each visit and if the subject's weight changes, the actual weight at each visit will be used to calculate amount of drug (mg) to be administered. The first 3 consecutive doses of Gamunex-C during the Run-in Phase (visits #1, #2, and #3) can be adjusted as needed by treating physicians to achieve a stable dose for subjects, and then such stable dose should be maintained throughout the remainder of the Run-in Phase (visits #4, #5, and #6). Doses during visits #4, #5, and #6 cannot vary from each other or from the dose given during visit #3 by more than 20%. Subjects who cannot achieve a stable dose of Gamunex-C during the Run-in Phase may not continue to the Gamunex-C PK Phase and will be withdrawn from the study (see Section 5.3.2).	Clarification of dosing by weight procedure
Section 4.2.2.1		Treatment visits for the Gamunex-C Run-In Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where Gamunex-C Run-In Phase visits may be conducted

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 4.2.2.2		Visits for the Gamunex-C PK Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where Gamunex-C PK Phase visits may be conducted
Section 4.2.3.1		Some treatment visits for the IVIG-PEG Treatment Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. IVIG-PEG #1 and IVIG-PEG #2 treatment visits are to be performed at the study site. If there are extenuating circumstances that prevent the subject from returning to the study site for these visits, the PI or designee is to discuss the situation with the sponsor. Sponsor approval may be granted to conduct the visit(s) at an alternate location under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where treatment visits may be performed, and the procedure to obtain approval for an alternate location
Section 4.2.3.2		Visits for the IVIG-PEG PK Phase may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where IVIG-PEG PK Phase visits may be conducted
Section 4.2.4		The Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where the Final Visit/Early Termination Visit may be conducted

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 4.3.1	For example, if the Investigators' center number is 301, subject number will be ~~3011001~~, 301~~1~~002, 301~~1~~003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.	For example, if the Investigators' center number is 301, subject number will be 3010001, 301<u>0</u>002, 301<u>0</u>003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.	Corrections to the subject numbering schema example
Section 4.4.1.1	IVIG-PEG consists of 9 to 11% IgG in 0.16 to 0.24 M glycine. ~~IGIV-~~PEG 10% may be supplied in vial sizes of 10, 25, 50, 100, 200 and 400 mL. For this study, ~~IGIV-~~PEG will be supplied in 100 mL vials.	IVIG-PEG consists of 9 to 11% IgG in 0.16 to 0.24 M glycine. IVIG-PEG 10% may be supplied in vial sizes of 10, 25, 50, 100, 200 and 400 mL. For this study, IVIG-PEG will be supplied in 100 mL vials.	Corrections to the acronym for one of the study drugs, IVIG-PEG
Section 5.1	2. 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 (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria	2. Documented and confirmed pre-existing diagnosis of PI with features of hypogammaglobulinemia requiring IV IgG replacement therapy including but not limited to the following humoral-based immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, common variable immunodeficiency), and combined immunodeficiency syndromes without lymphocytopenia (e.g., hyper immunoglobulin M [IgM] immunodeficiency syndrome). Please also refer to Exclusion Criteria	Clarification that eligible previous IgG replacement therapy must be intravenous
	3. IgG trough level ≥500 mg/dL at Screening Visit Note: Patients entering Group 1 must additionally have trough levels ≥500 mg/dL documented within the previous year. For patients entering Group 2, if Screening trough levels are not ≥500 mg/dL, the subject will be a Screen Failure, but may be rescreened following dose adjustment of their original IgG replacement therapy regimen and recording an IgG trough level ≥500 mg/dL	3. IgG trough level ≥500 mg/dL at Screening Visit Note: Patients entering Group 1 must additionally have trough levels ≥500 mg/dL documented within the previous year. For patients entering Group 2, if Screening trough levels are not ≥500 mg/dL, the subject will be a Screen Failure, but may be rescreened following dose adjustment of their original IV IgG replacement therapy regimen and recording an IgG trough level ≥500 mg/dL	Clarification that eligible previous IgG replacement therapy must be intravenous

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 6.1	Subjects will receive IVIG-PEG and Gamunex-C by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. IVIG-PEG and Gamunex-C will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.	Subjects will receive IVIG-PEG and Gamunex-C by means of an infusion pump at a dose of 200 to 800 mg/kg per infusion at an infusion rate of 1 mg/kg/min or up to 8 mg/kg/min depending on subject tolerance. The subject's usual mg/kg dose (given on either a 3 or 4 week repeating schedule) will be the same mg/kg dose and schedule that the subject was receiving prior to entering screening. This mg/kg dose and schedule will be used throughout the study duration. Note that the weight of the subject will be measured at each visit and if the subject's weight changes, the actual weight at each visit will be used to calculate amount of drug (mg) to be administered. IVIG-PEG and Gamunex-C will be administered every 3 weeks (±4 days) or 4 weeks (±4 days), depending on the subject's prior IVIG dosing schedule.	Clarification of dosing by weight procedure
	All infusions will be administered ~~at the study site~~ using a standard (~~eg~~, polyvinyl chloride) administration kit prepared by ~~the clinical site staff. Q~~ualified personnel, working to local standard operating procedures and under aseptic conditions~~, will prepare all infusions for both study drugs~~.	All infusions for both study drugs will be administered using a standard (e.g., polyvinyl chloride) administration kit prepared by qualified personnel, working to local standard operating procedures and under aseptic conditions.	Clarification of who can administer study drug, and removing the specification that it be conducted at the study site
Section 7.2.1.1	• Record demographics: year of birth, gender, race, and ethnic origin	• Record demographics: year of birth, age at screening (years), gender (if female, fertility status), race, and ethnic origin	Addition of age at screening and clarification of gender demographic for females to accurately reflect the Case Report Form data collection

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), <u>specific gravity</u>	Clarification of specific gravity as part of urinalysis
	- D-dimer	- D-dimer <u>(collected only once during this visit, before their standard of care infusion)</u>	Additional clarification of when blood for D-dimer level is to be collected
Section 7.2.1.2.1	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), <u>specific gravity</u>	Clarification of specific gravity as part of urinalysis
		<u>Gamunex-C Run-in #1, Run-in #3, and Run-in #5/#6 visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel</u>.	Addition of new paragraph to clarify where Gamunex-C Run-in visits may be performed
Section 7.2.1.2.2		<u>Gamunex-C Run-in #2, Run-in #4, and Run-in #5 visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.</u>	Addition of new paragraph to clarify where Gamunex-C Run-in visits may be performed
Section 7.2.1.2.3		<u>Gamunex-C PK Visits may be performed at the study site or, if deemed appropriate, at alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.</u>	Addition of new paragraph to clarify where Gamunex-C PK visits may be performed

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 7.2.1.3.1	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), <u>specific gravity</u>	Clarification of specific gravity as part of urinalysis
		<u>IVIG-PEG #3 and IVIG-PEG #5/#6 visits may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. The IVIG-PEG #1 treatment visit is to be performed at the study site. If there are extenuating circumstances that prevent the subject from returning to the study site for these visits, the PI or designee is to discuss the situation with the sponsor. Sponsor approval may be granted to conduct the visit(s) at an alternate location under the care and supervision of trained healthcare personnel.</u>	Addition of new paragraph to clarify where IVIG-PEG treatment visits may be performed, and how approval is to be sought for a change in location
Section 7.2.1.3.2		<u>IVIG-PEG #4 and IVIG-PEG #5 visits (as applicable) may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel. The IVIG-PEG #2 treatment visit is to be performed at the study site. If there are extenuating circumstances that prevent the subject from returning to the study site for these visits, the PI or designee is to discuss the situation with the sponsor. Sponsor approval may be granted to conduct the visit(s) at an alternate location under the care and supervision of trained healthcare personnel.</u>	Addition of new paragraph to clarify where IVIG-PEG treatment visits may be performed, and how approval is to be sought for a change in location

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 7.2.1.3.3		IVIG-PEG PK Visits may be performed at the study site or, if deemed appropriate, at alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where IVIG-PEG PK visits may be performed
Section 7.2.1.4	The assessments at this visit will be the same as the Final Visit, with the exception of an added PK sample for subjects who prematurely discontinue the study.	The assessments at this visit will be the same as the Final Visit, with the exception of an added PK sample for subjects who prematurely discontinue the study during the PK curves sampling periods (i.e., Gamunex-C PK Phase and IVIG-PEG PK Phase) and a sample for total IgG concentration for safety purposes for subjects prematurely discontinuing the study at any point.	Specifics about the PK sample and a separate safety sample for subjects who prematurely discontinue the study
	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal)	- Urinalysis: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), specific gravity	Clarification of specific gravity as part of urinalysis
	- Blood draw for total IgG concentration (only for subjects prematurely discontinuing the study)	- Blood draw for total IgG concentration for safety purposes (only for subjects prematurely discontinuing the study)	Reason for blood draw for total IgG concentration from subjects who prematurely discontinue participation in the study
		The Final Visit/Early Termination Visit may be performed at the study site or, if deemed appropriate, at an alternate site (e.g., subject's residence, local healthcare professional's site) under the care and supervision of trained healthcare personnel.	Addition of new paragraph to clarify where the Final Visit/Early Termination Visit may be performed

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Section 7.2.2	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.	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. Under extraordinary circumstances, some of the laboratory tests can be performed at the site's local laboratory if testing is unable to be performed by the central laboratory. When feasible and time permits, the site should discuss the extraordinary circumstances in advance with the sponsor and/or Contract Research Organization (CRO).	Circumstances under which some laboratory tests may be performed at the site's local laboratory, and that the site should discuss the circumstances with the sponsor and/or CRO
Table 7-1	Total IgG levels will consist of trough (pre-dose) measurements in all subjects, and for PK profiling of IVIG-PEG	Total IgG levels will consist of trough (pre-dose) measurements in all subjects, and for PK profiling of IVIG-PEG and a total IgG concentration for safety purposes for subjects prematurely discontinuing the study	Clarification of blood draw for total IgG concentration from subjects who prematurely discontinue participation in the study
	~~Qualitative~~ serum β-HCG for females of child-bearing potential will be performed at Screening	Quantitative serum β-HCG for females of child-bearing potential will be performed at Screening	Correction for serum β-HCG, which is a quantitative test
	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)	Microscopic evaluation is done only with cause. pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of the urine if abnormal), specific gravity, and urine sediment	Addition to accurately reflect urinalysis
Section 8.2.5.1	Subjects will be monitored by the Investigator and/or study staff for signs and symptoms of arterial and venous TE events occurring between the first infusion (either the first infusion of Gamunex-C during the Run-in Phase or the first infusion of IVIG-PEG during the IVIG-PEG Treatment Phase) and the Final Visit/Early Termination Visit.	Subjects will be monitored by the Investigator and/or study staff for signs and symptoms of arterial and venous TE events at Screening and occurring between the first infusion (either the first infusion of Gamunex-C during the Run-in Phase or the first infusion of IVIG-PEG during the IVIG-PEG Treatment Phase) and the Final Visit/Early Termination Visit.	Clarification that subjects would also be monitored for TE events at Screening

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
	During all infusion visits, TE events risk will be assessed using:	At Screening and during all infusion visits, TE events risk will be assessed using:	Clarification that subjects would also be monitored for TE events at Screening
	1. D-dimer blood levels (within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion)	1. D-dimer blood levels (within 8 hours prior to the study IP infusion and 30 ±10 minutes after the completion of the infusion) Note: The sample for the D-dimer blood level is only collected before the subject's standard-of-care infusion at the Screening Visit.	Clarification that the infusion is of the study IP, and the timing of the D-dimer blood test sample
Section 8.3.9.1	~~contract research organization~~	CRO	Use of abbreviation, as this is the second time the term appears in the protocol
Section 9.2	An approximate ~~25~~ subjects are planned to be enrolled to have 20 evaluable subjects in the PK population for PK analysis	An approximate 35 subjects are planned to be enrolled to have 20 evaluable subjects in the PK population for PK analysis.	Increased sample size to ensure a minimum of 20 evaluable subjects for PK analysis
Section 16	4. Immune Globulin (Human), 10% Caprylate/Chromatography Purified (~~IGIV-~~C) Investigator's Brochure. Grifols. 2019.	4. Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IVIG-C) Investigator's Brochure. Grifols. 2019.	Correction of acronym
Appendix 1, Table A, footer i	Urinalysis will include: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal).	Urinalysis will include: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), and specific gravity.	Clarification of specific gravity as part of urinalysis
Appendix 1, Table A, footer j	During infusion visits, D-dimer testing is to be performed within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion. Wells scoring is to be performed post-infusion. 7.2	During study IP infusion visits, D-dimer testing is to be performed within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion. At the Screening Visit, blood for the D-dimer level will only	Clarifying wording to specify which infusion, the timing of the blood

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
	describes at each visit evaluation of clinical signs and symptoms of thromboembolic events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of infusion (Appendix 3)	be collected prior to the subject's standard of care infusion. Wells scoring is to be performed post-infusion. Section 7.2 describes at each visit evaluation of clinical signs and symptoms of thromboembolic events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of infusion (Appendix 3)	sample for D-dimer level, and to specify Section in reference to the number provided
Appendix 1, Table A, footer p	PK samples will be obtained as follows: 30 minutes prior to the start of the intravenous infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day PK sample applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion.	PK samples will be obtained as follows: within 30 minutes prior to the start of the intravenous infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day PK sample applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion. An added PK sample will be requested for subjects who prematurely discontinue the study during the PK curves sampling periods (i.e., Gamunex-C PK Phase and IVIG-PEG PK Phase).	Clarifying wording regarding timing of the first PK sample, and the added PK sample for subjects who prematurely discontinue participation
Appendix 1, Table A, footer r	Clinical evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post infusion) and by a phone call at 10 days (±2 days) after each infusion.(Appendix 4).	Clinical evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post infusion) and by a phone call by the Investigator or appropriate study staff (medical doctor) at 10 days (±2 days) after each infusion.(Appendix 4).	Additional clarity about who would evaluate hemolysis signs and symptoms
Appendix 1, Table A,	PK samples will only be taken at a subject's final visit if they discontinue the study prematurely.	PK samples will only be taken at a subject's final visit if they discontinue the study prematurely. A sample for total IgG concentration for safety purposes will be	Clarification of the total IgG concentration sample from subjects

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footer t		taken from subjects prematurely discontinuing the study.	prematurely discontinuing the study
Appendix 1, Table B, footer i	Urinalysis will include: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal).	Urinalysis will include: pH, protein, glucose, ketones, bilirubin, nitrites, urobilinogen, blood, leukocyte esterase (with microscopic examination of urine sediment if abnormal), and specific gravity.	Clarification of specific gravity as part of urinalysis
Appendix 1, Table B, footer j	During infusion visits, D-dimer testing is to be performed within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion. Wells scoring is to be performed post-infusion. 7.2 describes at each visit evaluation of clinical signs and symptoms of thromboembolic events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of infusion (Appendix 3)	During study IP infusion visits, D-dimer testing is to be performed within 8 hours prior to the infusion and 30 ±10 minutes after the completion of the infusion. At the Screening Visit, blood for the D-dimer level will only be collected prior to the subject's standard of care infusion. Wells scoring is to be performed post-infusion. Section 7.2 describes at each visit evaluation of clinical signs and symptoms of thromboembolic events (e.g., pain, dyspnea, discoloration [paleness or redness] in lower extremities) after the completion of infusion (Appendix 3)	Clarifying wording to specify which infusion, the timing of the blood sample for D-dimer level, and to specify Section in reference to the number provided
Appendix 1, Table B, footer p	PK samples will be obtained as follows: 30 minutes prior to the start of the intravenous infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day PK sample applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion.	PK samples will be obtained as follows: within 30 minutes prior to the start of the intravenous infusion, immediately upon the completion of the infusion (within 10 minutes of infusion completion), and at 1, 3, and 6 hours (±10 minutes), 24 and 48 hours (±2 hours), and 4 (±2 hours), 7 (±1 d), 14 (±1 d), 21 (±2 d), and 28 (±2 d) days (the 28 day PK sample applies only for subjects on every 4 weeks dosing regimen) after the end of the infusion. An added PK sample will be requested for subjects who prematurely discontinue the study during the PK curves sampling periods (i.e., Gamunex-C PK Phase and IVIG-PEG PK Phase).	Clarifying wording regarding timing of the first PK sample, and the added PK sample for subjects who prematurely discontinue participation

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Appendix 1, Table B, footer r	Clinical evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post infusion) and by a phone call at 10 days (±2 days) after each infusion.(Appendix 4).	Clinical evaluation of the signs and symptoms of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) during the infusion visit (pre-infusion and post infusion) and by a phone call by the Investigator or appropriate study staff (medical doctor) at 10 days (±2 days) after each infusion.(Appendix 4).	Additional clarity about who would evaluate hemolysis signs and symptoms
Appendix 1, Table B, footer t	PK samples will only be taken at a subject's final visit if they discontinue the study prematurely.	PK samples will only be taken at a subject's final visit if they discontinue the study prematurely. A sample for total IgG concentration for safety purposes will be taken from subjects prematurely discontinuing the study.	Clarification of the total IgG concentration sample from subjects prematurely discontinuing the study
Appendix 3, Table 1	During Screening Visit	Once during Screening Visit, prior to IVIG infusion	Clarification of timing of blood sample for D-dimer level
Appendix 3, Table 1, footer a	A blood sample for D-dimer testing will be collected within 8 hours pre-infusion and 30 ±10 minutes post-completion of infusion.	A blood sample for D-dimer testing will be collected within 8 hours pre-infusion and 30 ±10 minutes post-completion of infusion. At the Screening Visit, blood for the D-dimer level will only be collected prior to the subject's standard of care infusion.	Clarification of timing of blood sample for D-dimer level

Sections	Change From: (Version 3.0, dated 29 Jul 2020) (Strikethrough is added to highlight deleted text.)	Change To: (Version 4.0) (Underline is added to highlight new text.)	Rationale:
Appendix 3	Any subject with a total Wells prediction score ≤1 for DVT assessment and a positive D-dimer value (i.e., above baseline and out of normal range of the reporting laboratory) in combination with clinical signs or symptoms of a TE event (as per AEs assessment and such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 1).	Any subject with a total Wells prediction score ≤1 for DVT assessment and a positive D-dimer value (i.e., above baseline and out of normal range of the reporting laboratory) in combination with clinical signs or symptoms of a TE event (as per AEs assessment and such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 1). <u>For this purpose, "baseline" refers to the first study infusion (Run-In #1 or Gamunex-C PK visit).</u>	Clarification of what is meant by 'baseline'
	Any subject with a total Wells prediction score ≤4 for PE assessment and a positive D-dimer value (i.e., above baseline and out of normal range of the reporting laboratory) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 2).	Any subject with a total Wells prediction score ≤4 for PE assessment and a positive D-dimer value (i.e., above baseline and out of normal range of the reporting laboratory) should have further diagnostic testing per study site standard of care to confirm the occurrence of a TE event (Figure 2). <u>For this purpose, "baseline" refers to the first study infusion (Run-In #1 or Gamunex-C PK visit).</u>	Clarification of what is meant by 'baseline'
Appendix 4	3. Evaluation of clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) evaluated by the Investigator or appropriate study staff (medical doctor) at any time on the day of infusion before the infusion and after the completion of the infusion, and via a phone call 10 days (±2 days) after the initiation of the infusion.	3. Evaluation of clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) evaluated by the Investigator or appropriate study staff (medical doctor) at any time on the day of infusion before the infusion and after the completion of the infusion, and via a phone call 10 days (±2 days) after the initiation of the infusion <u>by the Investigator or appropriate study staff (medical doctor).</u>	Clarification of who is to evaluate clinical parameters

Sections	**Change From:** **(Version 3.0, dated 29 Jul 2020)** (Strikethrough is added to highlight deleted text.)	**Change To:** **(Version 4.0)** (Underline is added to highlight new text.)	**Rationale:**
	3. At least 2 of the following: • Increased ARC[1] • Increased LDH level[1] • Low haptoglobin level[1] • Unconjugated hyperbilirubinemia[2] [1] Changes from baseline values [2] Results from blood and urine testing performed after infusion and/or at Day 10 after infusion of the IP.	3. At least 2 of the following: • Increased ARC[1] • Increased LDH level[1] • Low haptoglobin level[1] • Unconjugated hyperbilirubinemia[2] [1] Changes from baseline values (For this purpose, "baseline" refers to the first study infusion [Run-In #1 or Gamunex-C PK visit].) [2] Results from blood and urine testing performed after infusion and/or at Day 10 after infusion of the IP.	Clarification of what is meant by 'baseline'