CLINICAL PROTOCOL

2004C009G

A Phase 3, Multinational, Multicenter, Open-Label Study of the Safety, Tolerability, Efficacy, and Pharmacokinetics of ProMetic BioTherapeutics Immune Globulin Intravenous (Human) 10% in Adults and Children with Primary Immunodeficiency Diseases

Clinical Development Phase:	3
Sponsor:	ProMetic BioTherapeutics, Inc. 1330 Piccard Drive, Suite 201 Rockville, MD 20850
Medical Monitor:	Joseph Parker, MD
Clinical Study Manager:	Atlantic Research Group, Inc.
Issue Date:	December 22, 2016
Version:	Version 5

CONFIDENTIAL – PROPRIETARY INFORMATION

SIGNATURES

Sponsor Signature

Study Title:	A Phase 3, Multinational, Multicenter, Open-Label Study of the Safety, Tolerability, Efficacy, and Pharmacokinetics of ProMetic BioTherapeutics Immune Globulin Intravenous (Human) 10% in Adults and Children with Primary Immunodeficiency Diseases
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This protocol has been approved by ProMetic BioTherapeutics, Inc. This study will be conducted in compliance with the protocol, US Code of Federal Regulations, EU Studies Directives, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), and any other applicable requirements.

Signed: Joseph M. Parker, MD Digitally signed by Joseph M. Parker, MD DN: cn=Joseph M. Parker, MD, o=ProMetic BioTherapeutics, ou, email=j.parker@prometic.com, c=US Date: 2016.12.22 17:44:30 -05'00' Date: _____

Signature of Principal Investigator

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I, the undersigned, have read the protocol and agree to conduct this study in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), EU Studies Directives, and all applicable local and federal regulatory requirements.

I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the investigational product and the study. I understand that the study may be terminated or enrollment suspended at any time by the sponsor with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

Signed:_____ Date: _____

Name: _____

Title: _____

Address: _____

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Telephone: _____

Protocol Synopsis

Name of Sponsor: ProMetic BioTherapeutics, Inc. Name of Investigational Medicinal Product (IMP): Immune Globulin Intravenous (Human) 10% (IGIV)	Protocol # 2004C009G IND# 016287

Protocol Title:	A Phase 3, Multinational, Multicenter, Open-Label Study of the Safety, Tolerability, Efficacy, and Pharmacokinetics of ProMetic BioTherapeutics Immune Globulin Intravenous (Human) 10% in Adults and Children with Primary Immunodeficiency Diseases
Clinical Phase:	Phase 3 (Pivotal)
Treatment Indication:	For the treatment of children and adults with primary immunodeficiency diseases (PIDD) who require immunoglobulin G (IgG) replacement therapy
Purpose and Objectives:	**Purpose** To assess the tolerability, safety, efficacy and pharmacokinetics (PK) of the investigational medicinal product (IMP), ProMetic Immune Globulin Intravenous (Human) 10%, in subjects with PIDD. **Efficacy Objectives** <u>Primary Objective</u> • To examine the rate of clinically documented serious bacterial infections (SBIs) in subjects treated with the IMP to achieve a rate of less than one SBI per year. <u>Secondary Objectives</u> To examine the effect of the IMP on the following: • Serum trough concentrations of total IgG obtained prior to each IMP infusion; • Number of episodes of fever (≥100.4°F); • Number of days out of work/school/kindergarten/daycare or unable to perform normal daily activities due to infections; • Number of days of hospitalization due to infections; • Number of days of antibiotic use for infection prophylaxis and/or treatment;

	• Incidence of infections other than acute serious bacterial infections. **Safety Objectives** • To examine the safety and tolerability of the IMP; • To collect adverse events (AEs) from the signing of informed consent to 21 days (± 2 days) or 28 days (± 2 days) days after the last infusion, depending on the subject's treatment schedule; • To examine total AEs and the observed proportion of AEs considered by the Sponsor to be IMP related; • To examine AEs temporally associated (during and within 72 hours after the end of the infusion) with the IMP infusion, which will be recorded regardless of relationship to the IMP; • To examine infusion- and rate-related AEs, regardless of relationship to the IMP; • To monitor safety approximately 7 days post infusion; • To examine long-term safety with virology testing from Screening to the Long-Term Safety Visit (LTSV); • To monitor for immunogenic reactions by testing for antibodies to ß-2 glycoprotein I (ß2GPI) and to ß-2 glycoprotein I domain I (β2GPI-DI), from baseline to the LTSV; • To monitor for thrombogenicity and hemolysis by performing post-infusion clinical evaluations and laboratory testing. **Pharmacokinetic Sub-study Objectives** • To determine the steady state serum concentrations of total IgG; • To determine the PK profiles for total IgG following administration of the IMP.
Study Plan:	This is a pivotal phase 3, open-label, single-arm, multinational, multicenter study to assess the tolerability, safety, efficacy, and pharmacokinetics of the IMP in adults and children with PIDD. The study will be conducted at up to 20 sites in the United States and Russia. All subjects will be treated as outpatients with ProMetic BioTherapeutics Immune Globulin Intravenous Solution 10% (the IMP) for approximately 1 year. A total of approximately 75 subjects aged 2-80 years will be enrolled in the study: approximately 50 subjects aged 17-80 years (Cohort 1) and approximately 25 children aged 2 to <17 years (Cohort 2). Only subjects 18 years of age and older, treated with commercially licensed

immune globulin product, will be enrolled by Russian sites, in accordance with Russian national legislation.

This is an open-label study; no subject or study personnel will be blinded.

A subset of subjects will be asked to participate in a PK sub-study (Section 6.13). Subjects who consent to participate in the PK sub-study will undergo a series of blood draws to assess the PK profile of the IMP before and after Infusion 6 (21-day cycle subjects) or Infusion 5 (28-day cycle subjects).

Safety Precautions at Enrollment

To enhance subject safety, IMP will initially be given only to subjects aged 18-80 years currently treated with a stable dose of immune globulin, with the timing of the first IMP infusion at staggered intervals in Groups 1 and 2. The study will proceed to Group 3 only after evaluation and Food and Drug Administration (FDA) review of safety data obtained at Week 4 (or Week 3 for patients on a 3-week treatment regimen) after the first IMP infusion in 15 subjects. The procedures will be as follows:

- **Group 1**: The first IMP infusion in the first five subjects will be staggered at 2-week intervals, and blood samples for interim safety testing, including the three assays for antibodies to β2GPI (two for total β2GPI and one for β2GPI-DI), will be drawn before the second infusion (at Week 4 in subjects on a 4-week treatment regimen; Week 3 in subjects on a 3-week treatment regimen). While these first five subjects continue on IMP and before further subjects receive IMP, the results will be evaluated by the Investigators and the Data Safety Monitoring Board (DSMB) and submitted to the FDA for review.
- **Group 2:** Contingent on FDA and DSMB approval after review of the interim safety results in Group 1, 10 further subjects will receive the first IMP infusion staggered at an interval to be determined by the FDA after review of the Group 1 results. As in Group 1, blood samples for safety testing will be drawn before the second infusion (Week 4 or 3, depending on treatment regimen). While these 10 subjects continue on IMP and before further subjects receive IMP, the results will be evaluated by the Investigators and the DSMB and submitted to the FDA for review.
- **Group 3:** Contingent on FDA and DSMB approval after review of the interim safety testing in Group 2, the study will continue with IMP infusions in approximately 60 further subjects, including approximately 35 adults to complete Cohort 1 and approximately 25 children in Cohort 2. The starting date of the first IMP infusion in this group will not be staggered.

If special circumstances of clinical management, and anticipated treatment cycle scheduled date, make it necessary to reduce the 2-week staggering interval for subjects in Group 1, the interval between subjects may be decreased to a minimum of 10 days.

To overcome the challenges of scheduling subjects for their first IMP infusion to fit their current treatment schedule, all eligible subjects will be screened by study sites and enrolled in the study after giving informed consent. Enrolled subjects will continue treatment with their current commercially licensed immune globulin product under the care of the Investigator until the scheduled time of their first IMP infusion. Subjects who have previously been receiving immune globulin as part of a clinical trial, or coming off of IGSC, will be treated with a commercially available IGIV selected by the Investigator in consultation with their treating physician.

Eligible subjects aged 18-80 years will be randomized in a 1:1:1 fashion to Groups 1, 2, and 3. When 5 subjects have been enrolled in Group 1, this group will be closed, and randomization will continue 1:1 to Groups 2 and Group 3. Group 2 will be closed when 10 subjects have been enrolled, and all subjects subsequently enrolled in the study will be placed in Group 3. Once the FDA and the DSMB has approved the safety profile of Groups 1 and 2, all subjects in Group 3 will begin to receive IMP. To be eligible for enrollment, subjects must have been treated with a stable dose of commercially licensed immune globulin administered intravenously (IGIV) for at least 3 consecutive treatments at 21 or 28 day intervals with documented trough levels, or subcutaneously (IGSC) for at least 12 weeks with documented steady state levels, as defined in the Inclusion Criteria (Section 4.3.1). The following subjects will not be eligible for randomization and will be assigned to Group 3:

- Subjects receiving treatment with another investigational immune globulin at enrollment (SC or IV)
- Subjects receiving IGSC
- Subjects aged < 18 years

This randomization scheme is designed to:

- Minimize potential selection bias, so that the interim safety analyses will be based on randomly assigned subject populations
- To ensure no child is enrolled into the safety groups and receive IMP before the FDA has approved the safety of the product in adults
- To allow subjects currently receiving another Investigational Medical Product to be stabilized on an approved commercially-available IGIV for at least 3 months prior to receiving IMP

- Provide data on adverse events, including episodes of hemolysis or thrombosis, as well as immunologic testing (anti-β2GPI and anti-β2GPI-DI antibodies) in subjects currently receiving commercially licensed IGIV product, as well as in subjects receiving the IMP.

This schema for the staggered administration of IMP will result in the following two time periods for each individual subject:

Waiting Period: This is the elapsed time from enrollment to the first administration of IMP. During this time period, subjects will receive either their current commercially licensed product (CP) or a CP chosen by the Principal Investigator in consultation with their treating physician. All relevant safety and efficacy endpoints will be recorded and summarized for this time period.

IMP Treatment Period: For each subject, this is the elapsed time from the first administration of IMP to study completion. During this time period, subjects will receive the IMP, ProMetic BioTherapeutics Immune Globulin Intravenous (Human) 10%. All planned safety and efficacy endpoints will be recorded and summarized for this time period. All primary and secondary efficacy analysis is restricted to data collected during this time frame.

Treatment

Waiting Period on Commercial Product

Subjects who enroll in the study while on commercial immune globulin product and who need to wait for the scheduled start of their IMP treatment will continue on their usual dose and treatment cycle during the Waiting Period on commercial product.

Subjects who have been receiving another IGIV or IGSC investigational product and subjects who have been receiving commercial IGSC will be switched to a commercial IGIV product as selected by the Investigator in consultation with their treating physician on enrollment.

IMP Treatment Period

Subjects on commercial IGIV therapy before study entry, who will continue on their usual regimen during the Waiting Period, will switch to IMP at the same dose and treatment interval. For subjects on IGSC therapy before study entry, the IMP dose will be calculated based on the current IGSC dose, and the IMP treatment interval will be the same as their prior IGIV treatment interval (Section 13.6.1).

Doses can be adjusted by the Principal Investigator (PI) as described in Section 13.6.1 and IMP infusion rates will be adjusted during all visits to a tolerable level according to a preset algorithm described in Section 13.6.2.

	Evaluations Analyses of all primary and secondary efficacy endpoints will be restricted to data collected during the IMP treatment period (Section 5 and Section 12). However, the same assessments will be recorded and summarized for the period on commercial product as for the IMP treatment period (Section 6). The interim safety evaluations of Groups 1 and 2 will look for evidence of immunogenicity, hemolysis and thrombosis based on clinical signs and laboratory tests (hematology, blood chemistry, urinalysis, hemolysis, d-dimer, protein C and protein S concentrations, antibodies to ß2GPI and β2GPI-DI) in samples drawn before the second infusion (at Week 4 in subjects on a 4-week treatment cycle; Week 3 in subjects on a 3-week treatment cycle) (Section 8.1).
Subject Population:	**Main Study** To achieve 60 evaluable subjects, approximately 75 eligible subjects aged 2 to 80 years will be enrolled. Two cohorts will be separately enrolled to ensure an adequate number of subjects in each age group. Cohort 1 will enroll approximately 50 subjects aged 17 to 80 years to achieve at least 40 evaluable subjects. Cohort 2 will enroll approximately 25 subjects to achieve at least 20 evaluable subjects. Cohort 2 will enroll up to 6 subjects aged 2 to <6 years, at least 6 subjects aged 6 to <12 years, and at least 6 subjects aged 12 to <17 years. Note: Only adult subjects (≥18 years) can be randomized to Groups 1, 2, and 3 during the Evaluation Period. Pediatric subjects (< 18 years) are directly enrolled into Group 3. After randomization is closed for Groups 1 and 2, additional subjects, regardless of age, will be enrolled in Group 3. **PK Sub-study** The PK sub-study will be conducted in a subset of each cohort: • Approximately 25 subjects in Cohort 1 will be enrolled to achieve 18 evaluable subjects for PK analysis. • Approximately 18 subjects in Cohort 2 will be enrolled to achieve 12 evaluable subjects for PK analysis. Up to 6 subjects will be analyzed for PK in each of the following age groups: 2 to <6 years, 6 to <12 years, and 12 to <17 years.
Inclusion Criteria:	1. Subject is male or female between the ages of 2 and 80 years at Screening.

- For Russian sites, only subjects 18 years of age and older, treated with commercially licensed immune globulin product will be enrolled.
- For Cohort 1, all subjects will be aged ≥17 to 80 years.
- For Cohort 2, subjects will be aged 2 to <17 years

2. Subject or parent(s)/legal guardian has given written informed consent/assent (as applicable). Pediatric subjects are defined as 2 to <17 years of age at study entry and will require assent forms as appropriate.
3. Subject or parent(s)/legal guardian agrees to comply with the requirements of the protocol.
4. Female subjects of childbearing potential must have a negative urine pregnancy test documented at the visit at which they receive the first infusion of IMP and must agree to employ adequate birth control measures, as determined by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC), for the duration of the study.
5. The subject must have established one of the following three diagnoses (isolated PIDD of other types will be excluded):
   - Common variable immunodeficiency (CVID)
   - X-linked agammaglobulinemia (XLA)
   - Hyper-IgM syndrome and documented low IgG levels (< 4.5 mg/mL [< 450 mg/dL]).
6. Subjects must have been treated with a stable dose of immune globulin administered intravenously (IGIV) or subcutaneously (IGSC), as defined below.
   - For IGIV, a stable dose is defined as administration of a dose of 200-800 mg/kg, with no more than 25% change during at least 3 consecutive treatments at 21-day (±4 days) or 28-day (±4 days) dosing intervals.
   - For IGSC, a stable dose is defined as administration of a dose of 300-900 mg/kg/month IV (or Sub-cutaneous equivalent), regardless of dosing schedule, with no more than 25% change during at least 12 weeks.
7. Subjects who are receiving IGSC when they enter the study must have received at least one documented IGIV infusion in the past without an associated serious adverse event.
8. Documented trough or steady state levels
   - Subjects who are receiving IGIV when they enter the study have at least 2 documented serum IgG trough levels of

	≥ 5 mg/ mL measured in the prior 6 months. One of these can be the serum IgG level at Screening. o Subjects who are receiving IGSC have at least 2 documented serum IgG steady state levels of ≥ 5 mg/mL in the prior 24 weeks. One of these can be the serum IgG level at Screening. 9. Authorization to access personal health information.
Exclusion Criteria:	1. Subject has secondary immunodeficiency or has been diagnosed with dysgammaglobulinemia or isolated IgG subclass deficiency. 2. Subject has ever had a history of severe anaphylactic or anaphylactoid reaction to immunoglobulins or other blood products. 3. Subject has a known history of immunoglobulin A (IgA) deficiency and known anti-IgA antibodies. (Note that subjects with IgA deficiency without known antibodies to IgA may be enrolled.) 4. Subject has had a thrombotic event, such as deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism, at any time. 5. Subject has received blood products except IGIV, IGSC, or albumin within the previous 12 months. 6. Subject has participated in another study (except IGIV, IGSC studies) within the previous 4 weeks. 7. Subject has had cancer in the past 5 years, except for basal cell or squamous cell cancers of the skin. 8. Subject has current or prior diagnosis of malignancies of lymphoid cells such as lymphocytic leukemia, non-Hodgkin's lymphoma, or immunodeficiency with thymoma. 9. Subject has known hypoalbuminemia (< 3 gm/dL), protein-losing enteropathy, or nephrotic syndrome. 10. Subject has had a documented active infection within 7 days prior to Screening, or subject is on continuous prophylactic antibiotics. Subjects receiving a course of antibiotic treatment for a recent bacterial infection, which is controlled, can be enrolled into the study. 11. Subject is positive for human immunodeficiency virus (HIV)-1 or HIV-2. 12. Subject has a positive hepatitis C virus (HCV) or hepatitis B virus (HBV) nucleic acid test (NAT) performed by qualitative or

	quantitative polymerase chain reaction (PCR) in the past 12 months. 13. Subject has levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN). 14. Subject has serum creatinine >1.5 times the ULN or a severe chronic condition such as renal failure with proteinuria. 15. Subject has anemia with a hemoglobin level ≤ 8 g/dL. 16. Subject has severe neutropenia with neutrophil count ≤ 1,000 per mm^3 or has lymphopenia with < 500 per mm^3. 17. Subject is taking prednisone at a dose ≥ 0.15 mg/kg/day. (Topical steroids for skin conditions, steroid eye drops, chronic use of inhaled steroids for asthma, and intranasal steroids for rhinitis are allowed). Exception: A brief course of systemic steroids above this threshold (i.e., a steroid burst) is allowed for treatment of a short-term condition such as an asthma exacerbation or poison ivy exposure. 18. Subject is receiving other immunosuppressive drugs or chemotherapy. 19. Subject has known atrial fibrillation requiring anticoagulant therapy; congestive heart failure (New York Heart Association Class III/IV); cardiomyopathy; or cardiac arrhythmia associated with thromboembolic events, unstable or advanced ischemic heart disease, or hyperviscosity. 20. Subject has known decreased Protein C and/or Protein S levels. 21. Subject is positive for antibodies to β2GPI and/or β2GPI-DI at Screening. 22. Female subject who is pregnant, breast-feeding, or planning a pregnancy during the course of the study. 23. A history of epilepsy or multiple episodes of migraine (defined as at least one episode within 6 months of enrolment) not completely controlled by medication, or any condition that is likely to interfere with evaluation of the IMP or satisfactory conduct of the study in the Investigator and Medical Monitor's opinion.
Study Sites:	This study will be conducted at up to 20 sites in the United States and Russia.
Investigational Medicinal Products, Dose, Dosage	ProMetic BioTherapeutics IGIV is a 10% liquid formulation of human IgG in 50 mL vials containing 100 mg/mL of IgG.

regimen, Treatment period, Formulation, Mode of Administration	The IMP will be administered every 3 or 4 weeks, depending on the subject's previous IGIV treatment schedule, for approximately 1 year. To maintain a trough IgG level of at least 5 mg/mL, the dose of the IMP administered will be calculated by the Investigator using the subject's body weight and, for subjects previously receiving IGIV, will be consistent with the previous IGIV dose. For determination of the IGIV dosage for subjects previously receiving IGSC, the total IGSC dose corresponding to one 3- or 4-week cycle will be divided by a dose-adjustment coefficient as indicated by package insert (see Section 13.6.1). The maximum infusion rate per minute must not exceed 8.0 mL/min in any subject. **Infusion Rate for Infusion 1 and Infusion 2** The first two infusions will be administered according to the following algorithm: For the first 30 minutes, IMP will be initiated at an infusion rate of 0.01 mL/kg/min. If, in the Investigator's opinion, the rate is well tolerated, the rate may be increased to 0.02 mL/kg/min for the next 30 minutes. If the increase is well tolerated, the infusion rate may be increased to 0.04 mL/kg/min for the next 30 minutes. If well tolerated, the remainder of the infusion may be administered at a maximum infusion rate of between 0.06 mL/kg/min and 0.08 mL/kg/min, depending on the subject's body weight. The maximum infusion rate per minute must not exceed 8.0 mL/min in any subject. If an AE occurs during the first dose, the infusion rate should be adjusted or halted in accordance with Section 10.2. **Infusion Rate for Infusion 3 Onward** The rate for infusion 3 onward will follow the same algorithm of infusion rate increase for the first two doses, but the increases can be implemented every 15 minutes instead of 30 minutes.
Study Duration:	**Duration of Subject Participation** The screening period before administration of the first dose of IMP will depend on the subject's infusion cycle: 21 days for subjects on a 21-day cycle, 28 days for subjects on a 28-day cycle, and up to 17 days for subjects on IGSC infusions. To cover seasonal variations, all subjects will be treated with the IMP for approximately one year. After the last infusion, AEs will be monitored for 21 days (±2 days) or 28 days (±2 days) days, depending on the infusion cycle, and all subjects will then return for a long-term safety visit (LTSV), at Week 51 for subjects on a 21-day cycle and Week 52 for those on a 28-day cycle.

	However, the expected total duration of subject participation from enrollment to LTSV will include the Waiting Period on commercial product treatment. This period will vary, depending on the date of enrollment and the start of IMP treatment in the assigned scheduling group. The safety evaluation phase (including an evaluation at Week 4 for subjects on a 4-week treatment regimen; Week 3 for subjects on a 3-week treatment regimen after the first IMP infusion in five subjects and another at Week 4 or 3, depending on treatment regimen, after the first IMP infusion in the next 10 subjects, with the start of IMP treatment at staggered intervals) is expected to be completed by Study Week 36. Thus, if there is no delay in completing the two evaluations, a subject enrolled in the study at the beginning of recruitment and assigned to Group 3 (start of IMP after both evaluations are complete) would have a Waiting Period on commercial product of 36 weeks. The total study duration for this subject would be 88 weeks (approximately 21 months). Subjects who enroll at a later time and are assigned to Group 3 would have a shorter Waiting Period and a correspondingly shorter total study duration. **Total Study Duration** This study will be conducted at up to 20 adult and pediatric centers in the US and Russia which specialize in treating patients with immunodeficiencies. The study duration in adults will comprise recruitment, screening, and evaluation of the first 15 subjects to receive IMP, as well as continued screening during the safety evaluation period, and treatment with commercial IGIV product for subjects who must wait for the first scheduled IMP infusion. The total study time is expected to be at least 2 years for Cohort 1. Children will not be included in Groups 1 and 2, but they may be screened, enrolled into Group 3, and treated with commercial product during the evaluation period, and once the safety groups are approved by the FDA they can receive the first IMP infusion. If the adult cohort finishes before the pediatric cohort, there will be two database locks and two clinical study reports, one for adult licensure and one for pediatric licensure (Section 12.5).
Criteria for Evaluation:	**Primary Efficacy Endpoints:** The rate of clinically documented SBIs, defined as: • Bacterial pneumonia • Bacteremia and septicemia

- Osteomyelitis / septic arthritis
- Bacterial meningitis
- Visceral abscess

Secondary Efficacy Endpoints:

- Total serum IgG trough levels
- Episodes of fever (≥ 100.4°F)
- Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infection
- Number of days of hospitalization due to infection
- Number of days of antibiotic use for infection prophylaxis and/or treatment
- Number and duration of infections other than acute serious bacterial infections

Safety Endpoints:

- All AEs reported
- Rate (per infusion per subject), severity, and relatedness of AEs
- Frequency of temporally associated AEs
- Infusional AEs
- Assessment of local tolerability to IMP infusions
- Adverse reactions/suspected adverse reactions
- Vital sign changes, including changes in systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature
- Changes from Screening in physical examination findings
- Changes from Baseline in laboratory parameters (blood chemistry, hematology, urinalysis, hemolysis, d-dimer, protein S, and protein C concentrations, titers of antibodies to ß2GPI and β2GPI-DI)
- Frequency of clinical signs of hemolysis and/or thrombosis within 72 hours after infusion of the IMP
- IGIV-associated hemolysis
- Changes from Screening in viral markers (HAV, HBV, HCV, HIV-1, HIV-2, and B19)

	• Comparisons of safety variables during treatment with IMP and during the Waiting Period on commercial product will be made as described in Section 12.3.4. **Pharmacokinetic Endpoints (sub-study)** • Total IgG levels • Area under the concentration-time curve over 1 dosing interval (AUC_{0-t}) • Area under the concentration-time curve extrapolated to 0 concentration (AUC_{0-inf}) • Peak serum concentration (C_{max}) • Time to reach peak serum concentration (T_{max}) • The volume of distribution at steady-state (V_{ss}) • Mean residence time (MRT) • Total body clearance (CL) • Terminal half-life ($t_{1/2}$)
Statistical Methods:	**Sample size** To calculate the approximate power for this study, it is assumed that the number of SBIs experienced per subject per year follows a negative binomial distribution with mean μ and variance $\sigma^2 = \mu(1+\phi\mu)$ where ϕ represents an overdispersion parameter reflecting possible inter-subject variability in the rates of SBIs between subjects. To demonstrate efficacy, it is required that the observed mean number of SBIs across the study population should have an upper 99% one-sided confidence limit below 1 infection per subject per year. This is equivalent to testing the one-sided null hypothesis, H_0: $\mu \geq 1$, against the alternative hypothesis, H_0: $\mu < 1$, where μ is the population mean rate of SBI's per subject per year. Based on the mean and variance of the negative binomial distribution, standard one-sample power calculations for comparison of an observed mean with a theoretical alternative hypothesis indicate that for a study with 40 subjects (Cohort 1), the probability of the upper one-sided 99% confidence limit being less than 1 remains above 80% (power$\geq$0.798) for overdispersion ranging from $\phi=0$ (corresponding to a Poisson distribution with no overdispersion) to $\phi=2$ provided that the true mean number of SBIs per subject per year in the population lies below 0.50. For a sample of 20 subjects (Cohort 2), this probability remains at or above 80% (power$\geq$0.798) for overdispersion ranging from $\phi=0$ to $\phi=2$ provided that the true mean

number of SBIs per subject per year in the population lies below 0.40 (or 0.50 in the case when there is no overdispersion).

For practical purposes, the study should be considered adequately powered to demonstrate efficacy for a population in which the true incidence of serious acute bacterial infections is below 0.50 per subject per year.

General statistical approach

Analyses will be presented for the adult cohort (Cohort 1) and the pediatric cohort (Cohort 2) regardless of Study Group both separately and combined.

All subjects who are exposed to at least one dose of the IMP will be included in the safety analysis set. The primary efficacy analysis will be based on the all treated population analysis set, which will be identical to the safety set. In addition, a modified per-protocol population analysis set will be defined as only subjects who receive at least 6 infusions and provide data.

No data will be imputed.

Efficacy Analysis

Primary Efficacy Endpoint

For the primary endpoint, a 99% one-sided (upper) confidence limit for the incidence rate of SBIs (scaled to represent 12 months exposure if necessary) will be derived, and the objective of demonstrating that the true infection rate is below 1 per subject per year will be considered established if this upper limit is less than 1.

To calculate the confidence limit, a negative binomial regression model will be used. This model includes an over-dispersion parameter to account for possible intra-subject correlation as well as the actual time period each subject is on the study as an offset variable.

The null hypothesis for this analysis is that the true SBI rate is at least 1 per subject per year, and the alternative hypothesis is that this rate is less than 1 per subject per year. Rejection of the null hypothesis is therefore equivalent to demonstration of the study objective to show that the true rate is less than 1 SBI per subject per year.

The proposed method of analysis makes appropriate allowance for any intra-subject correlation in the incidence of SBIs. Such correlation would occur whenever variability in the subject-specific SBI rates exceeds what would be expected in the presence of true Poisson variability. The proposed statistical test is based on a negative binomial model that includes an overdispersion parameter reflecting any such inflated variance.

Subgroup analyses will be performed based on gender and region (USA, Russia).

Secondary Efficacy Endpoints

Secondary efficacy endpoints will be presented using the appropriate descriptive statistics and summarized according to treatment time periods (Waiting Period, IMP Treatment Period). No hypotheses will be tested.

No formal statistical analyses will be done comparing primary or secondary efficacy endpoints between the Waiting Period on commercial product and the IMP Treatment Period. However, any efficacy endpoints measured during both the Waiting Period on commercial product and IMP Treatment Period may be summarized side-by-side using the appropriate descriptive statistics. For the Waiting Period on commercial product, the summary descriptive statistics will be aggregated over all commercially licensed products.

Safety Endpoints

Evaluation of safety includes the analysis of laboratory investigations and the analysis of adverse events.

Laboratory Data:

A summary by treatment period (Waiting period, IMP treatment period) will be produced for each of the laboratory parameters at each visit. These safety summaries will include descriptive summary tables and the data will be summarized in the form of frequency count, mean, standard deviation, median, minimum and maximum by treatment period and visit.

Adverse Events:

The seriousness, severity and relationship to the study drug of adverse events (AEs) will be observed and recorded on repeated administrations of the study drug using the MedDRA dictionary for the coding of AEs and serious adverse events (SAEs).

The number and proportion of subjects who have one or more AEs will be tabulated by seriousness, severity, and relationship to treatment according to body system and treatment period. Temporally associated AEs will be similarly summarized. Rates of AEs will be estimated on a per infusion per subject basis and tabulated by seriousness, severity, and relationship to treatment according to body system and treatment period.

The observed proportion will be reported for infusions with one or more temporally associated (during and within 72 hours after the end of the infusion) AEs (including any AEs considered product related). Infusional AEs will also be tabulated by the prevailing infusion rate.

The number of infusions with a temporally associated AE (including any AEs considered product related) will be analyzed using a negative binomial regression model with the objective of demonstrating that the rate of infusions with one or more temporally associated AEs is less than 40 infusions per 100 patient infusions. This will be accomplished by fitting an intercept-only negative binomial regression model to the data where the response for each subject is the number of affected infusions (i.e., the number of infusions with one or more temporally-associated AEs). A two-sided 90% confidence limit on the intercept will then be computed on the inverse link scale to achieve an upper one-sided 95% confidence limit on the on the expected mean number of infusions per 100 patient infusions having one or more temporally associated AEs. This upper limit should be below 40 in order to statistically demonstrate the safety of the infusion process.

The operational definition of adverse reaction/suspected adverse reaction for analysis purposes will be all AEs meeting any of the following criteria: (a) the event began during or within 72 hours following the last IMP infusion; (b) the event was considered by the investigator and/or the sponsor to be at least possibly related to the IMP administration; or (c) the causality assessment was missing or indeterminate.

The operational definition of IGIV-associated hemolysis for this analysis is defined as any event meeting the following criteria occurring within 10 days following IGIV administration: (a) a fall of at least 1 g/dL in hemoglobin from the previous value; (b) a positive Coombs test (direct anti-globulin test); and (c) at least 2 of the following: increased reticulocyte count, increased LDH, low haptoglobin, increased bilirubin, increased plasma free hemoglobin, increased urine hemosiderin.

No formal statistical analyses will be done comparing safety endpoints between the Waiting Period and the IMP Treatment Period. However, all safety endpoints measured during both the Waiting Period and IMP Treatment Period will be summarized side-by-side using the appropriate descriptive statistics. For the Waiting Period, the summary descriptive statistics will be aggregated over all commercially licensed products.

Pharmacokinetics Endpoints

For all subjects in the PK sub-study, blood samples will be collected for the assessment of serum concentrations of total IgG. The serum concentrations will be determined as defined in a laboratory assay plan. All PK parameters will be estimated by both compartmental and non-compartmental analysis using Phoenix® WinNonlin 6.3 (Pharsight) and summary statistics will be presented. For all subjects in the all treated population dataset, prior to each infusion, trough

serum IgG concentrations will also be determined. For the PK analysis, the data will be baseline (pre-dose) corrected.

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List of Abbreviations and Definitions of Terms

Abbreviation	Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
AUC_{0-t}	Area under the concentration-time curve over 1 dosing interval
AUC_{0-inf}	Area under the concentration-time curve extrapolated to zero concentration
ß2GPI	ß2 Glycoprotein I
β2GPI-D1	ß2GPI Domain I
B19	Human parvovirus b19
BUN	Blood urea nitrogen
CBC	Complete blood count
CK	Creatinine kinase
CL	Total body clearance
C_{max}	Peak serum concentration
CRA	Clinical research associate
CRO	Clinical research organization
CTA	Clinical trial application
CVID	Common variable immune deficiency
DAT	Direct anti-globulin test
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Immune globulin intravenous
IgM	Immunoglobulin M
IGSC	Immune globulin subcutaneous
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LTSF	Long-term safety follow-up
LTSV	Long-term safety visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NAT	Nucleic acid test
PCR	Polymerase chain reaction
PHI	Protected Health Information
PI	Principal Investigator
PIDD	Primary immunodeficiency diseases
PK	Pharmacokinetics
PP	Per protocol
QA	Quality assurance
QC	Quality control

RBC	Red blood cell
RDW	Red (cell) distribution width
SAE	Serious adverse event
SBI	Serious bacterial infection
SC	Subcutaneous
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
$T_{½}$	Terminal half-life
TCTV	Treatment completion/termination visit
TEE	Thromboembolic event
T_{max}	Time to reach peak serum concentration
TRALI	Transfusion-related acute lung injury
ULN	Upper limit of normal
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization
XLA	X-linked agammaglobulinemia

1 Introduction

1.1 Background

Primary immunodeficiency diseases (PIDD) are a class of disorders in which there is an intrinsic defect in the human immune system, in contrast to immune disorders that are secondary to infection, chemotherapy, or some other external agent. PIDD include a variety of disorders in which the intrinsic immune defect renders patients more susceptible to infections. As a consequence, patients are affected by recurrent protozoal, bacterial, fungal, and viral infections. Untreated PIDD may be characterized by frequent life-threatening infections.

More than 220 different PIDD are currently recognized by the World Health Organization (Immune Deficiency Foundation, 2015). Antibody deficiencies, also referred to as B-cell or humoral immunodeficiencies, comprise the largest group of PIDD (International Union of Immunological Societies, 1999). Common PIDD include disorders of humoral immunity (affecting B-cell differentiation or antibody production), T-cell defects and combined B- and T-cell defects, phagocytic disorders, and complement deficiencies (Reust, 2013).

ProMetic proposes to include in the study the following three well-defined types of PIDD, which are associated with humoral immune deficiency and are conventionally treated with immunoglobulin therapy:

- Common variable immunodeficiency (CVID)
- X-linked agammaglobulinemia (XLA)
- Hyper-immunoglobulin M (IgM) syndrome and documented low immunoglobulin G (IgG) levels (< 4.5 mg/mL)

Although PIDD are often described as rare disorders, remarkably little is known about the true incidence or prevalence in any population, either individually or in the aggregate (Bonilla, 2008; Boyle & Buckley, 2007). There is no universal screening for these defects at birth or at any time during life, anywhere in the world. Overall, there may be as many as 500,000 cases in the United States, of which about 50,000 cases are diagnosed each year (Schroeder, 2001). Some disorders, such as selective IgA deficiency, are quite common and may occur as often as 1 in 400 individuals (Conley, Notarangelo, & Etzioni, 1999; Cunningham-Rundles & Bodian, 1999). Others may be as rare as one individual affected per million. It has been estimated that 40% of cases are diagnosed in the first year of life, with another 40% diagnosed by the age of 5, and another 15% by the age of 16; only 5% of cases are diagnosed in adulthood (Conley & Stiehm, 1996).

The largest registry available on patients with PIDD is the European Society for Immunodeficiencies (ESID) Registry (Grimbacher & ESID Registry Working Party,

2014). As of June 2014, 19,355 patients were included. Children younger than age 15 years represented two-thirds of the subjects. More than half the patients (57%) had an antibody disorder, and this was also the group with the greatest number of adult patients. Treatment data were available on approximately 14,000 subjects, of whom 6,476 receive immunoglobulin treatment. It is believed that the Registry provides incomplete PIDD prevalence data; for example, the prevalence varies from 2 per 100,000 in Germany to 6 per 100,000 in France. The author believes the apparent difference in prevalence is due to the fact that in France there are designated documenters, financed by local grants, who visit centers to enter patients' data into the Registry.

Boyle and Buckley (Boyle & Buckley, 2007) performed a telephone survey of 10,000 randomly-selected US households and asked an open-ended question: "Has anyone in your household ever been diagnosed with a primary immuno-deficiency disease, such as common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, or any other immunodeficiency?" While admitting the multiple issues associated with this survey, the authors estimated a prevalence of diagnosed PIDD at 1 in 1,200 persons. The specific diagnoses recorded included common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, X-linked agammaglobulinemia, severe combined immunodeficiency, and chronic granulomatous disease.

Joshi et al (Joshi, Iyer, Hagan, St Sauver, & Boyce, 2009) examined trends in the incidence of primary immunodeficiency over 3 decades (1976-2006) in Olmsted County, Minnesota, using 27 ICD-9 codes. This study therefore also included multiple types of primary immunodeficiency. According to this population-based historical cohort study, incidence rates did not differ by sex, but showed an increasing temporal trend in rates over the past 31 years. They found the overall incidence to be 4.6 per 100,000 person-years, with the incidence increasing with time to reach 10.3 per 100,000 persons in the final 5 years of the survey (2001-6). At all periods, the highest incidence of these disorders was in the age group 0-5 years. Overall B-cell defects represented 78% of the population and combined B- and T-cell defects another 10.5%. Among the B-cell defects, IgA deficiency was the most common, accounting for 30% of cases, followed by IgG subclass (IgG2, IgG3, and IgG4) deficiency (26%), and hypogammaglobulinemia (including IgG1 subclass deficiency) (23%). Common variable immunodeficiency was diagnosed in 15% of the cases.

Infections with encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most common presenting features of the antibody deficiency syndromes. Other common infectious presenting features include respiratory tract infections (including sinusitis), gastrointestinal infections, meningitis, septic arthritis, and osteomyelitis. Infections often respond to standard treatment, but recur once therapy has been finished. Prolonged and recurrent infection can have significant consequences: in

children poor growth and developmental delay, often as a result of end-organ damage in the respiratory tract. A positive family is of course a strong indicator that a congenital humoral immune deficiency may be present (Wood, 2009).

1.2 Immunoglobulin Replacement Therapy for PIDD with Antibody Deficiency

Immunoglobulin replacement therapy is the standard treatment for patients with these PIDD. Standard treatment is to administer IgG either intravenously (IV) or subcutaneously (SC) at regular intervals, with the aim of maintaining the trough level of total IgG above 5 mg/mL. This replacement therapy is effective in preventing most infections, resulting in improved quality of life (Eijkhout et al., 2001; Roifman & Gelfand, 1988).

1.3 Benefit/Risk Statement

Because of advances in our medical understanding and treatment of PIDD, patients who in the past would not have survived childhood are now able to live nearly normal lives with the lifelong administration of IGIV infusions. In subjects with a compromised immune system, prophylactic treatment with IGIV has been shown to increase the time between serious bacterial infections, decrease the incidence of overall bacterial infections, and reduce the number of hospitalizations required for treatment of infections (Boyle and Buckley, 2007; Bruton, 1952; Eijkhout et al., 2001; Roifman & Gelfand, 1988).

Replacement immunoglobulin given either IV or SC is standard practice for subjects with PIDD. Most patients receive IGIV infusions at intervals of 2, 3, or 4 weeks. Patients receiving subcutaneous treatment receive treatment weekly. Reductions in hospitalization and infection rates have been well documented in subjects receiving high doses (>400 mg/kg every 3 weeks) of IGIV; and maintaining trough levels of IGIV above 5 mg/mL is considered standard of care (Boyle and Buckley, 2007;Eijkhout et al., 2001; Roifman & Gelfand, 1988).

ProMetic's Immune Globulin (Human) Intravenous 10% solution is analytically comparable to currently marketed IGIV products that are widely used by patients with PID. ProMetic's IGIV is expected to provide similar therapeutic benefits as commercially available IGIV products. Since the levels of Anti-A/Anti-B hemagglutinins have been reduced by exposure to an Anti-A/Anti-B column, less hemolytic events may be expected with the ProMetic IGIV.

The following adverse reactions are known to be associated with IGIV products: chills, headache, fever, vomiting, allergic reactions, infusion site reactions, nausea, arthralgia, low blood pressure, and moderate low back pain. Rarely, human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases,

anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis, isolated cases of reversible hemolytic anemia/hemolysis, and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. An increase in serum creatinine level and/or acute renal failure has been observed.

There have been reports of transfusion-related acute lung injury (TRALI) in patients administered IGIV (Rizk, Gorson, Kenney, & Weinstein, 2001). TRALI typically occurs within 1-6 hours after infusion and is characterized by severe respiratory distress, pulmonary edema, hypoxemia, abnormal left ventricular function, and fever. Patients with TRALI may be managed using oxygen therapy with adequate ventilator support. Currently, there are no guidelines for the prevention of TRALI.

Rare occurrences of thromboembolic events, including stroke, myocardial infarction, pulmonary embolism, and deep vein thrombosis, have been reported following IGIV administration. Many of these rare serious reactions have been reported in patients who have significant risk factors or underlying diseases including advanced age, history of atherosclerosis, cardiovascular risk factors, hyperviscosity states, hypercoagulable disorders, or prolonged immobilization. Recently, impurities such as kallikrein and factor XIa (FXIa) have been identified as contributors to thromboembolic events (TEEs) following IGIV treatments. The manufacturing of ProMetic BioTherapeutics Immune Globulin Intravenous Solution 10% includes chromatography methods which will result in lower levels of impurities including kallikrein and FXIa in the final product (Data on File, ProMetic Biotherapeutics, Inc). It should be noted that the relationship between IVIG and thromboembolic events has been questioned (Basta, 2014).

ProMetic’s IGIV is not expected to pose any unexpected safety risk to patients. Standard safety monitoring procedures will be adopted during the clinical study. Risks related to TEEs are minimized by performing the assays described in the Investigator’s Brochure. Any signs and symptoms of TEE will be closely monitored during the clinical study. In addition, ProMetic’s IGIV product is evaluated for thrombogenicity in the rabbit venous stasis model (Wessler assay) as a release assay. ProMetic’s IGIV does not promote thrombogenic activity in that model.

There are three viral inactivation/removal steps in the IGIV process to help to assure safety of the patients from viral infectivity. However, as IGIV is a blood product, there is also a risk of transmission of unknown blood-borne infections. Hepatitis C transmission has been reported; however, there are no reports of transmission of HIV, hepatitis A or hepatitis B infection by IGIV therapy.

1.4 FDA and DSMB Approval of Interim Safety Results for Group 1 and Group 2

After reviewing the interim safety data from Group 1, the Data Safety Monitoring Board (DSMB) and Food and Drug Administration (FDA) approved dosing of ProMetic's IGIV utilizing a 3-day stagger interval in Group 2; approval dates were May 26, 2016 and June 16, 2016, respectively.

After reviewing the interim safety data from Group 2, the DSMB and FDA approved dosing of ProMetic's IGIV in Group 3; approval dates were October 13, 2016 and December 20, 2016, respectively.

2 Study Rationale and Objectives

2.1 Study Rationale

Polyclonal immunoglobulin preparations of human origin, including IGIV products, have historically been used as replacement therapy to reduce the frequency of serious bacterial infections in subjects with PIDD. Prior to the introduction of IGIV therapy, patients suffering from hypogammaglobulinemia and agammaglobulinemia due to PIDD experienced approximately four or more serious acute bacterial infections each year. However, maintenance of trough IgG serum levels ≥5 mg/mL prevents most recurrent infections and their chronic complications, which improves the patient's quality of life (Eijkhout et al., 2001; Roifman & Gelfand, 1988). Over the past 20 years, prophylaxis with IGIV has become the standard therapy for patients suffering from hypogammaglobulinemia and agammaglobulinemia due to PIDD.

2.2 Dosing Rationale

The optimal dose and frequency of administration must be determined individually for each patient. For patients with PIDD, doses of approximately 300-600 mg/kg infused every three to four weeks are commonly used. A number of studies have demonstrated an association of a steadily decreasing incidence of infections with an increasing frequency of IGIV administration in CVID patients. Each patient may demonstrate his or her own individual response to therapy and experience dramatic differences in the frequency and severity of infections with moderate changes in the dose of IGIV. Patients suffering from a serious acute infection often benefit from booster doses of IGIV. Ultimately, IGIV dosage must be individualized based upon the response of the patient (Schroeder, 2001).

2.3 Study Purpose and Objectives

2.3.1 Purpose

The purpose of this study is to assess the tolerability, safety, efficacy, and pharmacokinetics (PK) of the investigational medicinal product (IMP), ProMetic Immune Globulin Intravenous (Human) 10%, in subjects with PIDD.

2.3.2 Primary Efficacy Objective

The primary objective is to examine the rate of clinically documented serious bacterial infections (SBIs) in subjects treated with the IMP to achieve a rate of less than one SBI per year.

2.3.3 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are to examine the effects of the IMP on the following:

- Serum trough concentrations of total IgG obtained prior to each IMP infusion;
- Number of episodes of fever (≥100.4°F);
- Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections;
- Number of days of hospitalization due to infections;
- Number of days of antibiotics use for infection prophylaxis and/or treatment;
- Incidence of infections other than acute serious bacterial infections.

2.3.4 Safety Objectives

The safety objectives are:

- To examine the safety and tolerability of the IMP
- To collect adverse events (AEs) from the start of the signing of informed consent to 21 days (± 2 days) or 28 days (± 2 days) after the last infusion, depending on the subject's treatment schedule
- To examine total AEs and the observed proportion of AEs considered by the Sponsor to be IMP related;
- To examine AEs temporally associated (during and within 72 hours after the end of the infusion) with the IMP infusion, which will be recorded regardless of relationship to the IMP
- To examine infusion and rate-related AEs, regardless of relationship to the IMP

- To monitor safety approximately 7 days post infusion
- To examine long-term safety with virology testing from Screening to the Long-Term Safety Visit (LTSV)
- To monitor for immunogenic reactions by testing for antibodies to β2GPI and β2GPI-DI, from baseline to the LTSV
- To monitor for thrombogenicity and hemolysis by performing post-infusion clinical evaluations and laboratory testing

2.3.5 Pharmacokinetic Objectives

The PK objectives are:

- To determine the steady state serum concentrations of total IgG;
- To determine the PK profiles for total IgG following administration of the IMP.

3 Study Plan

This is a pivotal phase 3, open-label, single-arm, multinational, multicenter study to assess the tolerability, safety, efficacy, and pharmacokinetics of the IMP in adults and children with PIDD. The study will be conducted at up to 20 sites in the United States and Russia. All subjects will be treated on an outpatient basis with ProMetic BioTherapeutics Immune Globulin Intravenous Solution 10% (the IMP) for approximately 1 year.

A total of approximately 75 subjects aged 2-80 years will be enrolled in the study: approximately 50 subjects aged 17-80 years (Cohort 1) and approximately 25 children aged 2 to <17 years (Cohort 2). Only subjects 18 years of age and older and treated with commercially licensed immune globulin product will be enrolled by Russian sites, in accordance with Russian national legislation.

This is an open-label study; no subject or study personnel will be blinded.

A subset of subjects will be asked to participate in a PK sub-study (Section 6.13). Subjects who consent to participate in the PK sub-study will undergo a series of blood draws to assess the PK profile of the IMP before and after Infusion 6 (21-day cycle subjects) or Infusion 5 (28-day cycle subjects).

3.1 Safety Precautions at Enrollment

To enhance subject safety, IMP will initially be given only to adults aged 18-80 years treated with a stable dose of immune globulin, with the timing of the first IMP infusion at staggered intervals, in Groups 1 and 2. The study will proceed to Group 3 only after evaluation and FDA review of safety data obtained at Week 4 (or Week 3 for subjects on

a 3-week treatment regimen) after the first IMP infusion in 15 subjects. The procedures will be as follows:

- **Group 1:** The timing of the first IMP infusion in the first five subjects will be staggered at 2-week intervals, and blood samples for interim safety testing, including three assays for antibodies to β2GPI (two for total β2GPI and one for β2GPI-DI), will be drawn before the second infusion (at Week 4 in subjects on a 4-week treatment regimen; Week 3 in subjects on a 3-week treatment regimen). While these first five subjects continue on IMP and before further subjects receive IMP, the results will be evaluated by the Investigators and the DSMB and submitted to the FDA for review.
- **Group 2:** Contingent on FDA and DSMB approval after review of the interim safety results in Group 1, 10 further subjects will receive the first IMP infusion staggered at an interval to be determined by the FDA after review of the Group 1 results. As in Group 1, blood samples for safety testing will be drawn before the second infusion (Week 4 or 3, depending on treatment regimen). While these 10 subjects continue on IMP and before further subjects receive IMP, the results will be evaluated by the Investigators and the DSMB and submitted to the FDA for review.
- **Group 3:** Contingent on FDA and DSMB approval after review of the interim safety results in Group 2, the study will continue with IMP infusions in approximately 60 further subjects, including approximately 35 more adults to fill Cohort 1 and approximately 25 children in Cohort 2. The starting date of the first IMP infusion in this group will not be staggered.

If special circumstances of clinical management, and anticipated treatment cycle scheduled date, make it necessary to reduce the 2-week staggering interval for subjects in Group 1, the interval between subjects may be decreased to a minimum of 10 days.

To overcome the challenges of scheduling subjects for their first infusion contingent on infusions in the previous subject, potentially eligible subjects will be screened and enrolled in the study as they become available. Enrolled subjects will continue treatment with a commercially licensed immune globulin product as selected by the Investigator in consultation with their treating physician until the scheduled time of their first IMP infusion. Subjects who have previously been receiving immune globulin as part of a clinical trial, or coming off of IGSC, will be treated with a commercially available IGIV selected by the Investigator in consultation with their treating physician.

Eligible subjects aged 18 to 80 years will be randomized in a 1:1:1 fashion to Groups 1, 2, and 3. When 5 subjects have been enrolled in Group 1, this group will be closed, and randomization will continue 1:1 to Groups 2 and Group 3. Group 2 will be closed when 10 subjects have been enrolled, and all subjects subsequently enrolled in the study will be placed in Group 3. Once the FDA and the DSMB has approved the safety profile of Groups 1 and 2, all subjects in Group 3 will begin to receive IMP. To be eligible for

enrollment, subjects must have been treated with a stable dose of commercially licensed IGIV for at least 3 consecutive treatments at 21 or 28 day intervals with documented trough levels, or subcutaneously (IGSC) for at least 12 weeks with documented steady state levels, as defined in the Inclusion Criteria (Section 4.3.1). The following subjects will not be eligible for randomization and will be assigned to Group 3:

- Subjects receiving treatment with another investigational immune globulin at enrollment (SC or IV)
- Subjects receiving IGSC.
- Subjects aged < 18 years.

This randomization scheme is designed to:

- Minimize potential selection bias so that the interim safety analyses will be based on randomly assigned subject populations
- To ensure no child is enrolled into the safety groups and receive IMP before the FDA has approved the safety of the product in adults
- To allow subjects currently receiving another Investigational Medical Product to be stabilized on a commercially available immune globulin for at least 3 months prior to receiving IMP
- Provide data on adverse events, including episodes of hemolysis or thrombosis, as well as immunologic testing (anti-β2GPI and anti-β2GPI-DI antibodies) in subjects currently receiving commercially licensed IGIV product, as well as in subjects receiving the IMP.

This schema for the staggered administration of IMP will result in the following two time periods for each individual subject:

Waiting Period: This is the elapsed time from enrollment to the first administration of IMP. During this time period, subjects will receive either their current commercially licensed product (CP) or a CP chosen by the Principal Investigator in consultation with their treating physician. All relevant safety and efficacy endpoints will be recorded and summarized for this time period.

IMP Treatment Period: For each subject, this is the elapsed time from the first administration of IMP to study completion. During this time period, subjects will receive the IMP, ProMetic BioTherapeutics Immune Globulin Intravenous (Human) 10%. All planned safety and efficacy endpoints will be recorded and summarized for this time period. All primary and secondary efficacy analysis is restricted to data collected during this time frame.

3.2 Treatment

3.2.1 Waiting Period (Commercial Product Period)

Subjects who enroll in the study while on IV infusions of a commercial immune globulin product and who need to wait for the scheduled start of their IMP treatment will continue on their current product with their usual dose and treatment cycle during the Waiting Period.

Subjects who have been receiving another investigational immune globulin product will be switched to commercially available IGIV product as selected by the Investigator at enrollment in consultation with their treating physician.

Subjects on IGSC therapy before study entry will be switched to commercially available IGIV product as selected by the Investigator at enrollment in consultation with their treating physician.

For any subjects who are switched from IGSC or investigational immune globulin product to a commercial IGIV product, the waiting period on the commercial IGIV will be at least 3 cycles prior to IMP infusion 1.

Any necessary changes in dosage will be determined by the Investigator according to the usual standards of care.

3.2.2 IMP Treatment

Subjects on IGIV therapy before study entry will receive the IMP at the same dose and treatment cycle as in their usual regimen. In subjects on IGSC therapy before study entry, the IMP dose will be calculated based on the current IGSC dose, and the IMP treatment interval will be based on their previous IGIV treatment interval (Section 13.6). Thus, within each age cohort, study visits and infusions will be scheduled either at 21-day or 28-day intervals.

Doses can be adjusted by the PI as described in Section 13.6.1 and IMP infusion rates will be adjusted during all visits to a tolerable level according to a preset algorithm described in Section 13.6.2.

3.3 Evaluations

Analyses of all primary and secondary efficacy endpoints will be restricted to data collected during the IMP treatment period (Section 5 and Section 12). However, the same assessments will be recorded and summarized for the period on commercial product as for the IMP treatment period (Section 6).

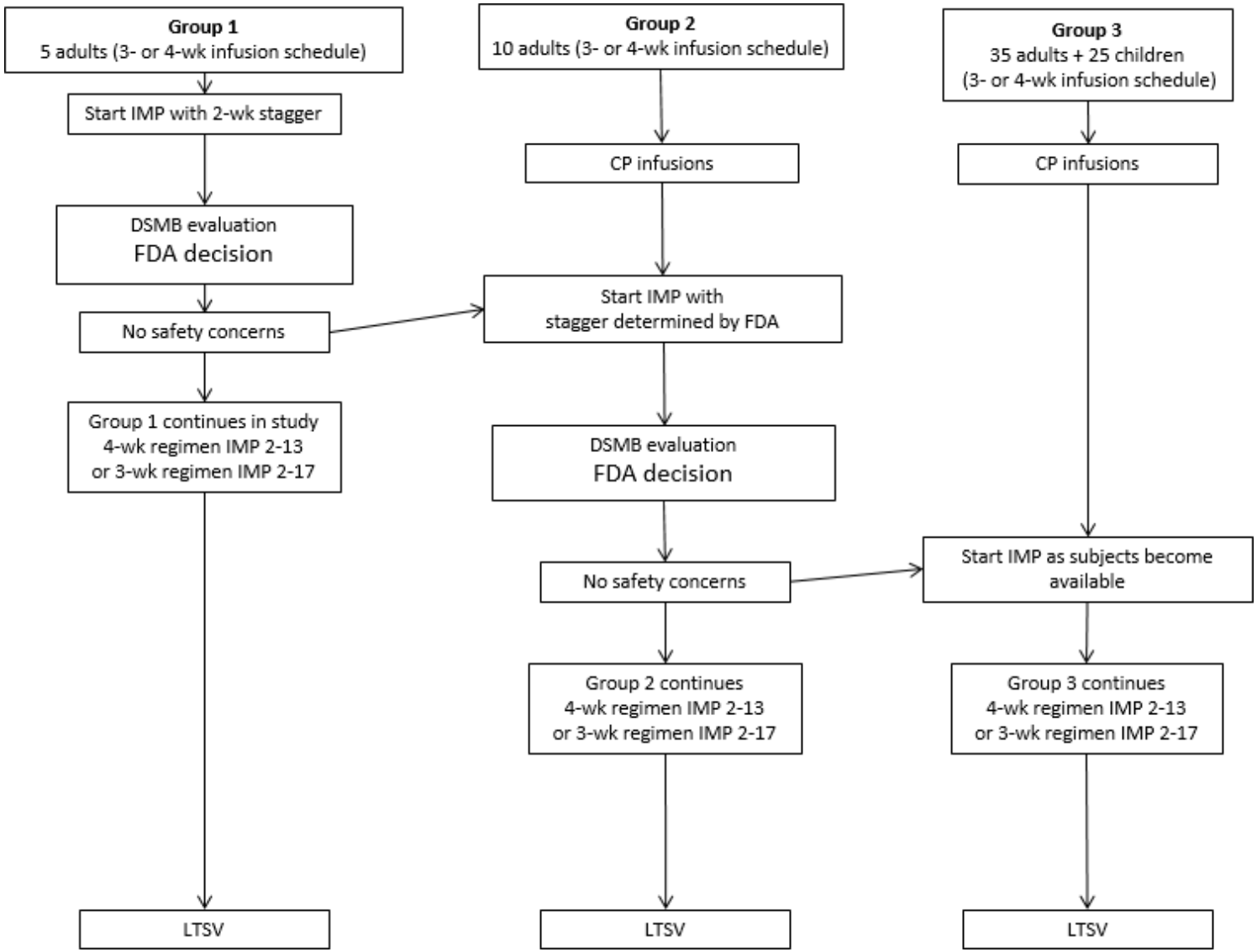
The interim safety evaluations of Groups 1 and 2 will look for evidence of immunogenicity, hemolysis and thrombosis based on clinical signs and laboratory tests (hematology, blood chemistry, urinalysis, hemolysis, d-dimer, protein C and protein S

concentrations, antibodies to ß2GPI and β2GPI-DI) in samples drawn before the second infusion (at Week 4 in subjects on a 4-week treatment cycle and at Week 3 in subjects on a 3-week treatment cycle) (Section 8.1).

3.4 Study Flow Chart

A schematic diagram of the study plan is given in Figure 1 below. The rules and procedures for suspending or stopping the study and for discontinuation of subjects with specific characteristics in the event of safety concerns are explained in Section 8.1.

Figure 1. Safety Evaluation Phase – Randomized Assignment to Scheduling Group



3.5 Study Duration

3.5.1 Duration of Subject Participation

The Screening Visit will be conducted 21 days (±2 days) before the Baseline Visit (Infusion 1 IMP, or CP for Subjects in Waiting Period) for subjects on a 21-day cycle, 28 days (±2 days) before Baseline for subjects on a 28-day cycle, or up to 17 days before the Baseline Visit for subjects receiving IGSC when they enter the study.

To cover seasonal variations, all subjects will be treated with the IMP for approximately 1 year. After the last infusion, AEs will be monitored for 21 days (±2 days) or 28 days (±2 days) days, depending on the infusion cycle, and all subjects will then return for a long-term safety visit (LTSV), at Week 51 for subjects on a 21-day cycle and Week 52 for those on a 28-day cycle.

However, the expected total duration of subject participation from enrollment to LTSV will include the Waiting Period on commercial product treatment. This period will vary, depending on the date of enrollment and the start of IMP treatment in the assigned scheduling group.

The safety evaluation phase (including an evaluation at Week 4 for subjects on a 4-week treatment regimen; Week 3 for subjects on a 3-week treatment regimen after the first IMP infusion in 5 subjects and another at Week 4 or 3, depending on treatment regimen, after the first IMP infusion in the next 10 subjects, with the start of IMP treatment at staggered intervals), is expected to be completed by Study Week 36. Thus, if there is no delay in completing the two evaluations, a subject enrolled in the study at the beginning of recruitment and assigned to Group 3 (start of IMP after both evaluations are complete) would have a Waiting Period on commercial product of 36 weeks. The total study duration for this subject would be 88 weeks (approximately 21 months). Subjects who enroll at a later time and are assigned to Group 3 would have a shorter Waiting Period and a correspondingly shorter total study duration.

3.5.2 Total Study Duration

This study will be conducted at up to 20 adult and pediatric centers in the US and Russia which specialize in treating patients with immunodeficiencies.

The study duration in adults will comprise recruitment, screening, and evaluation of the first 15 subjects to receive IMP, as well as continued screening during the safety evaluation phase, and treatment with commercial IGIV product for subjects who must wait for the first scheduled IMP infusion. The total study time is expected to be at least 2 years for Cohort 1.

Children will not be included in Groups 1 and 2, but they may be screened, enrolled into Group 3 and treated with commercial product during the evaluation period, and once the safety groups are approved by the FDA, they can receive the first IMP infusion.

If the adult cohort finishes before the pediatric cohort, there will be two database locks and two clinical study reports, one for adult licensure and one for pediatric licensure (Section 12.5).

Table 1. Projected Study Duration - Adults

	Weeks (Months)
Study initiation activities (expected time for central[b] IRB/IEC approval, etc.)	4 (1)
Recruitment and screening (minimum total time), including:	12 (3)
– Identification of potential subjects from site records	8 (2)
– Screening of identified potential subjects before the first subject receives IMP[a]	4 (1)
Total study time (minimum time from enrollment of the first subject to the last long-term safety visit in the last subject, including:	88 (21)
– Evaluation period, including	36 (9)
o Staggered scheduling of first IMP infusion in 15 subjects (Groups 1 and 2) with interim evaluations and FDA review of safety data, and o Recruitment, screening, and commercial product treatment for subjects waiting for the first scheduled IMP infusion	
– IMP period per subject	52 (12)
o 48 weeks from first to last IMP infusion o long-term safety visit at Wk 51 (3-wk treatment schedule) or Wk 52 (4-wk treatment schedule)	
Close-out time	8 (2)
Minimum total time	112 (27)

[a]Recruitment and screening will continue during the 36-week evaluation period, which would allow a total of approximately 10months for recruitment after identification of potential subjects.

[b]Sites with local IRB/IEC may have longer review/approval period.

Table 2. Projected Study Duration - Children

	Weeks (Months)	
Study initiation activities (expected time for central[b] IRB/IEC approval, etc.)	4	(1)
Recruitment and screening (minimum total time), including:	12	(3)
– Identification of potential subjects from site records	8	(2)
– Screening of identified potential subjects before the first subject receives IMP[a]	4	(1)
Total study time (minimum time from enrollment of the first subject to the last long-term safety visit in the last subject, including:	100	(24)
– Recruitment, screening and commercial product treatment for subjects waiting for the first scheduled IMP infusion (continued during the safety evaluation phase for adults)	36	(9)
– Extra time for recruitment and screening of children	12	(3)
– IMP period per subject 48 weeks from first to last IMP infusion and long-term safety visit at Wk 51 (3-wk treatment schedule) or Wk 52 (4-wk treatment schedule)	52	(12)
Close-out time	8	(2)
Minimum total time	124	(30)

[a]Recruitment and screening will continue during the 36-week evaluation period, and as children may be more difficult to recruit an additional 12 weeks (3 months) is allowed. This would push back the start of IMP treatment in some pediatric subjects by a further 3 months. The maximum time is 1 year for recruitment of children.

[b]Sites with local IRB/IEC may have longer review/approval period.

4 Study Population

Subjects with a diagnosis of primary humoral immunodeficiency will be selected for the study. To achieve 60 evaluable subjects, approximately 75 eligible subjects aged 2 to 80 years will be enrolled. Two cohorts (Cohort 1 [adults] and Cohort 2 [children]) will be separately enrolled to ensure an adequate number of subjects in each age group. The PK sub-study will be conducted in a subset of each cohort. Subjects randomly assigned to Groups 1, 2, and 3 during the evaluation period must be from Cohort 1. After randomization is closed, both Cohorts 1 and 2 can be enrolled in Group 3.

4.1 Main Study

Cohort 1 will enroll approximately 50 subjects aged 17 to 80 years to achieve at least 40 evaluable subjects.

Cohort 2 (children) will enroll approximately 25 subjects to achieve at least 20 evaluable subjects. Cohort 2 will enroll up to 6 subjects aged 2 to <6 years, at least 6 subjects 6 to <12 years, and at least 6 subjects aged 12 to <17 years.

4.2 PK Sub-study

Approximately 25 of the subjects in Cohort 1 will be enrolled in the PK sub-study to achieve at least18 evaluable subjects for PK analysis.

Approximately 18 of the subjects from Cohort 2 will be enrolled in the PK sub-study to achieve at least 12 evaluable subjects for PK analysis. Up to 6 subjects will be analyzed for PK in each of the following age groups: 2 to <6 years, 6 to <12 years, and 12 to <17 years.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

1. Subject is male or female between the ages of 2 and 80 years at Screening.
    - For Russian sites, only subjects 18 years of age and older, treated with commercially licensed immune globulin product will be enrolled.
    - For Cohort 1, all subjects will be aged ≥17 to 80 years.
    - For Cohort 2, subjects will be aged 2 to <17 years
2. Subject or parent(s)/legal guardian has given written informed consent/assent (as applicable). Pediatric subjects are defined as 2 to 17 years of age at study entry and will require assent forms as appropriate.
3. Subject or parent(s)/legal guardian agrees to comply with the requirements of the protocol.

4. Female subjects of childbearing potential must have a negative urine pregnancy test documented at the visit which they receive the first infusion of IMP and must agree to employ adequate birth control measures, as determined by their IRB/IEC, for the duration of the study.
5. The subject must have established one of the following three diagnoses (isolated PIDD of other types will be excluded):
    - Common variable immunodeficiency (CVID)
    - X-linked agammaglobulinemia (XLA)
    - Hyper-IgM syndrome and documented low IgG levels (<4.5 mg/mL [450 mg/dL]).
6. Subjects must have been treated with a stable dose of immune globulin administered intravenously (IGIV) or subcutaneously (IGSC), as defined below.
    - For IGIV, a stable dose is defined as administration of a dose of 200-800 mg/kg with no more than 25% change during at least 3 consecutive treatments at 21-day (±4 days) or 28-day (±4 days) dosing intervals.
    - For IGSC, a stable dose is defined as administration of a dose of 300-900 mg/kg/month IV (or Sub-cutaneous equivalent), regardless of dosing schedule, with no more than 25% change during at least 12 weeks.
7. Subjects who are receiving IGSC when they enter the study must have received at least one previous documented IGIV infusion without an associated serious adverse event.
8. Documented trough or steady state levels
    - Subjects who are receiving IGIV when they enter the study have at least 2 documented serum IgG trough levels of ≥ 5 mg/ mL measured in the prior 6 months. One of these can be the serum IgG level at Screening.
    - Subjects who are receiving IGSC have at least 2 documented serum IgG steady state levels of ≥ 5 mg/mL in the prior 24 weeks. One of these can be the serum IgG level at Screening.
9. Authorization to access personal health information.

4.3.2 Exclusion Criteria

1. Subject has secondary immunodeficiency or has been diagnosed with dysgammaglobulinemia or isolated IgG subclass deficiency.
2. Subject has ever had a history of severe anaphylactic or anaphylactoid reaction to immunoglobulins or other blood products.
3. Subject has a known history of immunoglobulin A (IgA) deficiency and known anti-IgA antibodies. (Note that subjects with IgA deficiency without known antibodies to IgA may be enrolled.)
4. Subject has had a thrombotic event, such as deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism, at any time.
5. Subject has received blood products except IGIV, IGSC, or albumin within the previous 12 months.
6. Subject has participated in another study (except for IGIV, IGSC studies) within the previous 4 weeks.
7. Subject has had cancer in the past 5 years, except for basal cell or squamous cell cancers of the skin.
8. Subject has current or prior diagnosis of malignancies of lymphoid cells such as lymphocytic leukemia, non-Hodgkin's lymphoma, or immunodeficiency with thymoma.
9. Subject has known hypoalbuminemia (<3 gm/dL), protein-losing enteropathy, or nephrotic syndrome.
10. Subject has had a documented active infection within 7 days prior to Screening, or subject is on continuous prophylactic antibiotics. Subjects receiving a course of antibiotic treatment for a recent bacterial infection, which is controlled, can be enrolled into the study.
11. Subject is positive for human immunodeficiency virus (HIV)-1 or HIV-2.
12. Subject has a positive hepatitis C virus (HCV) or hepatitis B virus (HBV) nucleic acid test (NAT) performed either by qualitative or quantitative polymerase chain reaction (PCR) in the past 12 months.
13. Subject has levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN).
14. Subject has serum creatinine >1.5 times the ULN or a severe chronic condition such as renal failure with proteinuria.
15. Subject has anemia with a hemoglobin level ≤8 g/dL.

16. Subject has severe neutropenia with neutrophil count ≤1000 per mm^3 or has lymphopenia with <500 per mm^3.
17. Subject is taking prednisone at a dose ≥0.15 mg/kg/day. (Topical steroids for skin conditions, steroid eye drops, chronic use of inhaled steroids for asthma, and intranasal steroids for rhinitis are allowed.) Exception: A brief course of systemic steroids above this threshold (i.e., a steroid burst) is allowed for treatment of a short-term condition such as an asthma exacerbation or poison ivy exposure.
18. Subject is receiving other immunosuppressive drugs or chemotherapy.
19. Subject has known atrial fibrillation requiring anticoagulant therapy; congestive heart failure (New York Heart Association Class III/IV); cardiomyopathy; or cardiac arrhythmia associated with thromboembolic events, unstable or advanced ischemic heart disease, or hyperviscosity.
20. Subject has known decreased Protein C and/or Protein S levels.
21. Subject is positive for antibodies to β2GPI and/or β2GPI-DI at Screening.
22. Female subject who is pregnant, breast-feeding, or planning a pregnancy during the course of the study.
23. A history of epilepsy or multiple episodes of migraine (defined as at least one episode within 6 months of enrolment) not completely controlled by medication, or any condition that is likely to interfere with evaluation of the IMP or satisfactory conduct of the study in the Investigator's opinion.

5 Efficacy, Safety, and Pharmacokinetic Endpoints

5.1 Efficacy Endpoints

5.1.1 Primary Endpoint

The rate of clinically documented SBIs, defined as:

- Bacterial pneumonia
- Bacteremia and septicemia
- Osteomyelitis / septic arthritis
- Bacterial meningitis
- Visceral abscess

5.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed:

- Total serum IgG trough
- Number of episodes of fever (≥100.4°F)
- Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infection
- Number of days of hospitalization due to infection
- Number of days of antibiotic use for infection prophylaxis and/or treatment
- Number and duration of infections other than acute serious bacterial infections

5.2 Safety Endpoints

Safety will be evaluated via the following assessments:

- All reported AEs
- Rate (per subject per infusion), severity, and relatedness of AEs
- Frequency of temporally associated AEs
- Infusional AEs
- Assessment of local tolerability to IMP infusions: Reactions at infusion site
- Adverse reactions/suspected adverse reactions
- Vital sign changes, including changes in systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature
- Changes from Screening in physical examination findings
- Changes from Baseline in laboratory parameters (blood chemistry, hematology, urinalysis, hemolysis, d-dimer, protein S, and protein C concentrations, titers of antibodies to ß2GPI and β2GPI-DI)
- Frequency of clinical signs of hemolysis and/or thrombosis within 72 hours after infusion of the IMP
- IGIV-associated hemolysis
- Changes from Screening in viral safety markers (HAV, HBV, HCV, HIV-1, HIV-2, and B19)
- Comparisons of safety variables during treatment with IMP and during the Waiting Period on commercial product will be made as described in Section 12.3.4.

5.3 Pharmacokinetic Endpoints

The PK profile will be analyzed for the following endpoints in subjects participating in the PK sub-study:

- Total IgG levels
- Area under the concentration-time curve over 1 dosing interval (AUC_{0-t})
- Area under the concentration-time curve extrapolated to zero concentration (AUC_{0-inf})
- Peak serum concentration (C_{max})
- Time to reach the peak serum concentration (T_{max})
- The volume of distribution at steady-state (V_{ss})
- Mean residence time (MRT)
- Total body clearance (CL)
- Terminal half-life ($t_{1/2}$)

6 Study Procedures/Evaluations

6.1 Medical History

During Screening, all subjects will provide a relevant medical history including surgeries during the past 2 years, serious bacterial infections documented in the last 5 years, medications taken in the last 4 weeks, and any adverse drug reactions (ADRs) in the past 6 months.

6.2 Subject Diary

To obtain some of the data for evaluation of secondary endpoints, each subject (or parent/guardian, as appropriate) will be asked to fill in a diary throughout the study. The diary will be given to the subject at the baseline visit (Infusion 1 IMP/CP), along with instructions on how to complete it. The subject will be asked to record the following information in the diary from the first study visit until the LTSV:

- Any episode of fever (≥100.4°F) measured at home with a thermometer provided by the study staff
- The number of days out of work/school/kindergarten/day care or unable to perform normal activities due to the underlying PIDD
- Date and duration of any hospitalizations (in case hospitalization is not at the site/location where the subject is being treated in the study)
- Any antibiotic treatments or other medications and the number of separate occasions they are taken during the study period
- Any other changes in medical history

Each time a subject returns to the study site, the Subject Diary will be reviewed for completeness and accuracy. Any discrepancies, especially from the phone call documentation up to 72 hours will be corrected by the subject at each visit, as necessary. Staff will review concomitant medications, AEs, and other safety information contained on the Subject Diary prior to administering CP or IMP. In addition, any other safety information (for example, laboratory results from prior visits) will also be reviewed prior to administration of CP or IMP. The diary will be returned to the subject at each visit with instructions to complete the diary and return with the diary at the next visit. Thermometers will be replaced only if lost or not functioning.

6.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature, will be recorded at Screening; at each infusion visit before, during, and after each infusion (IMP or CP), and at the LTSV.

At each infusion visit, vital signs will be measured at rest at the following time points:

- ≤30 minutes pre-infusion
- 10 minutes (±3 minutes) after the start of the infusion
- 10 minutes (±3 minutes) after each increase of the infusion rate
- 30 minutes post infusion (±5 minutes)
- 60 minutes post infusion (±15 minutes)

At the LTSV, vital signs will be recorded before administration of the subject's standard immunoglobulin treatment, but no post measurement is required.

6.4 Physical Examination

6.4.1 Organ Systems

A physical examination will be performed at each visit and will focus on organs or systems that are known to be the target of complications in PIDD: skin; head, eyes, ear, nose, and throat (HEENT), respiratory, cardiovascular, abdominal, breasts (optional), genitourinary (optional), rectal (optional), musculoskeletal, and neurologic.

6.4.2 Evaluation for Infection

When a subject is suspected of having an acute serious bacterial infection, the subject will be evaluated for the infection according to the *FDA Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency,* as outlined in Section 21.1.

All incidences of acute serious bacterial infection will be recorded in the electronic case report form (eCRF) together with the confirmatory tests for the diagnosis.

6.4.3 Height and Weight

Height will be recorded at Screening, and weight will be recorded at every visit.

6.4.4 Chest X-ray

All subjects will have a chest X-ray performed between the Screening visit and IMP Infusion 1, unless a chest X-ray has been performed within 6 months prior to the first study drug infusion (CP or IMP) and demonstrates a normal result or has shown no indication of active disease process, as determined by the PI/designee.

6.5 Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test will be performed at every visit prior to infusion of IMP/CP.

6.6 Serum IgG Trough Levels

IgG trough levels will be determined from blood samples collected from all subjects at Screening, during the IMP treatment period prior to each infusion of IMP, and at the LTSV before the subject's standard IgG treatment. Subjects on CP Waiting Period need two IgG trough/steady state levels of ≥ 5 mg/ mL documented within 6 months prior to IMP Infusion 1.

6.7 Viral Safety Markers

Viral safety markers (HAV, HBV, HCV, HIV-1, HIV-2, and B19) will be tested as follows:

- Virology samples drawn at the following time points will be tested using NAT (preferably quantitative PCR, if available) and serology assays:
    - Blood samples will be obtained at Screening for determination of the subject's pre-exposure viral status and to exclude subjects with a positive test for any of the following viruses: HIV, HCV, or HBV in accordance with the exclusion criteria.
    - Prior to IMP dosing at IMP Infusion 1 when subject comes off CP Waiting Period
    - Prior to administration of the IMP at Week 12 (Infusion 5 for subjects on the 21-day cycle; Infusion 4 for subjects on the 28-day cycle)
    - Prior to administration of standard IgG at LTSV

- Retention samples for potential later testing will also be drawn prior to administration of the IMP/CP at the following visits:
    - Infusion 1 IMP/CP, Baseline for all subjects
    - LTSV
- Retention samples will be sent to the central laboratory and stored at -20°C or below for future viral testing if needed.
- All viral safety measurements will be performed by the central laboratory.

6.8 General Safety Laboratory Assessments

Samples for general laboratory safety assessments will be collected at the following time points:

- **All subjects** at Screening
- **All subjects** before administration of IMP or CP at infusions 1 (baseline value), 2, 3 and 4 and then before every fourth infusion (8, 12, 16, etc.), TCTV (Treatment Completion/Termination Visit) and at the LTSV
- Post-Infusion **IMP treatment for Groups 1 and 2** during Safety Evaluation Phase
    - 7 days (±1 day) after administration of IMP at infusions 1, 2, and 4 and then after every fourth IMP infusion (8, 12, 16) when IMP treatment ends;
- Post-Infusion **IMP treatment for Group 3**
    - 7 days (±1 day) after administration of IMP at infusions 1 and 4

If it is difficult for subjects (particularly children) to return to the study site for these tests, blood samples may be drawn by a home healthcare nurse.

General safety laboratory assessments include the following tests:

Hematology

CBC, hemoglobin, hematocrit, white blood cell (WBC) count and differential, red blood cell (RBC) count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red cell distribution width [RDW]), and platelets

Blood chemistry

Glucose, total bilirubin, creatinine, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST)

Urinalysis

Protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick; sediment analysis

6.9 Hemolysis

Tests for hemolysis include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test).

Samples for hemolysis assessments will be collected at the following time points:

- **All subjects** at Screening
- **All subjects** before administration of IMP or CP at infusions 1 (baseline value), 2, 3 and 4 and then every fourth infusion (8, 12, 16, etc.), TCTV and at the LTSV
- Post-Infusion **IMP treatment for Groups 1 and 2** during Safety Evaluation Phase
    - 2-3 days after administration of IMP after administration of IMP infusions 1 (baseline value), 2 and 4;
    - 7 days (±1 day) after administration of IMP at infusions 1, 2, and 4 and then after every fourth infusion (8, 12, 16) until IMP treatment ends;
- Post-Infusion **IMP treatment for Group 3**
    - 7 days (±1 day) after administration of IMP at infusions 1 and 4

If it is difficult for subjects (particularly children) to return to the study site for these tests, blood samples may be drawn by a home healthcare nurse.

For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up.

6.10 Immunogenicity Testing

Immunogenicity testing for the detection of antibodies to β2GPI and β2GPI -DI will include the following tests:

- β2GPI Domain 1 QUANTA Flash Kit, INOVA Diagnostics
- β2GPI IgG Ab QUANTA Flash Kit, INOVA Diagnostics
- β2GPI IgM Ab QUANTA Flash Kit, INOVA Diagnostics

Blood samples for detection of antibodies to β2GPI and β2GPI -DI will be drawn at the following time points:

- **All subjects** at Screening
- **All subjects** before administration of IMP or CP at infusions 1 (baseline value), 2, 4, and 8, LTSV before infusion of the subject's standard immunoglobulin treatment

- Retention samples will be drawn at every visit for subjects on **IMP treatment**, from baseline through the LTSV

If any subject after receiving IMP seroconverts from negative to positive, with an elevated antibody titer at least 12 weeks apart, as defined in Section 8.1.1, then all prior retention samples for ß2GPI and/or β2GPI-DI for all subjects should be analyzed.

6.11 3-4 Hour Post-infusion Safety Testing – Indicators of Thrombosis

For **all subjects**, blood samples will be drawn 3-4 hours after the end of IMP/CP infusion at Infusion 1, 2, 4, 8, 12 and 16.

Tests include:

- D-dimers
- Retention sample for protein C and protein S determination, in case d-dimer results indicate potential thrombosis or the PI determines a need for such testing from his evaluation (Note: a retention sample for protein C and protein S will also be taken at Screening to allow for a comparison of the subject's baseline status in the event of a later thrombotic episode or thromboembolic vascular event.)

6.12 Post-infusion Clinical Evaluation for AEs, Hemolysis, and Thrombosis

6.12.1 AEs

All subjects will be observed for 3-4 hours after the first infusion of IMP or CP, and for 1 hour after all further infusions, and AEs will be recorded by observation and report (see Section 10).

6.12.2 One Hour Post Infusion (IMP/CP)

6.12.2.1 Hemolysis Clinical Evaluation

For **all subjects**, at each infusion visit the Investigator will examine the subject within approximately one hour (±15 minutes) after IMP/CP infusion to look for the following clinical signs of hemolysis:

1. Abnormal paleness or lack of color of the skin
2. Jaundice, or yellowing of the skin, eyes, and mouth
3. Fever
4. Weakness
5. Dizziness
6. Confusion

7. Intolerance to physical activity
8. Enlargement of the spleen and liver
9. Increased heart rate (tachycardia)
10. Heart murmur

Positive assessments will lead to a full hemolysis work-up immediately, according to the facility's standard of care.

6.12.2.2 Thrombosis Clinical Evaluation

For **all subjects**, in addition to the assessment of hemolysis described above, the Investigator will also perform an assessment for the following clinical signs of thrombosis within approximately one hour (±15 minutes) after each IMP/CP infusion:

1. Tenderness along line of femoral or popliteal veins (NOT just calf tenderness)
2. Entire limb swollen
3. Pitting edema
4. Lower leg pain
5. Warmth and redness of limb
6. Weakness or decreased sensation of one side of the body
7. Facial droop or decreased sensation
8. Aphasia
9. Dizziness or vertigo
10. Visual loss or blurred vision
11. Sudden severe headache
12. Confusion
13. Chest pain or discomfort
14. Shortness of breath at rest or with exertion
15. Pain in the left arm or jaw
16. Pleuritic chest pain
17. Syncope

Positive assessments will lead to an immediate full thrombosis work-up according to the facility's standard of care. If a thromboembolic event is concerned this will trigger testing of that subject's retention samples for β2GPI and β2GPI-DI.

6.12.3 Phone Calls 24 and 72 Hours after IMP/CP Infusion

For **all subjects**, the study staff will telephone each subject 24 (+6) hours and 72 (+12) hours after each infusion of IMP/CP. Emails or text messages may be used instead as long as every required question is asked and answered.

6.12.3.1 AEs

During the phone calls, the staff will ask open-ended questions about the subject's wellbeing and to ensure that AEs are being documented in the Subject Diary.

The staff will also ask the following specific questions to determine whether a work-up for hemolysis and/or thrombosis is necessary:

6.12.3.2 Hemolysis Clinical Questions

The study staff will review these specific questions with the subject and ensure subject is completing the diary.

1. Have you noticed your urine is darker than usual?
2. Are you feeling dizzy or weak?
3. Are you feeling confused?
4. Does your skin look pale or discolored?
5. Have you had a fever above 100.4°F?

If any of the above questions is answered yes, the study coordinator will report this to the PI or sub-investigator immediately. The PI will decide whether the subject should come in for a full work-up. If so, the site will call the subject in for a full hemolysis work-up as per the facility's standard of care.

6.12.3.3 Thrombosis Clinical Questions

The study staff will review these specific questions with the subject and ensure subject is completing the diary.

1. Do you have pain and/or swelling of an arm or leg with warmth over the affected area?
2. Is there discoloration of an arm or leg?
3. Is there any numbness or weakness on one side of the body?
4. Do you have difficulty speaking?
5. Have you had changes in your vision or new headaches?
6. Are you experiencing dizziness or a feeling that the room is spinning?
7. Are you experiencing unexplained shortness of breath?

8. Do you have chest pain or discomfort that worsens on deep breathing?
9. Do you have unexplained rapid heartbeat?
10. Have you passed out or felt like you might pass out?
11. Are you experiencing any chest pain or discomfort?
12. Do you have pain in your left arm or jaw?
13. Have you experienced nausea and sweating?

If any of the above questions is answered yes, the study coordinator will report this to the PI or sub-investigator immediately. The PI will decide whether the subject should come in for a full work-up. If so, the site will call the subject in for a full thrombosis work-up as per the facility's standard of care. In addition, the Central Laboratory will perform the full thrombosis work-up tests on retention samples (including testing for antibodies to β2GPI and to β2GPI-DI) held for the subject.

6.13 Pharmacokinetic Sub-study

Subjects in Cohorts 1 and 2 who consent to participate in the PK sub-study will have blood samples drawn for PK analysis before and after Infusion 6 (Week 15 ±2 days) for 21-day cycle subjects or Infusion 5 (Week 16 ±2 days) for 28-day cycle subjects at the time points listed in Section 6.13.1 for Cohort 1 and Section 6.13.2 for Cohort 2 below.

Total IgG levels will be measured at all time points for the PK study, in addition to being measured prior to administration of IMP at all visits for all subjects.

All attempts will be made to perform the PK blood draws from Day 7 onwards on the specified day per protocol, but a window of ±1 day will be allowed.

6.13.1 PK Time Points for Cohort 1 (adults):

- Pre-dose at 10 to 30 minutes before IMP Infusion 6 for 21-day cycle subjects or IMP Infusion 5 for 28-day cycle subjects
- 15 minutes (±1 minute) after the end of the infusion
- 1 hour (±5 minutes) after the end of the infusion
- 4 hours (±15 minutes) after the end of the infusion
- 24 hours (±1 hour) after the end of the infusion
- 7 days (±1 day) after the end of the infusion
- 14 days (±1 days) after the end of the infusion
- 21 days (±1 days) after the end of the infusion (immediately before infusion at Infusion 7 for 21-day cycle subjects)

- 28 days (±1 days) after the end of the infusion (immediately before infusion at Infusion 6 for 28-day cycle subjects)

6.13.2 PK Time Points for Cohort 2 (children):

- Pre-dose at 10 to 30 minutes before IMP Infusion 6 for 21-day cycle subjects or IMP Infusion 5 for 28-day cycle subjects
- 15 minutes (±1 minute) after the end of the infusion
- 4 hours (±15 minutes) after the end of the infusion
- 24 hours (±1 hour) after the end of the infusion
- 10 days (±1 day) after the end of the infusion
- 21 days (±1 day) after the end of the infusion (immediately before infusion at Visit 7 for 21-day cycle subjects)
- 28 days (±1 day) after the end of the infusion (immediately before infusion at Visit 6 for 28-day cycle subjects)

7 Study Schedule

7.1 Schedule of Assessments and Study Events

The schedule of assessments and procedures for the Screening visit is included in Table 3 and 4. Table 3 gives assessments and procedures for the Waiting Period on commercial product (CP) before IMP treatment starts. The schedule of assessments and study events for IMP treatment is given in Table 4. Subjects in the Waiting Period on CP will switch to IMP at their first scheduled IMP infusion.

Table 3. Schedule of Assessments and Study Events for Waiting Period on Commercial Product Treatment

	Baseline	Variable Number of CP Infusions Depending on Evaluations in the First 15 Subjects with IMP													
Visit/Infusion [a]	Screen [r]	CP1	CP 2	CP3	CP4	CP5	CP6	CP7	CP8	CP9	CP10	CP11	CP12	CP13	Prior to IMP
Week (21-day cycle)	-3 week	0	3	6	9	12	15	18	21	24	27	30	33	36	
Week (28-day cycle)[a]	-4 week	0	4	8	12	16	20	24	28	32	36	40	44	48	
Pre-infusion:															
Medical history and prior ADRs specific to IgG treatment	X	X													X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of eligibility criteria	X	X													X
Subject diary review		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG trough levels [f]	X														X
Anti-β2GPI and Anti-β2GPI-DI [g]	X	X	X		X				X						X
Viral testing [h]	X														
Retention sample for viral testing (pre-infusion) [i]		X													X
Pre-infusion laboratory safety assessments – general [j]	X	X	X	X	X				X				X		X

	Baseline			Variable Number of CP Infusions Depending on Evaluations in the First 15 Subjects with IMP											
Visit/Infusion [a]	Screen [r]	CP1	CP 2	CP3	CP4	CP5	CP6	CP7	CP8	CP9	CP10	CP11	CP12	CP13	Prior to IMP
Week (21-day cycle)	-3 week	0	3	6	9	12	15	18	21	24	27	30	33	36	
Week (28-day cycle)[a]	-4 week	0	4	8	12	16	20	24	28	32	36	40	44	48	
Pre-infusion hemolysis assessments [q]	X	X	X	X	X				X				X		X
CP infusion [k]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Post-infusion															
Vital signs [b]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical evaluation for hemolysis & thrombosis: 1h after infusion [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	
D-dimer: 3-4h after infusion [m]		X	X		X				X				X		
Retention sample for protein C & protein S: 3-4h after infusion [n]	X	X	X		X				X				X		
Phone calls 24 h & 72 h [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event assessment [o]		X	X	X	X	X	X	X	X	X	X	X	X	X	

ADR = adverse drug reaction; IgG = immunoglobulin G; NAT = nucleic acid test; PCR = polymerase chain reaction.

[a] The number of weeks on CP will depend on the timing of recruitment of the first 15 subjects to receive IMP. If safety review of the first 5 subjects is satisfactory and the staggering interval for the next 10 subjects (Schedule 2) can be reduced, the number of weeks on CP will be shorter than shown here. If recruitment of these subjects does not take place as quickly as planned, the number of weeks on CP may be longer.

[b] Vital signs will be recorded before, during, and after the infusion at time points listed in Section 6.3.

[c] Physical examination will focus on organs and systems known to be the target of complications in PIDD: skin, head, eyes, ear, nose, and throat (HEENT), respiratory, cardiovascular, abdominal, breasts (optional), genitourinary (optional), rectal (optional), musculoskeletal, neurologic (Section 6.4). Serious bacterial infections will be diagnosed as outlined in Section 21.1. Screening visit includes height measurement.

[d] If at any visit after baseline, a subject's body weight has changed by 5% or more from the baseline value, the CP dose will be adjusted according to standards of care.

[e] Female subjects of childbearing potential.

[f] For subjects receiving IGIV at entry, baseline IgG levels are trough levels; for those receiving IGSC at entry, baseline IgG levels are steady state levels. Subjects on CP Waiting Period need two IgG trough/steady state levels of ≥ 5 mg/ mL documented within 6 months prior to IMP Infusion 1.

[g] Antibody titers for anti-β2GPI and anti-β2GPI-DI will be determined at Screening, before the CP infusion 1 as the baseline value, then before CP infusions 2, 4, and 8.

[h] Viral testing includes HAV, HBV, HCV, HIV-1, HIV-2, and B19 using nucleic acid test (NAT) or preferably quantitative PCR, if available, and serology assays.

[i] Viral testing includes HAV, HBV, HCV, HIV-1, HIV-2, and B19 using nucleic acid test (NAT) or preferably quantitative PCR, if available, and serology assays. Performed prior to IMP dosing at IMP Infusion 1 when subject comes off Waiting Period. Retention sample also collected prior to Infusion 1 IMP/CP baseline for all subjects.

[j] Pre-infusion general laboratory safety tests include hematology, blood chemistry, and urinalysis. For subjects in the Waiting Period, testing will be done on samples collected before administration of the first four CP infusions (1, 2, 3, 4) and then before every fourth CP infusion (8, 12, 16, etc.) as long as the subject is in the Waiting Period.

[k] Infusion rate is adjusted according to standard care. CP infusions will continue until the subject's first scheduled IMP infusion can occur.

[l] Approximately 1 hour after each infusion, the Investigator will examine the subject to look for clinical signs of hemolysis and thrombosis (Section 6.12.2). Positive assessments will lead to a full work-up for hemolysis or thrombosis, as appropriate, according to the facility's standard of care.

[m] Approximately 3-4 hours after CP infusions 1, 2, 4, 8, 12, 16 a blood sample will be drawn for measuring d-dimer levels.

[n] Approximately 3-4h after CP infusions 1, 2, 4, 8, 12, 16 a retention sample will be drawn for testing of protein C and protein S in case d-dimer results after the first infusion indicate potential thrombosis or the PI determines a need for protein C and protein S testing based on his evaluation (Section 6.11). A retention sample will be drawn at Screening pre-infusion for later testing of protein C and protein S in case d-dimer results are positive after first infusion of CP.

[o] Subjects are monitored for infusional AEs during CP infusions, for 3-4 hours after the first infusion, and for 1 hour after further infusions. Other AEs are recorded in the subject diaries and collected and reviewed at each visit (Section 10). All subjects are monitored for temporally associated AEs in the 24-hour and 72-hour phone calls from staff to the subject.

[p] The study staff will call subjects 24 hours (+6 hours) and 72 hours (+12) after each infusion to evaluate the potential for hemolysis, thrombosis, and any other AEs. Positive answer on any of the five hemolysis questions or on any of the thrombosis questions will be reported to the PI for a decision as to whether a full work-up is necessary (Section 6.12.3).

[q] Pre-infusion hemolysis laboratory tests will include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test). Pre-infusion hemolysis testing will be done for all subjects before administration of CP at infusions 1 (baseline value), 2, 3, 4 and then every fourth infusion (8, 12, 16, etc.). For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).

[r] Screening visit will include demographics. Subjects treated with commercial IGIV or IGSC may receive their current treatment infusion either before the screening visit or at the screening visit if screening laboratory samples are taken prior to the infusion. Subjects receiving IGSC when they enter the study will have their screening visit up to 17 days prior to the Baseline Visit.

Table 4. Schedule of Assessments and Study Events for IMP Treatment

	Baseline	Treatment with IMP																TC[a]	LTSV [bb]
Visit/Infusion	Screen Visit [aa]	IMP 1[e]	IMP 2	IMP 3	IMP 4	IMP 5	IMP 6	IMP 7	IMP 8	IMP 9	IMP 10	IMP 11	IMP 12	IMP 13[b]	IMP 14[b]	IMP 15[b]	IMP 16[b]	IMP 17[c]	Standard 18[d]
Week (21-day cycle)	-3 weeks	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Visit/Infusion	Screen Visit [aa]	IMP 1[e]	IMP 2	IMP 3	IMP 4	IMP 5	IMP 6	IMP 7	IMP 8	IMP 9	IMP 10	IMP 11	IMP 12	-	-	-	-	IMP 13[c]	Standard 14[d]
Week (28-day Cycle)	-4 weeks	0	4	8	12	16	20	24	28	32	36	40	44	-	-	-	-	48	52
Pre-infusion																			
Medical History and prior ADRs to IgG	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review eligibility criteria	X	X																	
Subject diary review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG trough levels [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-β2GPI and Anti-β2GPI-DI [k]	X	X	X		X				X										X
Retention sample for immunogenicity [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Baseline	Treatment with IMP																TC[a]	LTSV [bb]
Visit/Infusion	Screen Visit [aa]	IMP 1[e]	IMP 2	IMP 3	IMP 4	IMP 5	IMP 6	IMP 7	IMP 8	IMP 9	IMP 10	IMP 11	IMP 12	IMP 13[b]	IMP 14[b]	IMP 15[b]	IMP 16[b]	IMP 17[c]	Standard 18[d]
Week (21-day cycle)	-3 weeks	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Visit/Infusion	Screen Visit [aa]	IMP 1[e]	IMP 2	IMP 3	IMP 4	IMP 5	IMP 6	IMP 7	IMP 8	IMP 9	IMP 10	IMP 11	IMP 12	-	-	-	-	IMP 13[c]	Standard 14[d]
Week (28-day Cycle)	-4 weeks	0	4	8	12	16	20	24	28	32	36	40	44	-	-	-	-	48	52
Viral testing [m,e]	X	X [e]			X [m]	X [m]													X
Retention sample for viral testing [e]		X																	X
Pre-infusion laboratory safety assessments [n]	X	X	X	X	X				X				X				X	X	X
Pre-infusion hemolysis assessments [y,z]	X	X	X	X	X				X				X				X	X	X
IMP infusion [o]		X[o]	X[o]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	
Post-infusion																			
Vital signs [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [f]
Clinical evaluation for hemolysis & thrombosis: 1 h post infusion [q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
D-dimer: 3-4 h post-infusion [r]		X [r]	X		X				X				X				X		
Retention sample for protein C & protein S: 3-4 h post-infusion [r]	X	X [r]	X		X				X				X				X		
Phone calls 24 h & 72 h [t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Baseline	Treatment with IMP																TC[a]	LTSV [bb]
Visit/Infusion	Screen Visit [aa]	IMP 1[e]	IMP 2	IMP 3	IMP 4	IMP 5	IMP 6	IMP 7	IMP 8	IMP 9	IMP 10	IMP 11	IMP 12	IMP 13[b]	IMP 14[b]	IMP 15[b]	IMP 16[b]	IMP 17[c]	Standard 18[d]
Week (21-day cycle)	-3 weeks	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Visit/Infusion	Screen Visit [aa]	IMP 1[e]	IMP 2	IMP 3	IMP 4	IMP 5	IMP 6	IMP 7	IMP 8	IMP 9	IMP 10	IMP 11	IMP 12	-	-	-	-	IMP 13[c]	Standard 14[d]
Week (28-day Cycle)	-4 weeks	0	4	8	12	16	20	24	28	32	36	40	44	-	-	-	-	48	52
7-day post-infusion lab safety assessments – general [u]		X	X		X				X				X				X		
2-3 day and 7-day post-infusion lab safety assessments–hemolysis [v]		X	X		X				X [v]				X [v]				X [v]		
PK sub-study						X [w]	X [w]												
Adverse event assessment [x]		X [x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADR = adverse drug reaction; IgG = immunoglobulin G; LTSV = long-term safety visit; LTSF = long-term safety follow-up; NAT = nucleic acid test; PCR = polymerase chain reaction; PK = pharmacokinetics; TC = treatment completion or termination visit.

[a] For subjects who terminate the study before the planned treatment completion visit, all procedures should be performed at the final scheduled visit. If a subject is terminating early and will be unable to return for the LTSV visit, additional procedures for LTSV (safety laboratory test, viral testing, and retention sample) must also be performed at the final visit.

[b] 21-day cycle only

[c] Subjects on the 21-day cycle will receive 17 infusions of the IMP, and subjects on the 28-day cycle will receive 13 infusions of the IMP in one year.

[d] Subjects resume standard IgG treatment.

[e] Viral testing includes HAV, HBV, HCV, HIV-1, HIV-2, and B19 using nucleic acid test (NAT) or preferably quantitative PCR, if available, and serology assays. Subjects coming off of Waiting Period must have viral testing prior to IMP Infusion 1.

[f] Vital signs will be recorded before, during, and after the IMP infusion at time points listed in Section 6.3. At the LTSV, vital signs will be recorded before administration of the subject's standard immunoglobulin treatment, but no post-infusion measurement is required.

[g] Physical examination will focus on organs and systems known to be the target of complications in PIDD: skin; head, eyes, ear, nose, and throat (HEENT); respiratory, cardiovascular, abdominal, breasts (optional), genitourinary (optional), rectal (optional), musculoskeletal, neurologic (Section 6.4). Serious bacterial infections will be diagnosed as outlined in Section 21.1. A chest X-ray will be performed between the Screening visit and the IMP Infusion 1, unless a chest X-ray has been performed within 6 months prior to the first study infusion (CP or IMP) and demonstrates a normal result. Screening visit includes height measurement.

[h] If at any visit after baseline, a subject's body weight has changed by 5% or more from the baseline value, the IMP dose will be adjusted accordingly (Section 13.6.1).

[i] Female subjects of childbearing potential.

[j] For subjects receiving IGIV at study entry, IgG levels are trough levels; for those receiving IGSC at study entry, baseline IgG levels are steady state levels. Subjects (including those coming off of the CP Waiting Period) need two IgG trough/steady state levels of ≥ 5 mg/ mL documented within 6 months prior to IMP Infusion 1.

[k] Antibody titers for anti-β2GPI and anti-β2GPI-DI, will be done at Screening, before IMP infusion 1 as the baseline value, then before infusions 2, 4, and 8, and at the LTSV.

[l] Retention samples for anti-β2GPI and anti-β2GPI-DI antibodies will be taken at every infusion visit.

[m] Interim viral testing will be performed at Week 12 (IMP Infusion 5 for subjects on the 21-day cycle; IMP Infusion 4 for subjects on the 28-day cycle). Retention sample also collected prior to Infusion 1 IMP/CP baseline for all subjects. Final viral testing will be performed at the LTSV (Section 6.7).

[n] Pre-infusion general laboratory safety tests include general safety (hematology, blood chemistry, and urinalysis) (Section 6.8).

[o] Infusion rate is adjusted every 30 minutes based on tolerability as described in Section 13.6.2.1.

[p] Infusion rate is adjusted every 15 minutes based on tolerability as described in Section 13.6.2.2.

[q] Approximately 1 hour after each infusion, the Investigator will examine the subject to look for clinical signs of hemolysis and thrombosis (Section 6.12.2). Positive assessments will lead to a full work-up for hemolysis (Section 6.12) or thrombosis, as appropriate, according to the facility's standard of care.

[r] Approximately 3-4 hours after the first IMP infusion (IMP baseline), a blood sample will be drawn for measuring d-dimer levels, and a retention sample will also be drawn for testing of protein C and protein S in case d-dimer results indicate potential thrombosis or the PI determines a need for protein C and protein S testing based on his evaluation (Section 6.11). A retention sample will be drawn at Screening pre-infusion for later testing of protein C and protein S in case d-dimer results are positive after the first infusion of IMP.

[t] The study staff will call subjects 24 hours (+6 hours) and 72 hours (+12 hours) after each infusion to evaluate the potential for hemolysis, thrombosis, and any other AEs. Positive answer on any of the five hemolysis questions or on any of the thrombosis questions will be reported to the PI for a decision as to whether a full work-up is necessary (Section 6.12.3).

[u] Post-infusion general laboratory safety tests will include hematology, blood chemistry, and urinalysis (Section 6.8). For Groups 1 and 2, post-infusion general safety laboratory testing will be done while receiving IMP, 7 days (±1 day) after IMP Infusions 1, 2, and 4, and then 7 days (±1 day) after every fourth infusion (8, 12, 16). For Group 3, post-infusion general safety laboratory testing will be done while receiving IMP, 7 days (±1 day) after IMP Infusions 1 and 4.

[v] Post-infusion hemolysis laboratory tests will include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9). For Groups 1 and 2, post-infusion hemolysis testing will be done while receiving IMP, 2-3 days and again 7 days (±1 day) after IMP Infusions 1, 2, and 4, and then 7 days (±1 day) after every fourth infusion (8, 12, 16). For Group 3, post-infusion hemolysis testing will be done while receiving IMP, 7 days (±1 day) after IMP Infusions 1 and 4.

[w] Subjects who participate in the PK sub-study will have blood samples drawn before and after IMP Infusion 6 (21-day cycle subjects) or IMP Infusion 5 (28-day cycle subjects) at time points listed in Section 6.13.

[x] Subjects are monitored for infusional AEs during the IMP infusions, for 3-4 hours after the first infusion, and for 1 hour after further infusions. Other AEs are recorded in the subject diaries and collected and reviewed at each visit (Section 10). All subjects are monitored for temporally associated AEs in the 24-hour and 72-hour phone calls from staff to the subject as described above.

[y] Pre-infusion hemolysis laboratory tests will include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9). Pre-infusion hemolysis testing will be done for all subjects before administration of IMP at infusions 1 (baseline value), 2, 3, 4 and every fourth infusion (8, 12, 16), TCTV and at the LTSV. For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9)

[z] All subject groups will have pre-infusion hemolysis testing prior to IMP/CP infusion 1. For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9)

[aa] Screening visit will include demographics. Subjects treated with commercial IGIV or IGSC may receive their current treatment infusion either before the screening visit or at the screening visit if screening laboratory samples are taken prior to the infusion. Subjects receiving IGSC when they enter the study will have their screening visit up to 17 days prior to the Baseline Visit.

[bb] For subjects who discontinue IMP due to events (hemolysis, thrombosis, anti-β2GPI immunogenicity), and for all subjects if study is stopped, follow-up LTSF will continue for additional cycles (Section 7.11). For subjects who discontinue IMP due to anti-β2GPI immunogenicity, subject will continue to be followed up and have the LTSF performed until immunogenicity titers are stabilized (or dropping) over 3 consecutive treatment cycles (21-day cycle/ 28-day cycle). (Section 7.11)

7.2 Pre-screening

To identify subjects who meet the eligibility criteria, Investigators will review their patient files according to their own center's procedures for pre-screening, ensuring that they comply with national regulations (in the United States, Health Insurance Portability and Accountability Act [HIPAA]). De-identified data will be recorded on a pre-screening log (Section 8.4). Prior to Screening, sites will prescreen subjects for general eligibility and seek approval from the CRO to screen. Enrollment will be competitive. Because there are required numbers of subjects in the different groups (scheduling groups, adults, children, PK, non-PK), subjects **must** receive approval from the CRO to ensure that there are adequate numbers of subjects in each group and that over-enrollment does not occur.

7.3 Screening Visit

Once approval for screening has been granted, the Screening Visit will be conducted 21 days (±2 days) before the Baseline Visit (Infusion 1 IMP, or CP for Subjects in Waiting Period) for subjects on a 21-day cycle, 28 days (±2 days) before Baseline for subjects on a 28-day cycle, or up to 17 days before the Baseline Visit for subjects receiving IGSC when they enter the study.

Informed Consent or Assent

Before any study procedures are performed, informed consent will be obtained from eligible subjects and parent(s) or legal guardians, and if applicable, assent will be obtained from subjects younger than 18 years, according to the procedures outlined in Section 16.3.

Once informed consent and/or assent has been obtained, subjects will undergo a screening visit to ascertain their eligibility. All subjects will be offered participation in the PK sub-study until the planned number of subjects is reached.

Demographic Information

Demographic information will be collected to include the subject's date of birth, race, ethnicity, and sex.

Complete Medical History

Subjects will give a relevant medical history including surgeries during the past two years and serious bacterial infections documented in the last 5 years.

Prior and Current Medications

<u>Prior and Current Immunoglobulin Treatment</u>

Documentation of prior use of immunoglobulin treatment (IGIV or IGSC), including the regimen cycle and rate/dose, will be reviewed so that selection criteria are met (Section 4.3.1). To be eligible for enrollment, subjects must have been treated with a

stable dose of commercially licensed immune globulin, administered intravenously (IGIV), for at least 3 consecutive treatments at 21 or 28 day intervals with at least 2 documented trough levels, or administered subcutaneously (IGSC) for at least 12 weeks with at least 2 documented steady state levels, as defined in the inclusion criteria (Section 4.3.1). In addition, subjects must have had at least two documented IgG trough or steady state levels of ≥5 mg/mL measured in the 6 months prior to IMP treatment.

Subjects who switch from an investigational immune globulin or IGSC are not part of the randomization scheme and will be automatically assigned to Group 3. These subjects are required to receive a stable dose of a commercial IGIV product for at least 3 cycles during the Waiting Period before they can be given the IMP. In addition, subjects must have had at least two documented IgG trough or steady state levels of ≥ 5 mg/mL measured in the 6 months prior to IMP treatment.

For subjects who are receiving IGIV, the current IGIV dose will be documented for use in calculating the starting dose for the baseline infusion, and for those who are receiving IGSC, the current IGSC dose will be documented for use in calculating the starting IGIV dose for the baseline infusion (see Section 13.6.1). As required by inclusion criteria (Section 4.3.1), at least one IGIV infusion in the past without an associated serious adverse event must be documented for such subjects.

Prior Adverse Drug Reactions to Immunoglobulin Treatment

If available in the documentation, data will be captured of known Adverse Drug Reactions the subjects previously exhibited when being treated with immunoglobulins (IV or SC). The subject will be queried about adverse reactions in the last 6 months.

Miscellaneous Medications

Information on prior and current medication will be collected including non-prescription, prescription, herbal medications, and transfusions. All routes, doses, schedules, infusions rates, and indications will be recorded as appropriate. Data will be collected for the past 4 weeks before the screening visit.

As the use of pre-medication for pain relief and/or diphenhydramine prior to an IMP infusion is only permitted if the subject is using these pre-medications as part of routine IGIV or IGSC treatment.

Vital Signs

Vital signs will be collected to include body temperature, blood pressure, respiratory rate, and heart rate prior to infusion.

Physical Examination

The physical examination will focus on organs or systems are known to be the target of complications in PIDD as described in Section 6.4.

Height and weight will be recorded.

Laboratory Assessments

As noted below, subjects are allowed to receive their last IGIV or IGSC dose(s) at the screening visit as long as screening laboratory samples are taken prior to the infusion. Specimens for the following laboratory analyses will be obtained to ascertain whether the subject meets eligibility criteria.

- Urine pregnancy test, if applicable (Section 6.5)
- Serum IgG trough level (Section 6.6)
- Viral testing (Section 6.7)
- Safety assessments, including general safety (hematology, blood chemistry, and urinalysis) (Section 6.8)
- Laboratory hemolysis testing, including urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9)
- Retention sample for protein C and protein S to allow for a comparison of the subject's baseline status in the event of a later thrombotic episode or thromboembolic vascular event (Section 6.11)
- Immunogenicity sample (Section 6.10), testing for antibodies to β2GPI and β2GPI-DI.
- Chest X-ray will be performed between the Screening visit and IMP Infusion 1, unless a chest X-ray has been performed within 6 months prior to the first study infusion (CP or IMP) and demonstrates a normal result or has shown no indication of active disease process, as determined by the PI/designee.

Review of Eligibility Criteria and Randomization

The medical history, prior medication, physical exam, and other collected tests/data and safety parameters will be reviewed to ascertain whether the subject meets all inclusion criteria and does not meet any of the exclusion criteria. The Investigator will ascertain whether the subject is eligible to participate and will follow the protocol throughout the subject's participation in the study.

Randomization codes for the three scheduling groups described in Section 3.1 will be assigned as subjects become eligible for randomization. If a subject withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused.

Children, subjects treated with IGSC, and subjects on another investigational product at enrollment will not be part of the randomization scheme and will be assigned to Group 3.

All subjects enrolled after Groups 1 and 2 have been closed will also be assigned to Group 3.

The Sponsor will produce the randomization code and scheme. Once the subject has been assessed for all inclusion/exclusion criteria and deemed eligible for the study, the study coordinator will log into an interactive response technology (IRT), such as interactive web response system (IWRS), and enter the subject ID. The IRT/IWRS will randomize the subject and assign the randomization number and enrollment group, which will include the group number at the end of the Subject Identification Number.

Infusion of Current Immunoglobulin Product (if needed)

Subjects treated with commercial IGIV or IGSC may receive their current treatment infusion either before the screening visit or within 1 day after all screening-related laboratory assessments are completed. The first study infusion visit (whether the start of ProMetic IMP or continuation of CP during the Waiting Period) will be scheduled according to the subject's usual treatment cycle. (Subjects on another IGIV or IGSC investigational product at study entry may receive the last administration of that product at screening. They will not be part of the randomization scheme and will be assigned to Group 3 and switched to commercially licensed IGIV selected by the Investigator in consultation with their treating physician. They will continue CP for the duration of the Waiting Period and at a minimum of 3 months in order to satisfy requirement for 3 months on a stable dose of commercial product prior to first IMP infusion.)

Safety Evaluation Phase (Groups 1 and 2)

The safety evaluation phase includes an evaluation of Group 1 and then Group 2. Interim safety testing will be performed prior to the second infusion (at Week 4 in subjects on 28 day cycle, and Week 3 in subjects on 21 day cycle) in five subjects starting IMP treatment at staggered 2-week intervals (Group 1). The results from these 5 subjects are evaluated by the Investigators and the DSMB and submitted to the FDA for review. These subjects will continue on IMP while awaiting review, but no further subjects will be started on IMP. Contingent on FDA and DSMB approval after review of the interim safety results in Group 1, 10 further subjects (Group 2) will receive the first IMP infusion staggered at an interval to be determined by the FDA. The safety evaluation phase continues for Group 2 with interim safety testing as done in Group 1, and the results from these next 10 subjects are evaluated by the Investigators and the DSMB and submitted to the FDA for review. Contingent on FDA and DSMB approval after review of the interim safety testing in Group 2, IMP infusions for the next 60 subjects, including 35 adults (Cohort 1) 25 children (Cohort 2) will start. The starting date of the first IMP infusion in this last group will not be staggered.

7.4 Baseline and IMP/CP Infusion 1

For subjects on a 21-day cycle, this visit will occur 21 days (±2 days) after the Screening Visit. For subjects on a 28-day cycle, this visit will occur 28 days (±2 days) after the Screening Visit. For IGSC subjects this visit must occur within up to 17 days after the Screening Visit.

Medical History and Medication Review

A review of medical history and current medication will be performed to assess for any changes or missing information. For subjects entering the study, laboratory results from Screening will be reviewed to assess safety and to ascertain baseline levels. For subjects starting IMP after the Waiting Period on CP, events and laboratory results from the CP period will be reviewed.

Adverse Event Assessment

Any and all adverse events will be captured starting from the Screening Visit.

Review of Eligibility Criteria

For subjects entering the study, the eligibility criteria, including results of screening laboratory tests, will be reviewed and updated, and eligibility will be assessed and verified. For subjects starting IMP after the Waiting Period on CP, any changes in eligibility will be evaluated. Subject will again be queried about any adverse drug reactions prior to treatment with immunoglobulins.

Subject Diary Distribution and Completion Instructions

The Subject Diaries and thermometers will be distributed, along with instructions for recording the data, as described in Section 6.2. Staff will review concomitant medications, AEs, and other safety information contained on the Subject Diary at each visit prior to administering CP or IMP for all subjects.

Pre-infusion Vital Signs

Vital signs will be collected within 30 minutes prior to Infusion 1 (IMP or CP) to include body temperature, blood pressure, respiratory rate, and heart rate (Section 6.3).

Physical Examination

The physical examination will focus on organs or systems that are known to be the target of complications in PIDD and the subject will be evaluated for infection as described in Section 6.4.

The subject's weight will be measured as a basis for calculating the IMP or CP dose (Section 13.6.1).

Chest X-Ray

A chest X-ray will be performed between the Screening visit and IMP Infusion 1, unless a chest X-ray has been performed within 6 months prior to the first study infusion (CP or IMP) and demonstrates a normal result or has shown no indication of active disease process, as determined by the PI/designee.

Pre-Infusion Laboratory Assessments

Blood samples for the following laboratory tests will be obtained prior to administration of the IMP/CP:

- Urine pregnancy test, if applicable (Section 6.5)
- Serum IgG trough level prior to Infusion of IMP (Section 6.6)
- Antibodies to β2GPI and β2GPI-DI (Section 6.10)
- Retention sample for potential future immunogenicity testing (Section 6.10), only for subjects receiving IMP infusions
- Viral testing (Section 6.7) for subjects coming off of CP Waiting Period
- Retention blood sample for potential future virology testing (Section 6.7)
- Safety assessments, including general safety (hematology, blood chemistry, and urinalysis) (Section 6.8)
- Hemolysis assessment, including urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9).
- For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).

Infusion of IMP or CP

The dose and volume of the IMP to be administered to each subject will be calculated based on the subject's weight (Section 13.6.1). The IMP should be prepared and administered according to the instructions in Sections 13.5 and 13.6.2.

The dose and administration of CP will be determined by the Investigator in consultation with their treating physician, as in the subject's usual care.

Vital Signs, Post-infusion

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded at the time intervals outlined in Section 6.3.

Post-infusion Clinical Evaluation for AEs, Hemolysis, and Thrombosis (All Groups)

- Subjects will be observed for AEs directly during the first IMP/CP infusion and for 3-4 hours after the infusion, and AEs will be recorded by observation and report (see Section 10.1 for definitions of infusional and temporally associated AEs and Section 10.3 for instructions on eliciting and reporting AEs).
- The Investigator will examine the subject approximately 1 hour (±15 minutes) after the first IMP/CP infusion to look for clinical signs of hemolysis and thrombosis as described in Section 6.12.2.
- Study staff will call the subjects 24 (+6) hours and 72 (+12) hours after the first IMP/CP infusion to ask open-ended questions about their wellbeing and to ensure that any AEs are being documented in the Subject Diary.
- During the 24- and 72-hour phone calls after the first IMP/CP infusion, study staff will also ask questions as described in Section 6.12.3 to determine whether a work-up for hemolysis and/or thrombosis is necessary

3-4 Hour Post-infusion Laboratory Thrombosis Indicators (All Groups)

Samples for the following tests will be drawn 3-4 hours after the end of infusion (Section 6.11):

- D-dimer
- Retention sample for protein C and protein S determination, in case d-dimer results indicate potential thrombosis or the PI determines a need for such testing

2- to 3-Day Post-infusion Hemolysis Testing (Groups 1 and 2 while on IMP)

Post-infusion hemolysis laboratory tests will include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9). This 2-3 day post infusion testing will only be done for Group 1 and 2 subjects receiving IMP.

7-Day (±1 day) General Laboratory Safety Testing (Groups 1, 2, and 3 while on IMP)

Post-infusion general laboratory safety tests including hematology, blood chemistry, and urinalysis (Section 6.8), and hemolysis laboratory tests (Section 6.9), will be done 7 days (±1 day) after the IMP infusions for Groups 1, 2, and 3. If it is difficult for subjects (particularly children) to return to the study site for these tests, blood samples can be drawn by a home healthcare nurse.

7.5 IMP/CP Infusions 2, 4, and 8

Subjects on a 21-day cycle may have infusions scheduled within ± 2 days of the 21-day cycle infusion time points throughout the study.

Subjects on a 28-day cycle may have infusions scheduled within ± 2 days of the 28-day cycle infusion time points throughout the study

Adverse Event Assessment and Concomitant Medication Review

A review of adverse events, laboratory results and current medication will be performed.

Subject Diary Review

The Subject Diary will be reviewed as described in Section 6.2.

Vital Signs Pre-Infusion

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded before the IMP infusion at the time intervals outlined in Section 6.3.

Physical Examination

The physical examination will focus on organs or systems that are known to be the target of complications in PIDD and the subject will be evaluated for infection as described in Section 6.4.

The subject's weight will be measured, and if the subject has gained or lost ≥5% body weight since baseline, the amount of IMP for infusion must be adjusted accordingly.

Pre-Infusion (IMP/CP) Laboratory Assessments

The following laboratory samples will be obtained prior to administration of IMP/CP:

- Urine pregnancy test, if applicable (Section 6.5)
- Serum IgG trough levels will be measured prior to each Infusion of IMP (Section 6.6)
- Safety assessments, including general safety (hematology, blood chemistry, and urinalysis) (Section 6.8)
- Antibodies to β2GPI and β2GPI-DI (Section 6.10)
- Retention sample for potential future immunogenicity testing (Section 6.10), only for subjects receiving IMP infusions
- Hemolysis assessment, including urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9).
- For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).

Infusion (IMP or CP)

The dose and volume of the IMP to be administered to each subject will be calculated based on the subject's weight (Section 13.6.1). The IMP should be prepared and administered according to the instructions in Sections 13.5 and 13.6.2.

The dose and administration of CP will be based on the subject's usual treatment and determined by the Investigator in consultation with the treating physician.

Post-infusion Vital Signs

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded after the infusion at the time intervals outlined in Section 6.3.

Post-infusion Clinical Evaluation for AEs, Hemolysis, and Thrombosis (All Groups)

- Subjects will be observed for AEs during the IMP/CP infusions and for approximately 1 hour (±15 minutes) after the infusion, and AEs will be recorded by observation and report (see Section 10.1 for definitions of infusional and temporally associated AEs and Section 10.3 for instructions on eliciting and reporting AEs).
- The Investigator will examine the subject approximately 1 hour (±15 minutes) after the IMP/CP infusions to look for clinical signs of hemolysis and thrombosis as described in Section 6.12.2.
- Study staff will call the subjects 24 (+6) hours and 72 (+12) hours after IMP/CP infusions to ask open-ended questions about their wellbeing and to ensure that any AEs are being documented in the Subject Diary.
- During the 24- and 72-hour phone calls after IMP/CP infusions, study staff will also ask questions as described in Section 6.12.3 to determine whether a work-up for hemolysis and/or thrombosis is necessary and/or testing of any retention samples for immunogenicity are required.
- All other AEs should be recorded in the subject diaries and collected and reviewed, along with any concomitant medications, at each visit (Section 10)

3-4 Hour Post-infusion Laboratory Thrombosis Indicators (All Groups)

Samples for the following tests will be drawn 3-4 hours after the end of infusion (Section 6.11):

- D-dimer
- Retention sample for protein C and protein S determination, in case d-dimer results indicate potential thrombosis or the PI determines a need for such testing

2- to 3-Day Post-infusion Hemolysis Testing (Groups 1 and 2 while on IMP)

Post-infusion hemolysis laboratory tests will include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9). This 2-3 day post infusion testing will only be done for Group 1 and 2 subjects after receiving IMP Infusions 2 and 4.

7-Day (±1 day) General Laboratory Safety and Hemolysis Testing (Groups 1, 2, and 3 while on IMP)

Post-infusion general laboratory safety tests including hematology, blood chemistry, urinalysis (Section 6.8), and hemolysis laboratory tests (Section 6.9) will be done 7 days (±1 day) after IMP infusions 2, 4, and 8 for Groups 1 and 2 and after IMP infusion 4 for Group 3 while receiving IMP.

If it is difficult for subjects (particularly children) to return to the study site for these tests, blood samples can be drawn by a home healthcare nurse.

7.6 IMP/CP Interim Infusion Visits

Subjects on a 21-day cycle may have infusions scheduled within ± 2 days of the 21-day cycle infusion time points throughout the study.

Subjects on a 28-day cycle may have infusions scheduled within ± 2 days of the 28-day cycle infusion time points throughout the study

Adverse Event Assessment and Concomitant Medication Review

A review of adverse events, laboratory results and current medication will be performed.

Subject Diary Review (Interim Infusion Visits)

The Subject Diary will be reviewed as described in Section 6.2.

Vital Signs Pre-Infusion (Interim Infusion Visits)

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded before the IMP infusion at the time intervals outlined in Section 6.3.

Physical Examination (Interim Infusion Visits)

The physical examination will focus on organs or systems that are known to be the target of complications in PIDD and the subject will be evaluated for infection as described in Section 6.4.

The subject's weight will be measured, and if the subject has gained or lost ≥5% body weight since baseline, the amount of IMP for infusion must be adjusted accordingly.

Pre-Infusion Laboratory Assessments (Interim Infusion Visits)

The following laboratory samples will be obtained prior to administration of IMP/CP Infusion:

- Urine pregnancy test, if applicable, prior to each Infusion of **IMP/CP** (Section 6.5)
- Serum IgG trough will be measured prior to each Infusion of **IMP** (Section 6.6)
- Retention sample for potential future immunogenicity testing (Section 6.10), only for subjects receiving **IMP** infusions

- Safety assessments, including general safety (hematology, blood chemistry, and urinalysis) (Section 6.8) at **IMP/CP** Infusions 3, 12, and 16
- Hemolysis assessment, including urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9) at **IMP/CP** Infusions 3, 12, and 16.
- For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).

Infusions (Interim Infusion Visits)

The dose and volume of the IMP to be administered to each subject will be calculated based on the subject's weight. The IMP should be prepared and administered according to the instructions in Sections 13.5 and 13.6.

The dose and administration of CP will be determined by the Investigator in consultation with the treating physician, as in the subject's usual care.

Post-infusion Vital Signs (Interim Infusion Visits)

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded after the infusion at the time intervals outlined in Section 6.3.

Post-infusion Clinical Evaluation for AEs, Hemolysis, and Thrombosis (Interim Infusion Visits)

- Subjects will be observed directly during each infusion and for 1 hour (±15 minutes) after each infusion, and AEs will be recorded by observation and report (see Section 10.1 for definitions of infusion and temporally associated AEs and Section 10.3 for instructions on eliciting and reporting AEs).
- The Investigator will examine the subject approximately 1 hour (±15 minutes) after each infusion to look for clinical signs of hemolysis and thrombosis as described in Section 6.12.2.
- Study staff will call the subjects 24 (+6) hours and 72 (+12) hours after each IMP/CP infusion to ask open-ended questions about their wellbeing and to ensure that any AEs are being documented in the Subject Diary.
- During the 24- and 72-hour phone calls after each IMP/CP infusion, study staff will also ask questions as described in Section 6.12.3 to determine whether a work-up for hemolysis and/or thrombosis is necessary and/or testing of any retention samples for immunogenicity are required.
- All other AEs should be recorded in the subject diaries and collected and reviewed, along with any concomitant medications, at each visit (Section 10).

3-4 Hour Post-infusion Laboratory Thrombosis Indicators (All Groups)

Samples for the following tests will be drawn 3-4 hours after the end of infusion (Section 6.11) at **IMP/CP infusions 12 and 16 (all subjects)**:

- D-dimer
- Retention sample for protein C and protein S determination, in case d-dimer results indicate potential thrombosis or the PI determines a need for such testing

7-Day (±1 day) General Laboratory Safety and Hemolysis Testing (Groups 1 and 2 while on IMP)

Post-infusion general laboratory safety tests including hematology, blood chemistry, urinalysis (Section 6.8), and hemolysis laboratory tests (Section 6.9) will be done 7 days (±1 day) after **IMP infusions 12 and 16 for Groups 1 and 2** while receiving IMP.

If it is difficult for subjects (particularly children) to return to the study site for these tests, blood samples can be drawn by a home healthcare nurse.

7.7 Viral testing (IMP Infusion 5 for 21-day cycle / IMP Infusion 4 for 28-day cycle)

Viral safety markers (HAV, HBV, HCV, HIV-1, HIV-2, and B19) laboratory test sample will be obtained prior to administration of the IMP at **Week 12** (Infusion 5 for subjects on the 21-day cycle; Infusion 4 for subjects on the 28-day cycle) as described in Section 6.7.

7.8 Pharmacokinetic Sub-study (IMP Infusion 6 for 21-day cycle / IMP Infusion 5 for 28-day cycle)

Subjects who participate in the PK sub-study will have PK blood samples drawn for Infusion 6 (Week 15 ±2 days) for 21-day cycle subjects or Infusion 5 (Week 16 ±2 days) for 28-day cycle subjects as described in Section 6.13.

D-dimer and retention samples for protein C & S are drawn at time-points outlined in Section 6.11 and Tables 3 and 4.

7.9 Treatment Completion/Termination Visit (TCTV): IMP Infusion 17 (21-day cycle) or IMP Infusion 13 (28-day cycle)

All study procedures at the TCTV are the same as those performed at Infusion 3, Interim Visit (Section 7.6).

If treatment is terminated before the TCTV (Infusion 17 for the 21-day cycle, Infusion 13 for the 28-day cycle), then all procedures for the TCTV should be performed at the final scheduled visit.

In addition, if the subject is terminating the study early and is unable to return for the LTSV, the procedures required for the LTSV, including safety laboratory assessments

(hematology, chemistry, and urinalysis) and virology testing, with a retention sample, should also be completed at this visit.

7.10 Long-Term-Safety-Visit (LTSV): Week 51 (21-day cycle) or Week 52 (28-day cycle)

Subjects on the 21-day cycle will return for the LTSV 21 days (±2 days) after their last infusion of IMP, and subjects on the 28-day cycle will return for the LTSV 28 days (±2 days) after their last infusion of IMP. The LTSV will be conducted prior to the administration of the subject's standard IgG treatment. The visit will consist of the following:

Adverse Event Assessment and Concomitant Medication Review

A review of adverse events, laboratory results and current medication will be performed. Current IgG treatment will be included under concomitant medication.

Subject Diary Review

The Subject Diary will be reviewed and collected as described in Section 6.2.

Vital Signs Pre-Infusion

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded before the IMP infusion at the time intervals outlined in Section 6.3.

Physical Examination

The physical examination will focus on organs or systems that are known to be the target of complications in PIDD and the subject will be evaluated for infection as described in Section 6.4.

The subject's weight will be measured, and if the subject has gained or lost ≥5% body weight since baseline, the amount of IgG for infusion must be adjusted accordingly per standard care.

Pre-Infusion Laboratory Assessments

The following laboratory samples will be obtained prior to administration of IMP/CP:

- Urine pregnancy test, if applicable (Section 6.5)
- Serum IgG trough levels will be measured prior to each Infusion of IMP (Section 6.6)
- Virology testing (Section 6.7), with a retention sample for future virology testing if necessary
- Retention blood sample for potential future virology testing (Section 6.7)
- Safety assessments, including general safety (hematology, blood chemistry, and urinalysis) (Section 6.8)

- Hemolysis assessment, including urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9).
- For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).
- Antibodies to β2GPI and β2GPI-DI (Section 6.10) and retention sample.

7.11 Long-Term-Safety-Follow-up visit (LTSF) for subjects who are discontinued from IMP due to adverse events and if study is stopped

For subjects who are discontinued from study drug due to thrombotic or hemolytic events, and for all subjects if the study is stopped, subject will continue to be followed up and have the LTSF performed for 2 additional cycles (21-day cycle/28-day cycle) after LTSV, for a total approximate 3-month safety follow-up. The assessments will be conducted prior to the administration of the subject's standard IgG treatment.

For subjects who are discontinued from study drug due to anti-β2GPI immunogenicity, subject will continue to be followed up and have the LTSF performed after LTSV until immunogenicity titers are stabilized (or dropping) over 3 consecutive treatment cycles (21-day cycle/28-day cycle) after their last IMP infusion, and while on the subject's standard IgG treatment. The assessments will be conducted prior to the administration of the subject's standard IgG treatment. A follow-up phone call with the subject will take place approximately 8 weeks after the last LTSF performed for a review of laboratory assessments, including immunogenicity β2GPI and β2GPI-DI, adverse events and concomitant medication.

Adverse Event Assessment and Concomitant Medication Review

A review of adverse events, laboratory results and current medication will be performed. Current IgG treatment will be included under concomitant medication.

Subject Diary Review

The Subject Diary will be reviewed and collected as described in Section 6.2.

Vital Signs Pre-Infusion

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded before the IMP infusion at the time intervals outlined in Section 6.3.

Physical Examination

The physical examination will focus on organs or systems that are known to be the target of complications in PIDD and the subject will be evaluated for infection as described in Section 6.4.

The subject's weight will be measured, and if the subject has gained or lost ≥5% body weight since baseline, the amount of IgG for infusion must be adjusted accordingly per standard care.

Pre-Infusion Laboratory Assessments

The following laboratory samples will be obtained prior to administration of IMP/CP:

- Urine pregnancy test, if applicable (Section 6.5)
- Serum IgG trough levels will be measured prior to each Infusion of IMP (Section 6.6)
- Virology testing (Section 6.7), with a retention sample for future virology testing if necessary
- Safety assessments, including general safety (hematology, blood chemistry, and urinalysis) (Section 6.8)
- Hemolysis assessment, including urine hemosiderin, serum haptoglobin, plasma free hemoglobin, Coombs test (direct anti-globulin test) (Section 6.9).
- For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).
- Antibodies to β2GPI and β2GPI-DI (Section 6.10) and retention sample.

Follow-up Phone Call at 8 weeks after last LTSF

A follow-up phone call with the subject will take place approximately 8 weeks after the last LTSF performed for a review of laboratory assessments, including immunogenicity β2GPI and β2GPI-DI, adverse events and concomitant medication.

8 Administrative Considerations

8.1 Interim Analyses and Stopping Rules for Subjects on IMP

The DSMB (see Section 8.7), Sponsor, or PI may elect to terminate the study early as defined by the clinical study agreement.

The study may also be stopped, suspended, or terminated for subjects with specific characteristics or for all subjects at any or all sites for any of the reasons described below.

As described in Section 3.1 and Section 12.5, two interim analyses will be performed, based on the following in Group 1 and Group 2:

- Testing for antibodies to ß-2 glycoprotein I (ß2GPI) and to ß-2 glycoprotein I domain I (β2GPI-DI);

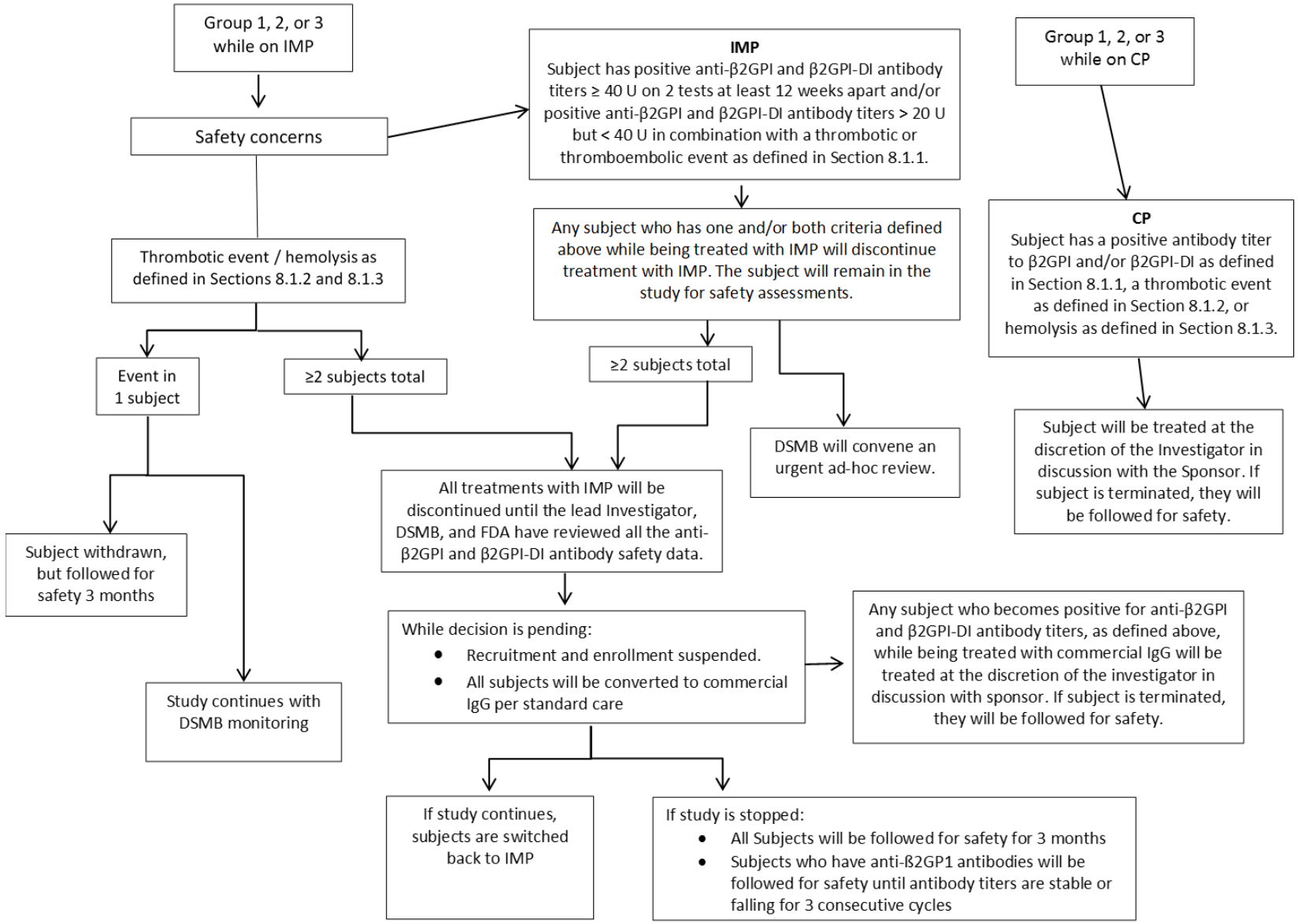
- General safety laboratory tests (hematology, chemistry, urinalysis) before Infusion and on Day 7 after Infusion;
- Hemolysis laboratory test before Infusion and at Day 2 or 3 and Day 7 after Infusion;
- Clinical hemolysis & thrombosis assessment 1 h, 24 h and 72 h after Infusion;
- D-dimers & retention sample for proteins C & S 3-4 h after Infusion;
- Adverse Event data.

The algorithm for study-stopping rules shown in Figure 2 will be followed.

- If ≥2 subjects showing either (a) treatment-emergent positive anti-ß2GPI and/or ß2GPI- DI antibody titers ≥ 40 U as defined in Section 8.1.1 or (b) treatment-emergent positive anti-ß2GPI and/or ß2GPI-DI antibody titers > 20 U but < 40 U in combination with a treatment-emergent thrombotic or thromboembolic event, or a combination of (a) and (b).
- If ≥2 subjects present with confirmed thromboembolic events, as defined in Section 8.1.2, following full work-up for thrombosis.
- If ≥2 subjects present with confirmed hemolytic events, as defined in Section 8.1.3, following full work-up for hemolysis.

In the event any of the above occurs, administration of IMP for all subjects will be on hold until the investigator, DSMB, and FDA have reviewed the safety data and agree to resume dosing with IMP.

Figure 2. Summary of Stopping Rules



8.1.1 Immunogenic Reactions

Diagnosis of an immunogenic reaction that may lead to a thrombotic event will be based on treatment-emergent positive anti-ß2GPI and β2GPI-DI antibody titers, defined as an antibody titer of ≥ 40 U found twice on tests that are at least 12 weeks apart and/or on treatment-emergent positive anti-ß2GPI and β2GPI-DI antibody titers > 20 U but < 40 U in combination with a treatment-emergent thrombotic or thromboembolic event (Unlu et al., 2015) by these definitions will be considered significant events. If any subject after receiving IMP seroconverts from negative to positive, with an elevated rising antibody titer at least 12 weeks apart, then all prior retention samples for ß2GPI and/or β2GPI-DI for all subjects should be analyzed.

Subjects who develop treatment-emergent anti-ß2GPI and/or β2GPI-DI antibody titers > 20 U following exposure to IMP will be followed closely by the investigator for thrombotic and/or thromboembolic events. These subjects will have periodic (no more than 8 weeks apart) anti-β2GPI and β2GPI-DI antibody titer testing until they have completed 52 weeks of treatment with IMP or until immunogenicity titers have stabilized or are declining over 3 consecutive treatment cycles (21 or 28 day cycles), whichever is later.

As shown in Figure 2:

1. Any subject who has a significant event as defined above for anti-β2GPI and/or β2GPI-DI antibodies while being treated with IMP will permanently discontinue treatment with the IMP. The subject will remain in the study for safety assessments up to the time of the final follow-up phone call after LTSF (see Section 7.11).
2. The occurrence of two such significant events as defined above for anti-β2GPI and/or β2GPI-DI antibodies will be referred to the DSMB for an urgent ad-hoc review to determine if this qualifies as a potential study-stopping event as defined above.
3. If two or more subjects treated with IMP are confirmed to meet the criteria for a significant event, as defined above, all treatments with the IMP will be discontinued until the lead investigator, the DSMB, and the FDA have reviewed all the anti-β2GPI and ß2GPI-DI antibodies safety data for subjects enrolled. During this time, no new subjects will be enrolled. If a subject should require a scheduled infusion during this time, they will continue therapy with a commercially available preparation (CP). IMP infusions will be recommenced if approval to continue the study is given by the DSMB and FDA.
4. Any subject who becomes positive for anti-β2GPI and/or ß2GPI-DI antibody titers, as defined above, while being treated with CP will be treated at the discretion of the Investigator in discussion with the sponsor.

The IRB/IEC and the US FDA/appropriate regulatory authority for trials outside the US will be immediately notified of any suspected ADRs involving immunogenic reactions.

8.1.2 Thrombotic Events

As shown in Figure 2:

- Investigator will examine subjects for clinical signs of thrombosis (Section 6.12.2). Positive assessments will lead to a full work-up for thrombosis, as appropriate, according to the facility's standard of care. In the case that d-dimer results indicate potential thrombosis, protein C and protein S testing will be done based on Investigator evaluation (Section 6.11).
- Any subject who is diagnosed with a thromboembolic event based on clinical and laboratory assessment while being treated with IMP will permanently discontinue treatment with the IMP and will receive standard medical care. The subject will remain in the study for safety assessments up to the time of the final follow-up phone call after LTSF (see Section 7.11). All such events will be referred to the DSMB for an urgent ad-hoc review to determine if this event qualifies as a potential study-stopping event as defined above.
- Any subject who is diagnosed with a thrombotic or thromboembolic vascular event based on clinical and laboratory assessment while being treated with the commercial product will receive standard medical care and continuation in the study will be at the discretion of the Investigator. If the subject is terminated from the study, the PI will determine continued treatment for managing the disease, in consultation with the subject's treating physician and per standards of care. The subject will remain in the study for safety assessments up to the time of the final follow-up phone call after LTSF (see Section 7.11).
- If two or more subjects experience confirmed thrombotic or thromboembolic vascular events in the trial as a whole in subjects receiving IMP, the DSMB will put the study on temporary hold while an assessment is made. All treatments with the IMP will be discontinued until the investigator, the DSMB, and the FDA have reviewed safety data for subjects enrolled. During this time, no new subjects will be enrolled. If a subject should require a scheduled infusion during this time, they will continue therapy with a commercially available preparation (CP). IMP infusions will be recommenced if approval to continue the study is given by the DSMB and FDA.

The IRB/IEC and the US FDA/appropriate regulatory authority for trials outside the US will be immediately notified of any suspected ADRs involving thromboembolic events.

8.1.3 Hemolysis

As shown in Figure 2:

- Investigator will examine subjects for clinical signs of hemolysis (Section 6.12.2). Positive assessments will lead to a full work-up for hemolysis, as appropriate, according to the facility's standard of care.
- For all subjects, a drop of ≥2.0 g/dL from the pre-infusion hemoglobin level or clinical signs of hemolysis between visits will lead to a full hemolysis work-up (Section 6.9).
- Any subject who is diagnosed for a hemolysis event based on clinical and laboratory assessment while being treated with IMP will permanently discontinue treatment with the IMP and will receive standard medical care. The subject will remain in the study for safety assessments up to the time of the final follow-up phone call after LTSF (see Section 7.11). Any such event will be referred to the DSMB for an urgent ad-hoc review to determine if this event qualifies as a potential study-stopping event as defined above.
- Any subject who is diagnosed with hemolysis based on clinical and laboratory assessment while being treated with the commercial product will receive standard medical care and continuation in the study will be at the discretion of the Investigator. If the subject is terminated from the study, the PI will determine continued treatment for managing the disease, in consultation with the subject's treating physician and per standards of care. The subject will remain in the study for safety assessments up to the time of the final follow-up phone call after LTSF (see Section 7.11).
- If two or more subjects experience confirmed hemolysis events in the trial as a whole in subjects receiving IMP, the DSMB will put the study on temporary hold while an assessment is made. All treatments with the IMP will be discontinued until the investigator, the DSMB, and the FDA have reviewed safety data for subjects enrolled. During this time, no new subjects will be enrolled. If a subject should require a scheduled infusion during this time, they will continue therapy with a commercially available preparation (CP). IMP infusions will be recommenced if approval to continue the study is given by the DSMB and FDA.

The IRB/IEC and the US FDA/appropriate regulatory authority for trials outside the US will be immediately notified of any suspected ADRs involving hemolysis.

8.1.4 Other Reasons for Termination

- The safety data reviewed by the DSMB demonstrate or strongly suggest that the study treatment (or participation in the study) is unsafe.

- The protocol or conduct of the study is flawed such that the safety or rights of the study subjects may be adversely affected.
- The IRB/IEC has withdrawn approval for the study and has denied reconsideration.
- Relocation of the PI, reallocation of the PI's responsibilities, or disqualification of the PI by order of the regulatory authority
- Non-adherence to the protocol or unavailability/lack of supervision by the PI and/or inadequate resource to conduct the study.
- Clinical hold imposed by the FDA/appropriate regulatory authority for trials outside the US.

Any decision to voluntarily suspend or terminate a clinical study will be carefully reviewed and fully justified. The sponsor will notify the FDA/appropriate regulatory authority for trials outside the US and the IRB/IEC of any suspension or termination, along with justification for restarting or terminating the study as applicable.

8.2 Withdrawal Criteria and Replacement of Subjects

Subjects will be withdrawn for any of the following reasons:

- The subject withdraws consent (no justification is required);
- The subject is pregnant;
- The subject develops a condition that in the investigator's opinion makes it medically necessary that the subject not continue in the study.

After an investigator and sponsor discussion, subjects may be withdrawn for the following reasons:

- An AE that in the Investigator's or sponsor's opinion requires the subject be withdrawn from the study;
- Violation of eligibility criteria;
- Major protocol violations or deviations from the treatment plan dictated by the protocol (e.g., incorrect IMP administration);
- Lost to follow-up after all attempts at contacting the subject; and/or
- Death.

In all cases, the reasons for withdrawal will be recorded in the subject's source documentation and in the eCRF. It is possible that some subjects may become lost to follow-up during the study. Every reasonable effort will be made to contact these subjects; all available efficacy and safety data collected for these subjects will be used, even if incomplete.

8.3 Screen Failures

Subjects who do not meet the entry criteria through Baseline will be ineligible for treatment and will be deemed screen failures. Subjects who fail screening will not receive the IMP; therefore, no efficacy, safety, or PK data will be collected for these subjects, and only demographic information will be collected on the eCRF. Subjects who fail screening will be considered screened but not enrolled. Only subjects who qualify for treatment with CP/IMP will be enrolled.

8.4 Subject Identification

Subjects will be identified by a numerical code in the site master log or the site database. Prior to approaching a subject, the site must look at the general eligibility criteria of the subject as a pre-screen check to ensure that the cohort is not already fully enrolled across the study. The process will be an approval process via the CRO. Once approval has been given to enroll and in which group, the site will begin the screening process. All subjects who sign the ICF/assent will receive a Subject Identification Number according to the following format: XX-YYY (site number-subject number) to be defined in a Study-specific Operations Manual. The anonymity of subjects will be maintained insofar as is required by law in order to protect the subjects' rights to privacy. Personal identifying information may only be obtained by the Investigator or their designee to complete the requirements of the protocol, and must be kept by the Investigator in strictest confidence and may not be released unless required by law. See Section 17 for additional information regarding confidentially.

8.5 Treatment Compliance

IMP will be provided by the sponsor and delivered to participating sites by the Central Drug Repository selected for the study. All subjects will be infused under the supervision of the PI and will receive the IMP dose ordered by the PI, and these data will be recorded in the eCRF. Only subjects who have been enrolled into the study will receive IMP. For more information on IMP dispensing and accountability, please see Section 13.

During the Waiting Period for IMP treatment, commercial product will be infused under the supervision of the PI according to standard care, and the data will be recorded in the eCRF. If a subject is enrolled directly from a clinical trial, the PI will make the determination which commercial product the subject will receive, in consultation their treating physician.

8.6 Protocol Deviations

Every effort will be made to avoid deviations from the protocol during the conduct of the study. When protocol deviations do occur, the Investigator should promptly inform the Monitor, and the implications of each deviation must be reviewed and discussed. Any deviation must be documented, stating the reasons, date, actions taken, and the impact for

the subject and/or study for each deviation. This documentation must be kept in the Sponsor Files, Investigator Files, and recorded in the eCRF. In case of any major protocol deviations (i.e., violations), the PI and sponsor will decide on the further participation of the affected submitted to the IRB/IEC according to the requirements of each of these institutions.

Unique scheduling windows are indicated throughout the protocol with the use the "±" or "+" symbols. Protocol-related activities that occur outside the scheduled time point but within the allotted "±" or "+" windows are allowed and are not considered deviations.

8.7 Data Safety Monitoring Board (DSMB)

In addition to the Sponsor and PI's responsibility for oversight, study oversight will be under the direction of an independent DSMB. The DSMB will be responsible for ongoing review of safety data. The PI will assess seriousness, causality, and intensity (severity) of an adverse event.

The processes, composition, and intervals of meetings will be described in detail in a separate DSMB charter written in accordance with the FDA *Guidance* [March, 2006].

The DSMB will include members with expertise in immunology and experience in clinical trials with immunoglobulin product. The DSMB will at minimum meet after all subjects in Group 1 have received their first infusion of IMP and the immunogenicity results are available, prior to Infusion 2. They will meet again once a further 10 subjects have received their first infusion of IMP and immunogenicity results are available prior to Infusion 2. These subjects will continue on IMP during review of safety data, but no further subjects will receive IMP until DSMB and FDA provide safety evaluation. At any time a thrombotic or hemolytic event is suspected or reported the DSMB will review the data of individual subjects and if needed additional subjects to make a determination.

All immunogenicity data except for the screening data, baseline and Infusion 2 (prior to infusion) will be batch tested. The DSMB can request that the retention samples for immunogenicity testing (anti-β2GPI and ß2GPI-DI antibodies) or Protein C and S can be tested at any time. Once Group 1 and Group 2 have been approved, a DSMB meeting will take place after 20 subjects in Group 3 receive at least 6 doses of IMP. In the event any safety concerns are raised in the periods between meetings by SAEs, the DSMB Chair will hold ad hoc meetings to ensure the safety of all subjects and determine whether the concern warrants applying the stopping rules.

The DSMB will provide its analysis and conclusions to ProMetic BioTherapeutics, to the IRBs, and to the FDA. The DSMB Charter is a separate document detailing the composition, governance, meeting preparation and conduct, voting rules and stopping rules.

9 Concomitant and Prohibited Medications

9.1 Commercial Product

Subjects who prior to entering the study were receiving commercially available IGIV will continue to receive the same product. Subjects who prior to entry were receiving IGSC or who were receiving another investigational IGIV will receive the commercially available IGIV chosen by the Investigator in consultation with their treating physician.

9.2 Concomitant Medications

The administration of concomitant medications, including topical steroids for skin conditions, steroid eye drops, chronic use of inhaled steroids for asthma, and intranasal steroids for rhinitis, is permitted during the study period in keeping with the standard of care for subjects with PIDD. A brief course of systemic steroids (i.e., a steroid burst) is allowed for treatment of a short-term condition such as an asthma exacerbation or poison ivy exposure. Any medications, including non-prescription medications, taken by the subject from 21 days (± 2 days) or 28 days (± 2 days) (depending on subjects' dosing interval) before baseline (Infusion 1) through the end of the study and the reason for use will be recorded and captured in the eCRF.

Hydration practices are allowed during the study. All fluids administered and the volumes used will be recorded and captured in the eCRF.

The use of pre-medication for pain relief and/or diphenhydramine prior to an IMP infusion is only permitted if the subject is using these pre-medications as part of routine IGIV or IGSC treatment.

9.3 Prohibited Medications

The following medications are prohibited in this study:

- Other immune globulin therapy after Baseline IMP infusion 1.
- Immunosuppressive drugs, e.g., chemotherapy drugs.
- Oral or parenteral corticosteroid at a dose ≥ 0.15 mg/kg/day prednisone or equivalent, except a steroid burst as described in Section 9.2.
- Continuous antibiotics intended for prophylaxis of bacterial infections.

9.4 Other Restrictions

Medications from other research studies or clinical studies are not permitted.

10 Reporting of Adverse Events

10.1 Definitions

10.1.1 Adverse Event

An AE is any untoward medical occurrence (whether or not considered to have a causal relationship to IMP) in a study subject administered an IMP. Therefore, an AE can be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. For the purposes of this protocol, all AEs occurring during the study are considered treatment-emergent AEs (TEAEs) associated with the use of the immunoglobulin product (either IMP or CP), whether or not the AE is determined to be product related.

10.1.2 Adverse Drug Reaction (ADR)

According to the FDA *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006)*, an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG.

10.1.3 Infusional and Temporally Associated Adverse Events

AEs that occur during the infusion of the IMP or CP will be recorded as Infusional AEs. Temporally associated AEs are those that occur during the infusion or within 72 hours following the end of the infusion, regardless of other factors that may impact a possible causal association with IMP/CP administration.

10.1.4 Serious Adverse Events (SAEs)

All AEs must be evaluated as potential serious adverse events (SAEs). An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred. (This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug) or
- Is a medically important event or reaction:
    - Events that did not result in death or hospitalization but may, based on appropriate medical judgment, jeopardize the subject or require intervention, to prevent one of the outcomes in the definition of SAE listed above, should also be considered SAEs.

10.1.5 Adverse Event Severity

The Investigator will assess the severity of AEs according to the criteria below:

- **Mild:** The AE is transient and does not interfere significantly with the subject's normal functioning level. The AE resolves spontaneously or may require minimal therapeutic intervention.
- **Moderate:** The AE produces limited functional impairment and may require therapeutic intervention. The AE produces no sequelae.
- **Severe:** The AE results in significant impairment of function and may lead to temporary inability to resume the subject's normal life pattern. The AE produces sequelae which require prolonged therapeutic intervention.

10.1.6 Adverse Event Relationship to IMP or CP

The following 4-point scale will be used by the Investigator to rate the relationship of the adverse event to the study product, and final determination of causality will be established by the Sponsor:

- **Definitely related:** A clinical event (including laboratory test abnormality) occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitively associated pharmacologically, using a satisfactory re-challenge procedure, if necessary.
- **Probably related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Possibly related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, but which could also be

explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- **Not related:** An event for which sufficient information exists to conclude that the etiology of the event is unrelated to the IMP.

Causality will be assessed as follows:

The Investigators will assign causality at their respective sites during the study, with final determination of causality established by the Sponsor. The DSMB will review the assigned causality for all AEs and SAEs prior to database lock. This assignment will be included in the study database and final study report. As noted in the FDA *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, decisions on whether there is some basis to believe there is a causal relationship will be based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and de-challenge experience, and (7) whether the adverse event is known to be caused by related drugs.

10.2 Handling and Reporting of Infusional and Temporally Related Adverse Events

10.2.1 Common Temporally Associated AEs or ADRs

Common temporally associated AEs or ADRs that may occur in approximately 5% of infusions or less include but are not limited to headache, fatigue, chills, dyspnea, pallor, backache, other body ache, leg cramps, light-headedness, fever, urticaria, flushing, elevation of blood pressure, nausea, vomiting, anaphylactic reactions, infusion site reactions, hypersensitivity reactions, oliguria, and anuria.

On rare occasions, immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the subject has shown no hypersensitivity to previous administrations. Cases of reversible aseptic meningitis, isolated cases of reversible hemolytic anemia/hemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin. Transfusion-related lung injury (TRALI) characterized by severe respiratory distress, pulmonary edema, fever, hypoxemia, and abnormal left ventricular function have also been reported, typically within 1 to 6 hours after the transfusion. Increases in serum creatinine levels and/or acute renal failure have been observed. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis may occur.

10.2.2 Subject Monitoring

The recommended infusion rates mandated by the protocol must be closely followed. Subjects must be closely monitored and carefully observed for any symptoms throughout the infusion period as per the protocol requirements.

Certain severe ADRs may be related to the rate of infusion.

Certain adverse reactions may occur more frequently:

- in patients with hypo- or agammaglobulinemia with or without IgA deficiency
- in case of high rate of infusion

All subjects will be monitored for the first hour after each infusion, except for the first infusion where they will be monitored for 3-4 hours after the infusion. During this time, the subject will be observed in order to detect potential adverse signs and conduct the post-infusion 60-minute vital sign measurement and assessment for signs of hemolysis or thrombosis. Handling of Infusional and Temporally Associated AEs

Infusional and temporally associated AEs will be closely monitored. For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE will be captured.

IMP will be administered according to the infusion rate titration schedule in Section 13.6.

Note: The dose and administration of CP for subjects on the Waiting Period will be per standard care, as determined by the Investigator in consultation with the treating physician.

If an infusional AE occurs during the first treatment course, the study staff will initiate one of the following actions, which will be graded from 1 to 4 depending on the nature and/or severity of the event:

1. Reduce the current infusion rate to one-half the rate of the infusion at which the AE was observed; or
2. Reduce the rate of the infusion more than one-half the rate at which the AE was observed, as necessary to subside symptoms; or
3. Reduce the rate of the infusion to one-half, or progressively reduces more than one-half, the rate at which the AE was observed and then stops the infusion, as necessary to subside symptoms; or
4. Stop the infusion to subside symptoms.

The study staff will evaluate the subject's AE and then:

- increase or resume the infusion at a rate tolerated by the subject once the symptoms have subsided; or

- stop the infusion and not resume it.

If a subject has an infusional AE at the same infusion rate twice, then subsequent infusion rate escalation, if any, should be halted at the rate before the AE, depending on the severity of the AE.

10.2.3 Reporting Infusional and Temporally Associated AEs

Infusional and temporally associated AEs will be reported as the number occurring during the infusion and within 1 hour, 24 hours, and 72 hours after the end of the infusion, and the total number of AEs that occur during or within 72 hours of an infusion will be given in the *Adverse Reactions* section of the product's draft package insert, along with the total number of infusions, and the mean number of such temporally associated AEs per infusion (see Section 12.3.4).

10.3 Eliciting and Reporting of Other Adverse Events

AEs will be captured from signing of Informed Consent/Assent to until 21±4 days or 28±4 days following the last infusion. AEs and ADRs will be elicited and reported as follows:

The condition of the subject will be monitored throughout the study. At each visit, AEs will be elicited using a standard non-leading question such as "*How have you been since the last visit / during the previous study period?*" AEs will also be elicited through the use of Subject Diary cards, which the Investigator will review in detail with the subject at each visit, ensuring accuracy and completeness of entries recorded by the subject.

The staff will also ask specific questions during phone calls to determine whether a work-up for hemolysis and/or thrombosis is necessary. During the phone calls, the staff will ask open-ended questions about the subject's wellbeing and to ensure that AEs are being documented in the Subject Diary. The study staff will review these specific questions with the subject and ensure subject is completing the diary. (Section 6.12.3)

Any AE or ADR occurring during the study will be noted in detail on the appropriate pages of the eCRF. If the subject reports several signs or symptoms, which represent a single syndrome or diagnosis, the latter should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious) and relatedness, with final determination of causality established by the Sponsor, as defined in Section 10.1.

In the event of abnormal laboratory findings considered clinically significant by the Investigator, the tests will be repeated and followed-up, as needed. Diseases, signs and symptoms, and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent a worsening.

The Investigator should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the subjects' AEs or ADRs.

10.4 SAE Reporting

All AEs assessed as serious must be reported beginning from the signing of Informed Consent/Assent to 21±4 days or 28±4 days following the last infusion. SAEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e., the subject or Investigator is unable to provide additional information or, the subject is lost to follow-up).

10.4.1 SAE Reporting to Safety

All SAEs will be reported within 24 hours of the Investigator becoming aware of the event and submit the Safety Report 24/7 to the Safety Department via the fax number/email below.

Toll Free Fax: 1-866-246-1693. Toll Free Telephone: 1-888-784-2723

Email: prometic_safety@integratedtsi.com

Full details of SAE reporting to the Safety Department will be defined in the Safety Management Plan.

It should be noted that reporting to the Safety Department within 24 hours of awareness is required for all SAEs regardless of their causal relationship with the IMP.

The Safety Department, together with the sponsor's medical monitor, will review all safety information/documentation and follow up with the investigative site to obtain any other required information. Follow-up information should be actively sought by the Investigator and reported to the Safety Department as it becomes available using the Safety Report.

The sponsor and the appointed for the study are responsible for reporting SAEs to the FDA/appropriate regulatory authority for trials outside the US, as applicable.

Serious adverse events that are unusual in the absence of drug therapy will be listed in the *Adverse Reactions* section of the draft package insert, even if there are only one or two reported events, unless it is clear that a causal relationship can be excluded.

10.4.2 Institutional Review Board/Independent Ethics Committee

A central IRB will be used for the majority of the sites in the US, and local IRBs/IECs for the remaining US sites and for the Russian sites. All AEs will be reported to the IRB/IEC according to the guidelines of the IRB/IEC. However, as a general guideline, IRBs need

to know about any AEs that are unknown or of a greater severity than what is reported in the Investigator's Brochure. Reporting is always required for all SAEs. Any new safety data (or other finding) that might alter the assessment of an IRB/IEC regarding their risks versus benefits analysis should always be reported to the IRB/IEC. The sponsor and the clinical research associate (CRA) will assist the Investigator in determining which events require reporting and in what timeframes.

10.4.3 Expedited Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting (Sponsor Responsibility)

The Sponsor will submit a written IND Safety Report (i.e., completed FDA Form 3500A) within 15 calendar days of receipt to the responsible new drug review division of the FDA for any observed or volunteered AE that is determined to be:

1. associated with the investigational drug or study treatment(s);
2. serious; and
3. unexpected.

In addition, if the event is fatal or life-threatening and meets the above criteria, a telephone or facsimile notification will be sent to the FDA as soon as possible, but no later than 7 calendar days after the sponsor's initial receipt, followed by a completed FDA Form 3500A within 15 calendar days after initial receipt.

Each IND Safety Report will be prominently labeled "IND Safety Report," and a copy will be provided to all participating site Investigators.

For each written IND Safety Report, the Sponsor will identify all previously submitted IND Safety Reports that addressed a similar adverse event experience and will provide an analysis of the significance of the newly reported adverse event in light of the previous, similar report(s).

If the results of the Sponsor's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting, the Sponsor will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days after the determination was made.

Follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the relevant information is available.

For study sites outside of the United States, the corresponding reporting procedures will be followed according to local regulations.

10.5 Pregnancy

Every effort will be made to avoid a pregnancy during the study. Contraceptives against pregnancy should be used (see Section 4.3.1), and the contraceptive techniques discussed

between the PI and subject at Screening should not be changed during the course of the study. A pregnancy test will be performed at all visits.

In case a subject becomes pregnant during the study, she has to be withdrawn from the study. Pregnancies occurring during the study after exposure to the IMP must be reported. The pregnancy notification form has to be sent to the Safety Department. Follow-up information on the outcome of both mother and fetus must also be reported.

10.6 Procedure for Breaking the Blind

As this is an open-label study, no subject or study personnel will be blinded.

10.7 Follow-up of Adverse Events

The responsible Investigator will follow up each AE through the LTSV or LTSF (as applicable) until it is resolved or until the medical condition of the subject is stable. AEs that are not resolved or stable at the time of study completion will be recorded as ongoing. All relevant follow-up information will be reported to the sponsor.

11 Pharmacokinetic Analysis

For all subjects in the PK sub-study, blood samples will be collected for the assessment of serum concentrations of total IgG. The serum concentrations will be determined as defined in a laboratory assay plan. All PK parameters will be estimated by both compartmental and non-compartmental analysis using Phoenix® WinNonlin 6.3 (Pharsight) and summary statistics will be presented. For all subjects in the all treated population dataset, prior to each infusion, trough serum IgG concentrations will also be determined. The data will be baseline (predose) corrected for the PK analysis.

The area under the concentration-time curve over 1 dosing interval (AUC0-t), the area under the concentration-time curve extrapolated to zero concentration (AUC0-inf) the maximum serum concentration (Cmax), the time to reach the maximum serum concentration (Tmax), the volume of distribution at steady-state (Vss), mean residence time (MRT), the total body clearance (Cl), and the terminal half-life (t1/2) will be determined from the total IgG serum concentrations measured at infusion of IMP at Infusion 6 (week 15 ± 2 days) for 21-day cycle subjects or Infusion 5 (week 16 ± 2 days) for 28-day cycle subjects (using the trough level immediately prior to this infusion as baseline). An additional sample will also be taken prior to the next infusion at Week 18 (± 2 days), Infusion 7 for subjects on a 21-day cycle, or at Week 20 (± 2 days), and Infusion 6 for subjects on a 28-day cycle.

12 Statistical Analysis

12.1 Analysis Populations

The safety analysis set will consist of all subjects who are enrolled into the study and received study product. The all treated population analysis set will be will be the same as the safety set. A modified per-protocol population analysis set will be defined as all subjects in the full all treated population set who remain in the study for at least 6 infusions.

A per-protocol (PP) analysis set will consist of all subjects in the all treated population set who complete the whole 12-month study period and who do not have any major protocol violations as described in the Data Handling Plan.

The analyses described below will be presented for all subjects in the all treated population, the modified PP population, and the PP population as follows:

- Cohort 1 only;
- Cohort 2 only;
- Each of the 3 age groups within Cohort 2;
- Cohorts 1 and 2 pooled.

The primary efficacy analysis will be based on the all treated population analysis set, with separate analyses for Cohort 1 and Cohort 2.

12.2 Handling of Missing Data

For the primary efficacy analysis, the method of maximum likelihood estimation will be used in conjunction with a negative binomial model to obtain a 99% one-sided upper confidence limit on the rate of serious bacterial infections. Since the resulting confidence interval leads to valid statistical inference assuming missing data are missing at random, no data imputation will be used in this analysis. With respect to safety and secondary endpoints, no data imputation will be used in the analysis of any other data from this study including the PK evaluations. Missing data will be omitted from summary statistics.

12.3 Statistical Analysis Plan

12.3.1 Descriptive analyses

Continuous variables will be summarized using a standard set of descriptive statistics, consisting of frequency count, mean, standard deviation, median, maximum, and minimum. Time to event endpoints will be presented using Kaplan-Meier plots. Binary endpoints and categorical data will be summarized by count and percentage. Count data will be summarized by total counts and rates per subject per infusion.

12.3.2 Primary Efficacy Endpoint

The primary efficacy endpoint in this clinical study is the rate of acute serious bacterial infections (pneumonia, bacteremia and septicemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess) per subject during the 12-month study observation period while receiving IMP. Serious bacterial infections (SBIs) must be confirmed with the tests and outcomes as described in Section 21.1.

The rate of occurrence of such infections will be calculated for each subject as $52n/w$ where n is the number of reported infections and w is the number of weeks on study.

For the primary endpoint, a 99% one-sided (upper) confidence limit for the incidence rate of SBIs (scaled to represent 12 months exposure if necessary) will be derived, and the objective of demonstrating that the true infection rate is below 1 per subject per year will be considered established if this upper limit is less than 1.

To calculate the confidence limit, a negative binomial regression model will be used. This model includes an over-dispersion parameter to account for possible intra-subject correlation as well as the actual time period each subject is on the study as an offset variable. The null hypothesis for this analysis is that the true SBI rate is at least 1 per subject per year, and the alternative hypothesis is that this rate is less than 1 per subject per year. Rejection of the null hypothesis is therefore equivalent to demonstration of the study objective to show that the true rate is less than 1 per subject per year.

The proposed method of analysis makes appropriate allowance for any intra-subject correlation in the incidence of SBIs. Such correlation would occur whenever variability in the individual subject-specific SBI rates exceeds what would be expected in the presence of true Poisson variability. The proposed statistical test based on a negative binomial model includes an overdispersion parameter reflecting any such inflated variance.

No formal statistical analyses will be done comparing the primary efficacy endpoint between the Waiting Period and the IMP Treatment Period.

12.3.3 Secondary Efficacy Endpoints

Secondary endpoints are:

- Total serum IgG trough levels
- Number of episodes of fever (≥ 100.4°F)
- Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infection
- Number of days of hospitalization due to infection
- Number of days of antibiotic use for infection prophylaxis and/or treatment

- Number and duration of infections other than acute serious bacterial infections

These endpoints will be analyzed descriptively, using frequency tables or the standard set of summary statistics as appropriate.

No formal statistical analyses will be done comparing secondary efficacy endpoints between the Waiting Period and the IMP Treatment Period. However, any efficacy endpoints measured during both the Waiting Period on commercial product and IMP Treatment Period may be summarized side-by-side using the appropriate descriptive statistics. For the Waiting Period, the summary descriptive statistics will be aggregated over all commercially licensed products.

12.3.4 Safety Endpoints

Evaluation of safety includes the analyses of laboratory investigations, adverse events, and adverse reactions/suspected adverse reactions. No formal statistical analyses will be done comparing any of the safety endpoints between the Waiting Period on commercial product and the IMP treatment period. However, all safety endpoints measured during both the Waiting Period on commercial product and the IMP treatment period will be summarized side-by-side using the appropriate descriptive statistics. For the Waiting Period on commercial product, the summary descriptive statistics will be aggregated over all commercially licensed products.

Laboratory Data:

A summary by treatment period (Waiting period, IMP treatment period) will be produced for each of the laboratory parameters at each visit. These safety summaries will include descriptive summary tables and the data will be summarized in the form of frequency count, mean, standard deviation, median, minimum and maximum by treatment period and visit.

Adverse Events:

The seriousness, severity and relationship to the study drug of adverse events (AEs) will be observed and recorded on repeated administrations of the study drug using the MedDRA dictionary for the coding of AEs and serious adverse events (SAEs).

The number and proportion of subjects who have one or more AEs will be tabulated by seriousness, severity, and relationship to treatment according to body system and treatment period. Temporally related AEs will be similarly summarized. Rates of AEs will be estimated on a per infusion per subject basis and tabulated by seriousness, severity, and relationship to treatment according to body system and treatment period.

The following observations will be summarized, using the standard set of summary statistics (see 12.3.1).

- The number of infusions administered

- The total number of AEs experienced (irrespective of causality)
- The total number of AEs temporally associated with infusions
- During the infusion
- Within 1 hour after the infusion
- Within 24 hours after the infusion
- Within 72 hours after the infusion
- The number and proportion of infusions with which one or more infusional AEs are associated
- The number of infusional AEs per infusion
- Rate-related AEs

AEs will also be tabulated for the 30 subjects who received the highest doses of IMP and commercial product.

The FDA recommends that for a novel IGIV formulation, a study should demonstrate that an upper 95% confidence limit on the rate of infusions having one or more temporally-associated AEs be less than 40 infusions per 100 patient infusions (0.40). An AE should be established as associated to the infusion of study drug by implicating temporal association (this includes all AEs regardless of relationship to product).

For the purpose of this study, AEs are considered temporally associated with the study drug infusion, if they occur in the period from the start of the infusion until 72 hours after the end of the infusion. To meet the recommended target for this safety endpoint, the number of infusions having one or more temporally-associated AEs will be analyzed using a negative binomial regression model with an over-dispersion parameter to account for possible intra-patient correlation and the number of infusions per patient as an offset variable. To calculate the required upper 95% confidence limit, an intercept-only negative binomial regression model will be fit to the data in which the response for each subject is the number of affected infusions (i.e., the number of infusions with one or more temporally-associated AEs). A two-sided 90% confidence limit on the intercept will then be computed on the inverse link scale to achieve an upper one-sided 95% confidence limit on the expected mean number of infusions per 100 patient infusions having one or more temporally associated AEs. This upper limit should be below 40 in order to demonstrate safety with respect to the infusion process.

Adverse Reaction/Suspected Adverse Reaction

The operational definition of adverse reaction/suspected adverse reaction for analysis purposes will be all AEs meeting any of the following criteria: (a) the event began during or within 72 hours following the last IMP infusion; (b) the event was considered by the

investigator and/or the sponsor to be at least possibly related to the IMP administration; or (c) the causality assessment was missing or indeterminate.

β2GPI and to β2GPI-DI Antibody Data

Data on formation of antibodies to β2GPI and to β2GPI-DI will be tabulated and discussed individually in the text.

Viral Safety Data

Viral safety data will also be listed (not tabulated) and any seroconversions will be discussed individually in the text.

Hemolysis Data

Data on potential IGIV-associated hemolysis will be tabulated and discussed in the text. The operational definition of IGIV-associated hemolysis for this analysis is defined as any event meeting the following criteria occurring within 10 days following IGIV administration: (a) a fall of at least 1 g/dL in hemoglobin from the previous value; (b) a positive Coombs test (direct anti-globulin test); and (c) at least 2 of the following: increased reticulocyte count, increased LDH, low haptoglobin, increased bilirubin, increased plasma free hemoglobin, increased urine hemosiderin.

12.3.5 Subgroup Analyses

Subgroup analyses will be performed based on gender and region (USA and Russia).

12.4 Sample Size

The power of this study to establish that the true infection rate is less than 1 per subject per year depends primarily on the unknown true infection rate. However, on the assumption that the number of serious bacterial infections (SBIs) per year follows a negative binomial distribution with mean μ and variance $\sigma^2 = \mu(1+\phi\mu)$ where μ is the population mean infection rate per year and ϕ is an overdispersion parameter reflecting possible variability in individual subject-specific rates, an estimate of the power can be made for a range of assumptions about the true infection rate.

The following table shows the estimated power of a study with 40 subjects (Cohort 1) or 20 subjects (Cohort 2) to achieve an upper 99% confidence limit below 1, for various true values of the population mean infection rate assuming a range of overdispersion from $\phi=0$ (corresponding to a Poisson distribution with no overdispersion) to $\phi=2.0$. These results were obtained using standard one-sample power calculations for testing the one-sided null hypothesis, H_0: $\mu\geq1$, against the alternative hypothesis, H_1: $\mu<1$, where μ is the population mean number of SBI's per subject per year. Specifically, the estimated power is given by Power = $1 - \beta = Pr[m + Z_{1-\alpha}\sigma<1|H_1]$ where m is the sample mean rate of infection, $Z_{1-\alpha} = 2.326$ is the standard normal quantile for an upper 99% confidence limit,

and $\sigma^2 = \mu(1+\phi\mu)$ is the true variance under the alternative hypothesis H_1 for some specified value μ that is less than 1.

Table 5. Calculations on Statistical Power

True population infection rate per subject per year and possible overdispersion		Chance of upper 99% one-sided confidence limit being below 1	
SBI rate μ	**Overdispersion parameter ϕ**	**N=40 (Cohort 1)**	**N=20 (Cohort 2)**
0.40	0 (Poisson) 2.0	99.9% 98.4%	97.2% 79.8%
0.45	0 (Poisson) 2.0	99.8% 92.4%	91.0% 63.1%
0.50	0 (Poisson) 2.0	98.4% 79.8%	79.8% 46.4%
0.55	0 (Poisson) 2.0	93.5% 62.6%	65.1% 32.5%
0.60	0 (Poisson) 2.0	82.6% 45.0%	49.3% 22.1%

The study therefore has adequate power (80% or greater when rounded) provided that the true rate of serious bacterial infections in the study population is 0.50 per subject per year or below for adults, or 0.40 per subject per year or below for children, and if the assumption of a negative binomial distribution (or Poisson distribution when $\phi=0$) is appropriate.

12.5 Interim Analysis

Two interim safety analyses will be performed to allow the DSMB and FDA to evaluate safety data from the first 15 subjects (Section 3.1) before Group 3 begin receiving the IMP.

No other interim analysis is planned. However, when all subjects in Cohort 1 have completed the LTSV, and all data have been fully reconciled, a database lock of Cohort 1 will occur, and a Clinical Study Report will be prepared in support of a BLA for the adult population. All available safety data relating to Cohort 2, available at the time of the Cohort 1 database lock, will be included in this report. When all subjects in Cohort 2 have completed the LTSV, this process will be repeated, and a separate Clinical Study Report will be prepared in support of a BLA for the pediatric population. This second report will also include the pooled analysis of the two cohorts.

13 Management of Investigational Medicinal Product

Detailed instructions are specified in the IMP Manual at each site.

13.1 Packaging and Labeling

The IMP, ProMetic BioTherapeutics Immune Globulin Intravenous Solution 10%, is a sterile, 10% liquid preparation of highly purified immune globulin (IgG) derived from pools of human plasma of at least 1000 donors (21 CFR, §640.102) for IV administration under aseptic conditions.

The IMP is filled in 50 mL (5 g) single-use, type-1 glass bottles seated with a rubber stopper and an aluminum seal with plastic flip-top cap.

Vial labels will include information to comply with US regulations:

- "Caution: New Drug - Limited by Federal (or United Sates) Law to Investigational Use Only"
- The protocol number "2004C009G"
- The product volume (50 mL) and 10% concentration
- The lot number
- The recommended storage conditions
- The name of the Sponsor
- Expiry date will not be included, as stability testing will be ongoing. Therefore, the documentation of the applicable expiry dates will be provided according to the lot number and stored in the IMP files at the site with the Investigator and/or Research Pharmacist, if applicable.
- Labeling for the shelf cartons will also bear this information.

Vial labels for non-US sites will include information to comply with local regulations.

13.2 Storage

The IMP must be stored refrigerated at 2-8°C in a secured area until used. The temperature in the storage area should be monitored with properly calibrated instruments and monitored on a temperature log.

13.3 Accountability

The PI or designee is responsible for maintaining accurate inventory records of IMP. The PI or designee will inventory all IMP shipments upon receipt, acknowledge possession by signing and returning all required documentation to the Sponsor or CRO. The PI must

ensure that all drug supplies are kept in a secure location at the site in accordance with recommended storage conditions. Inventory records for the IMP will include:

- Protocol name, number, and sponsor.
- Product name and description.
- Study site and PI name.
- Product lot number and Expiry Date(s)/Re-test date.
- Number of vials, sizes received from the Central Drug Repository.
- Number of vials dispensed, date and time of dispensing and study subject for whom product was dispensed.
- Product balance.
- Name and title of qualified individual dispensing product.

These records will be reviewed by the Monitor, and may be reviewed by regulatory agencies.

All correspondence with the sponsor regarding the stability and product release should be kept with the study specific documents at site and/or the pharmacy as applicable.

13.4 Shipment, Returns, and Destruction

The IMP will be shipped from ProMetic BioTherapeutics to a selected Central Drug Repository and from the Central Drug Repository to the sites at a temperature of 2-8°C. During shipment, the temperature of the drug will be monitored to ensure the required temperature conditions are maintained. The PI or designee will be responsible for checking the number of vials and the condition of the vials received and entering this information into the drug accountability records, reporting the condition to ProMetic BioTherapeutics, the CRO and/ or the Central Drug Repository and return the data logger and all required documentation to the Central Drug Repository. At the end of the study, or upon request by the sponsor, all unused, partially used or empty vials will be returned to the sponsor or the Central Drug Repository or destroyed at the site after accountability has been completed by the Monitor.

13.5 Preparation

The IMP should be inspected for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Solutions that are cloudy or have particulates **must not be used. Vials must not be shaken**.

The IMP can be infused directly from the vials or the IMP may be pooled and aseptically transferred into an empty sterile IV bag before administration as follows:

- The protective caps from the product vials must be removed.
- The exposed central portion of the rubber stopper must be wiped with an isopropyl alcohol swab.
- The dose will be calculated based on the prescription provided by the PI which will be based on the subjects' weight and trough levels and calculated in a mg/kg dose.
- IMP preparation will be made allowing for rounding up to the next 10mL.
- IMP preparation can also be rounded down to the previous 10mL as long as the dose remains in the range mandated by the protocol (200mg-800mg/kg)
- If the site pools the IMP into an infusion bag, then an appropriate volume of IMP will be drawn into a syringe, aseptically transferred into an appropriately sized sterile IV bag and labeled. The rounded dose will be pooled into the bag together with a predetermined extra volume per site for priming the tube, if applicable. Saline, DW5 or IMP can be used to flush the tubing, per standard of care.
- Flushing or priming the IV set with the IMP will be allowed, per the usual practices of the site. Any IMP used for this purpose will be included as part of the IMP dose.
- Any other approved fluid (Saline, DW5) used to flush or prime IV tubing must be documented in the eCRF and not included as the IMP dose volume.
- All vials empty and partial will be saved.

Pooled infusions must be prepared by a pharmacist or appropriately qualified designee.

In the event that a pharmacy will not be used, the IMP may be stored in an alternate location (e.g., a refrigerator monitored by site staff, etc.), as long as such location meets the requirements given in Section 13.2. In this case, the IMP should only be pooled if the aseptic technique described above can be ensured, and the person performing this task is appropriately qualified and working under the supervision of the Investigator.

Empty and partially used study drug vials must be maintained for drug accountability. These supplies should be clearly marked by subject (e.g., empty and partially empty vials from a single infusion should be placed in a plastic bag that bears the subject number and initials and date) and must not be discarded until authorization has been provided by the CRA. The volume left behind in partially empty vials will be recorded as

- <25%
- 25%-50%
- 50%-75%
- 75%-100%

For any single infusion to a subject, the same lot must be used; no mixing of lots. However, over the 13 or 17 infusions for a subject, different lots can be used. Prior to infusion, the IMP should be brought to room temperature or body temperature, and once this process has occurred, unused IMP should not be returned to the refrigerator for future use.

13.6 Dose and Administration of IMP

Note: The dose and administration of CP for subjects on the Waiting Period will be per standard care, as determined by the Investigator in consultation with the treating physician. This section only applies to IMP.

13.6.1 IMP Dose

The IMP dose should be consistent with previous IGIV or IGSC treatment.

When subjects receiving IGIV enter the study, the IMP will be administered initially at a dose and schedule based on the subject's previous IGIV dosing schedule (3- or 4-week interval). Subjects on a 21-day cycle when they enter the study will remain on a 21-day cycle, and subjects on a 28-day cycle will remain on a 28-day cycle. The study dose will be calculated by the Investigator using the subject's body weight (200-800 mg/kg, allowing for ≤25% change).

Subjects who are on IGSC when they enter the study must have previously tolerated IGIV use at either a 21-day or a 28-day cycle, and these subjects will be switched from IGSC to IGIV treatment at the same cycle as their previous IGIV treatment. However, because doses are adjusted in an ongoing manner for multiple reasons, including weight changes, the initial study dose may not be the same as the previous IGIV dose. Instead, the study IGIV dose may be based on the current IGSC dose and will be calculated by multiplying the weekly IGSC dose by 3 (for a 21-day cycle) or by 4 (for a 28-day cycle) and then dividing by the dose-adjustment coefficient as indicated by package insert.

The PI may change the dose and/or dosing interval in order to maintain a trough level of ≥ 5 mg/mL. For example, such changes may be necessary because of assessments of AEs or other safety assessments, or changes in the subject's weight. If at any visit after the first infusion of IMP, a subject's body weight has changed by 5% or more from the baseline value, the IMP dose will be adjusted accordingly. Any changes in the dose and/or dosing interval must be recorded on the subject's CRF, along with the reason for the change.

13.6.2 IMP Administration

Subjects can have a central or peripheral line for infusion per the subject's usual practice. The investigator will evaluate the subject's history during the past 2 years for infections and compliance for port management. Subjects with a central port who have had infection

in the past 2 years may not be suitable for the study and should be evaluated on a case-by-case basis by the investigator in discussion with the sponsor.

It is important to use separate vials, sterile syringe, and needle for each subject, to prevent transmission of infectious agents from one person to another. The IMP should be administered by IV infusion through a dedicated IV line. The IV line should be primed according to standard practice only with the IMP, Saline or DW5. No other medications should be injected into the IV line being used for IMP administration. Pre-medication is not allowed unless pre-medication is part of the subject's routine IGIV therapy.

Subjects will be hydrated prior to infusion of IMP per the site's routine standard of care and any hydration fluids will be documented.

Any bottle of the IMP that has been opened should be used promptly. Once vials are removed from the refrigerator they should not be replaced back into the refrigerator. Partially used bottles should be saved for drug accountability reconciliation by the Monitor before being discarded.

The IMP is to be administered only under the direct supervision of the PI or a qualified sub-Investigator identified on the Statement of Investigator form (Form FDA 1572). Under no circumstances will the PI allow IMP to be used other than as specified in the protocol.

13.6.2.1 IMP Infusion Rate for Infusion 1 and Infusion 2

The first two infusions will be administered according to the following algorithm: For the first 30 minutes, IMP will be initiated at an infusion rate of 0.01 mL/kg/min. If, in the Investigator's opinion, the rate is well tolerated, the rate may be increased to 0.02 mL/kg/min for the next 30 minutes. If the increase is well tolerated, the rate may be increased to 0.04 mL/kg/min for the next 30 minutes. If well tolerated, the remainder of the infusion may be administered at a maximum infusion rate of between 0.06 mL/kg/min and 0.08 mL/kg/min, depending on the subject's body weight. The total volume infused per minute must not exceed a rate of 8.0 mL/min in any subject. If an AE occurs during the first dose, the infusion rate should be adjusted or halted in accordance with Section 10.2.2.

13.6.2.2 IMP Infusion Rate for Infusion 3 Onward

The rate for Infusion 3 onward will follow the same algorithm of infusion rate increase for the first two doses, but the increases can be implemented every 15 minutes instead of 30 minutes.

If an AE occurs, the infusion rate must be decreased to the rate of the previous step; in addition, the infusion should be stopped if deemed appropriate by the Investigator.

14 Records Management

14.1 Direct Access to Source Data/Documents

The Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data and documents.

The Investigator or designee must record study participation details including enrollment, safety, and efficacy information for each subject onto source documents. The Investigator is responsible for maintaining complete and adequate case histories in the source records of each subject.

Source data must be preserved for the maximum period of time permitted by local regulations and made available by the Investigator in the cases described above.

14.2 Data Collection and Management

Data generated as per protocol will be entered onto the eCRF in accordance with the International Conference on Harmonisation (ICH) Topic E6 (R1) Guidelines for Good Clinical Practice (GCP) (CPMP/ICH/135/95). When the eCRFs have been completed, a monitor, with the assistance of the study site coordinator, will verify the source documentation records and review the data.

Subsequent electronic review of the data may result in queries being generated that will be forwarded simultaneously to the appropriate Investigator or designee and the CRO appointed for the study for prompt resolution. Resolutions will be sent back to Data Management in a timely fashion. All data modifications resulting from review or querying of the data will be electronically tracked.

Any errors detected by either the Clinical Study Monitor or the Investigator after query resolution should be communicated via eCRF data change forms. In all cases, an Investigator or designee signature will be required.

Coding of AEs and SAEs will be performed automatically by the Data Management using the MedDRA dictionary. Similarly, coding of all medications will occur using the WHO Drug Dictionary.

The medical monitor or designee will perform a periodic medical review of the coding and of the AE profile.

14.3 Record Keeping

The Investigator is responsible for maintaining all records pertaining to the clinical study and for ensuring complete and accurate documentation.

The Investigator is responsible for maintaining a subject identification log. This confidential subject identification code provides the link between named subject source records in the subject file and anonymous eCRF data provided to the sponsor.

The Sponsor requires that each Investigator retain records (all regulatory documents such as the protocol, study approval letters, all eCRFs, drug dispensing and accountability logs, all original subject consent forms and all correspondence pertaining to the conduct of the study) for a period of no less than 7 years from the date of final regulatory approval or as per local regulations, whichever is longer. If the study is discontinued, or if no application/license is to be filed or if the application/license is not approved for such indication, records should be retained for 7 years after the investigation is discontinued or as per local regulations, whichever is longer.

It is prohibited for study documents to be destroyed without prior written agreement between the Investigator and the sponsor. If the Investigator wishes to assign the study records to another party, or move them to another location, the sponsor must be notified in writing.

15 Quality Control and Quality Assurance

15.1 Quality Control by the Monitoring Team

The CRAs will monitor the data collected throughout the study thus providing quality control (QC) of the study. Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically at a minimum 5 selected sites by qualified quality assurance (QA) auditors.

The Investigator must make himself or herself available for CRAs during their visits and ensure that CRAs have direct access to all documents that they require, including direct access to the subjects' files. The Investigator agrees to cooperate with the CRAs to make certain that any problems detected in the course of monitoring visits are resolved. The Investigator will permit direct access to the source data and documents to the appropriate regulatory authorities to verify the accuracy of this data.

The present study sponsored by ProMetic BioTherapeutics, will be conducted in accordance with ICH GCP. The clinical team at the CRO will systematically control the essential documents generated during this study. The study will be monitored by the clinical team and will be subject to internal audits by Quality Assurance. All clinical study monitoring visits and audits by QA will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to sites after all visits and any findings should be addressed by the Investigator. The follow-up letters should be filed with the study correspondence and other essential documentation.

15.2 Quality Assurance by an Audit Team

Any study site may be selected for audit at any moment by an audit team originating from the Sponsor or from an external organization acting on behalf of the Sponsor.

The Investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved.

15.3 Quality Assurance by Data Management

An independent delegate from the CRO or Sponsor side will be responsible for QA and QC of the database and data management.

16 Ethics and Responsibility

16.1 Investigational Review Board

The IRB/IEC must operate in compliance with local regulations (in the United States, FDA regulations 21 CFR 50 and 21 CFR 56), and in conformance with applicable ICH E6 Guidelines on GCP: Section 3 Institutional Review Board/Independent Ethics Committee (IRB)/(IEC).

The Investigator-sponsor will obtain, from the IRB/IEC, prospective approval of the clinical protocol and corresponding informed consent/assent form(s); modifications to the clinical protocol and corresponding informed consent forms, advertisements (i.e., directed at potential research subjects) for study recruitment, and any other material presented to a subject.

This board or committee, the makeup of which must conform to applicable regulations and guidelines, will approve all aspects of the study, including the current protocol, written Informed Consent Form/Assent Form, prior to initiation of the study. The Investigator will provide the Sponsor with a paper copy from the IRB/IEC to the Investigator indicating approval of the protocol and consent form/assent form. All amendments to the protocol must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator will be responsible for obtaining annual IRB/IEC renewal and submitting SAE reports to the IRB/IEC for the duration of the study (as per IRB/IEC policies and procedures). Copies of the investigator's report and/or copies of the IRB/IEC extension approval must be sent to the Sponsor.

16.2 Ethical Conduct of the Study

The clinical study will be conducted in accordance with the current IRB/IEC-approved clinical protocol; ICH E6 Guidelines on GCP; and relevant policies, requirements, and regulations of the IRB/IEC and applicable federal agencies. Any violations by sites, CRO, or Sponsor will also be submitted to IRBs/IECs and relevant regulatory agencies.

The IRB/IEC and the FDA/appropriate authority for sites outside the US will be notified promptly of discontinuation of the entire clinical study. Respective protocol modifications will be submitted prospectively to the IRB/IEC and to the FDA/

appropriate authority for discontinuation or modification of parts of the clinical study. Enrolled subjects, Investigators, and sub-Investigators will be notified immediately of discontinuation of parts of the clinical study or if the study ends or the discontinuation of a subject is necessary.

If there are changes to the protocol and a new informed consent has been approved, subjects should be informed of the changes and of any changes to the risks/benefits of participation. Subjects will need to go through the informed consent process and sign a new approved informed consent form to be eligible to continue on the study.

If a subject decides she or he does not want to continue with the treatment portion of the study, a subject can give consent to be followed for safety only and can continue to allow access to Protected Health Information (PHI) even after withdrawal. However, the amended and approved ICF will need to be signed, and discontinuing treatment only should be clearly documented in a progress note in the subject's source documents. A subject still retains the right to withdraw participation in the study at any time and to discontinue further access to PHI. However, all data collected to that point will be made available to the sponsor and the CRO.

16.3 Informed Consent and Assent

Fully informed written consent will be obtained from the subject, or for subjects aged <18 years from the parent(s) or legal guardian in accordance with state and federal laws and the local IRB/IEC. The Investigator must explain to each subject, in language and terms they are able to understand, the nature of the study, the purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. The investigational product(s) should be identified as "experimental" and that its side effects are not completely known. Each subject or parent(s) or legal guardian must be informed that participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician. Adequate pregnancy protection must be listed in the ICF per the local IRB/IEC standards.

The subject or parent(s) or legal guardian should be given sufficient time to read the informed consent form and the opportunity to ask questions and consider the statement before signing and dating it, and should be given a copy of the signed document. No subject can enter the study before informed consent or assent with parental consent has been obtained.

During the study, subjects or parent(s) or legal guardian will be given any new information that may affect their decision to continue participation.

The Sponsor or its designee will supply a model informed consent form that complies with regulatory requirements and is considered appropriate for the study. Any changes to

the sample consent form suggested by the Investigator must be agreed to by the Sponsor or its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the Sponsor or the designated Medical Monitor after IRB/IEC approval.

Subjects under the age of 18 years will be given the same information at a level of understanding related to the age and comprehension of the subject. The subject will give assent to participate, with the parent or authorized representative giving consent, using the approved informed assent form and the informed consent form respectively, according to local state laws.

16.4 Changes in the Conduct of the Study

The Investigator may change the protocol without IRB/IEC or Sponsor approval, provided that it is necessary in order to safeguard the safety or rights of the subjects. Any protocol amendment must be submitted for information or consideration to the applicable regulatory agencies.

IRB/IEC approval will be requested for any change to this protocol that could affect the safety of subjects, the scope or design of the study.

Minor procedural changes will be implemented by Study Notes to File, with supporting documentation at each site, if appropriate.

A non-substantial amendment of a study protocol includes minor correction or clarification that have no significant impact on the way the clinical study is to be conducted and no effect on subject safety (i.e., administrative changes like change of telephone number(s), logistical changes, etc.).

Any changes of the protocol (substantial amendments and non-substantial amendments) will be integrated into an updated study protocol, with a listing of all changes and reasoning for them.

17 Confidentiality

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

The Investigator will ensure that the subjects' anonymity will be maintained. The privacy rules of the US HIPAA will be followed to obtain authorization for most uses and disclosures of Protected Health Information. On eCRFs or other documents submitted to the Sponsor or its designee, subjects will not be identified by their names, but by an identification code, consisting of the combination of subject's initials and study number. Documents not for submission to Sponsor or its designee (e.g., the site confidential subject enrollment log and original subjects' consent forms) will be maintained by the

Investigator in strict confidence. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IRB, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the Investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

18 Publication Policy

In collaboration with the sponsor, the CRO will prepare a draft study report after the completion of the study. The final draft study report will be submitted to the selected Investigators for information, review, and comments.

Publication of data generated in the study is governed by the Investigator Clinical Study Agreement.

19 Liabilities and Insurance

The sponsor will pay for all study-related costs. A separate financial agreement will be made (as appropriate) with the Investigator and/or Institutions.

The sponsor also carries insurance coverage for incidents of damage or injury to study subjects while participating in the study or taking study medication.

20 References

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21 Appendices

The primary endpoint of the study is the annual rate of validated acute serious bacterial infections per FDA *Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*, 2008. The primary endpoint will be assessed based on the diagnostic criteria provided in this *Guidance*, as outlined below.

21.1 Diagnostic Criteria for Serious Infection Types (FDA *Guidance*, June 2008)

Infection: Bacteremia/sepsis[a] *Symptoms*: chills, rigors *Physical findings*: fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction *Laboratory tests*: positive blood culture,[b] leukocytosis (white blood cell (WBC) count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis
Infection: Bacterial Meningitis *Symptoms*: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38°C oral or >39°C rectal *Laboratory tests*: positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay, positive blood culture[c], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose
Infection: Osteomyelitis/Septic Arthritis *Symptoms*: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults.) *Physical findings*: evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal *Laboratory tests*: positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture

Imaging studies: positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra
Infection: Bacterial Pneumonia[d] *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias *Physical findings*: rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or >39°C rectal, or <36°C, hypothermia (temperature <36°C oral or <37°C rectal) *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 <60 mmHg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum,[e] positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage (BAL) or protected brush sampling, *Imaging studies*: Pulmonary infiltrate with consolidation on chest X-Ray (CXR) (new in comparison with baseline CXR)
Infection: Visceral Abscess *Symptoms*: abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present) *Physical findings*: intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice *Laboratory tests*: positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen, positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess *Imaging studies*: typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan
Note: Items in bold are considered essential diagnostic features. [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 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms (Levy et al. 2001). 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 (International Consensus Conference on Pediatric Sepsis 2005).

[b] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGIV 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 Streptococcus pneumoniae, Neisseria meningitides, or Haemophilus influenzae, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (FDA Guidance, Acute Bacterial Meningitis July 1998).

[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 IGIV, 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 (FDA Guidance Community Acquired Pneumonia, July 1998).

[e] We recommend a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture (FDA Guidance Community Acquired Pneumonia, July 1998).

21.2 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of1/8"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, wellbeing and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development, and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best

proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic, or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional

affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical studies, the protocol must also describe appropriate arrangements for post-study provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence, and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent.

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to

withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage, and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention, and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    Extreme care must be taken to avoid abuse of this option.

Post-Study Provisions

34. In advance of a clinical study, sponsors, researchers, and host country governments should make provisions for post-study access for all participants who still need an intervention identified as beneficial in the study. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on

human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.