STATISTICAL ANALYSIS PLAN

Prometic Study 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

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned data summaries and statistical analyses for Study 2004C009G, entitled "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". It is meant to supplement the study protocol, v.5 dated 22 December 2016, which should be referred to for details regarding the objectives and design of the study. Any deviation to this SAP will be described in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1. Primary 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.

2.2. Secondary Objectives

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

- Serum total immunoglobulin G (IgG) trough concentrations 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 SBIs.

2.3. 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 (± 2 days) or 28 (± 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 beta 2 glycoprotein I (β2GPI), domain I of β2GPI (β2GPI-DI), from baseline to the LTSV
- To monitor for thrombogenicity and hemolysis by performing post-infusion clinical evaluations and laboratory testing.

2.4. Pharmacokinetic objectives

The pharmacokinetic objectives are:

- To determine the steady-state serum concentrations of total IgG
- To determine the PK profiles for total IgG following administration of Prometic IGIV 10%.

3. SUMMARY OF STUDY DESIGN

This is a pivotal Phase 3, open-label, single-arm, multinational, multi-center study to assess the tolerability, safety, efficacy, and pharmacokinetics (PK) of Prometic Immune Globulin Intravenous (Human) 10%, the investigational medicinal product (IMP), in adults and children with primary immunodeficiency diseases (PIDD).

A total of approximately 75 eligible subjects aged 2 to 80 years will be enrolled. Cohort 1 (adults) will enroll approximately 50 subjects aged 17 to 80. Cohort 2 (children) will enroll approximately 25 subjects aged 2 to <17.

- 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.

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.

A subset of subjects will be asked to participate in a PK sub-study. 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).

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. The study will proceed 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 5 subjects will be staggered at 2-week intervals. Before further subjects receive IMP, the results from these 5 subjects 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. 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.

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 immune globulin subcutaneous (IGSC), will be treated with a commercially available immune globulin intravenous (IGIV) product selected by the Investigator in consultation with their treating physician.

Subjects 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.

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

CP Treatment Period (referred to Waiting Period in the protocol): 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. All planned safety and efficacy endpoints will be recorded and summarized for this time period. All primary and secondary efficacy analyses are restricted to data collected during this time frame.

4. DETERMINATION OF 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 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: $\mu \geq 1$, 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 = $1 - ß = Pr[m + Z_{1-\alpha}\sigma<1|H_1]$ 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 1. 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)	99.9%	97.2%
	2.0	98.4%	79.8%
0.45	0 (Poisson)	99.8%	91.0%
	2.0	92.4%	63.1%
0.50	0 (Poisson)	98.4%	79.8%
	2.0	79.8%	46.4%
0.55	0 (Poisson)	93.5%	65.1%
	2.0	62.6%	32.5%
0.60	0 (Poisson)	82.6%	49.3%
	2.0	45.0%	22.1%

The study therefore has adequate power (80% or greater when rounded) provided that the true rate of SBIs 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.

5. ANALYSIS POPULATION

5.1. All Treated Population

The all treated population will consist of all subjects who are enrolled into the study and received study treatment (IMP or CP). All treated population will be used in efficacy analyses.

5.2. Safety Population

The safety analysis set will consist of all subjects who are enrolled into the study and received study treatment (IMP or CP). Safety population will be used in safety analyses.

5.3. PK Population

All PK sub-study subjects with evaluable PK parameter data and no major protocol deviations with an impact on PK data will be included in the PK analysis set.

6. STATISTICAL ANALYSES

6.1. General Considerations

Descriptive statistics and analyses will be provided by cohort, the age groups within Cohort 2 and, where appropriate, overall (combined all cohorts). Descriptive statistics for continuous variables will include the number of observations, mean, standard deviation (SD), median, minimum, and maximum values. For categorical variables, summary measures will include the number and percentage of subjects in each category.

Individual subject data will be presented in listings by cohort, subject identification number (ID), treatment schedule and, where appropriate, assessment.

All data summaries and tabulations will be prepared by using SAS® Version 9.1 or later.

For the purpose of reporting, subject weights and doses are rounded to zero decimal place.

Safety analyses will be summarized by the CP Treatment Period and by IMP Treatment Period.

Unless specifies otherwise, the efficacy analyses will be presented for all subjects in the all treated population as follows:

- Cohort 1 only
- Cohort 2 only
- Each of the 3 age groups within Cohort 2
- Cohorts 1 and 2 combined

The primary efficacy analysis will be based on the separate analyses for Cohort 1 for adult population and Cohort 2 for pediatric population using all treated population.

Efficacy data will be summarized similarly for CP Treatment Period.

PK analyses will be summarized by 21- or 28-day cycles for the IMP Treatment Period, unless otherwise specified.

6.2. Interim Analysis

Two interim safety analyses will be performed to evaluate safety data from the first 15 subjects to receive the IMP before Group 3 begin receiving the IMP. The first interim analysis will be performed for Group 1 subjects (5 subjects) and the second interim analysis will be performed for Group 2 subjects (10 subjects).

In addition, there will be an interim analysis after the first 20 subjects in Group 3 have completed 6 months of IMP dosing to support a DSMB review.

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 in order to close out study sites. When all subjects in Cohort 2 have completed the LTSV, a CSR will be prepared for the entire data set.

6.3. Methods for Missing Data

If lab data are missing for a visit and a retest was performed, the retest values may be used for the associated visit.

No other data imputation will be used in the analysis of this study including the PK evaluations.

6.4. Visit Windows

Data will be summarized and listed using the recorded nominal visit values, regardless of the actual study day on which a value was collected.

7. SUBJECT ENROLLMENT AND DISPOSITION

7.1. Subject Disposition

Subject disposition information will be summarized for all subjects by cohort and by Treatment Period. Summaries will include: the number of enrolled subjects, the number of subjects in each analysis population, the number of subjects completing the study, the number of subjects who are ongoing (for interim analyses only), the number of subjects discontinuing the study and the primary reason for study discontinuation. Additionally, total number of enrolled subjects by site will be summarized and listed.

7.2. Protocol Deviations

All protocol deviations will be documented throughout the study and will be provided in a listing.

8. EVALUATION OF BASELINE MEASUREMENTS

8.1. Demographics and Baseline Characteristics

Demographic data will include date of birth, age (based on date of informed consent), gender, race, and ethnicity; baseline characteristics data will include weight, height, PIDD diagnosis type, time since first PIDD diagnosis, IgG dose level prior to study enrollment, baseline IgG trough level, and chest X-ray results. Demographic and baseline characteristic data will be summarized for age, gender, ethnicity, baseline weight, height, PIDD diagnosis type, years since first PIDD diagnosis, IGIV dose level prior to study enrollment, IGSC dose level prior

to study enrollment, baseline IgG trough level, and chest X-ray. Demographic and baseline characteristics data will also be listed.

8.2. Medical History

A complete medical history that include past surgeries during the past 2 years, SBIs documented in the last 5 years, and any previous adverse drug reactions (ADRs) will be obtained. Medical history data will be coded and will be summarized by system organ class (SOC) and preferred terms (PT).

All medical and surgical history data will be listed.

9. EVALUATION OF TREATMENT EXPOSURE AND COMPLIANCE

9.1. Exposure to Study Treatment

Subject exposure to the study drug (IMP or CP), displayed as total number of infusions received, number of infusions per subject, total average IGIV dose per infusion (mg/kg) received, total weeks on study drug, lot numbers of IMP, number of subjects completing >= 6 and 12 months of dosing, and total exposure time in years will be summarized and listed.

CP administered will be summarized by the following IGIV products:

Gammaplex 5%

Carimune 6%

Gammagard Liquid 10%

Gamunex-C 10%

Octagam 10%

Privigen 10%

Octagam 5%

Bivigam 10%

Flebogamma 10%

Study drug administration data, including start and stop times and infusion rates, and treatment infusion interruption data for CP and IMP will also be provided in a listing.

9.2. Compliance to Study Drug

Subject compliance to study drug will be calculated as total volume administered (mL) divided by the total volume planned (mL), provided as a percentage. Compliance data for individual subjects will be provided in a listing and summarized using average compliance by subject.

10. EFFICACY ANALYSIS

10.1. Primary Efficacy Endpoint

The primary efficacy endpoint in this clinical study is the rate of clinically documented SBIs per subject during the 12-months study observation period. SBIs are defined as:

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

The rate of occurrence of such infections will be calculated for each subject as $52n/w$, where n is the number of reported SBIs 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 SBI 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 overdispersion 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.

H0: the acute SBI rate >= 1.0 per person-year

H1: the acute SBI rate < 1.0 per person-year

Rejection of the null hypothesis is therefore equivalent to demonstration of the study objective to show that the true SBI 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 CP Treatment Period and the IMP Treatment Period.

The following SAS code can be used.

```
proc genmod data = xx;
model count= /offset=logdur dist=poisson link=log dscale alpha = 0.02;
estimate 'estimate rate' intercept 1 / alpha=0.02;
```

```
ods output Estimates=Estimates;
run;
```

The primary efficacy analysis will be performed using all treated population for Cohort 1 only and for Cohort 2 only.

Additionally, the primary efficacy analysis will be repeated in the all treated population for each of the age groups within Cohort 2 and for Cohorts 1 and 2 combined. For the analysis within each of the age groups with Cohort 2, only point estimates will be provided. Their associated confident intervals will be suppressed due to limited number of subjects within each age group and no sufficient statistical power for the influential analyses.

In addition, a frequency table giving the number of subjects with 0, 1, 2 … acute SBIs, a description of each acute SBI and summary statistics for the duration of SBI will be summarized.

10.2. Secondary Efficacy Endpoints

The following secondary efficacy endpoints for the study will be summarized for the all treated population:

- Number, type and duration of infections other than acute SBIs
- Total serum IgG trough levels
- Episodes of fever (≥ 100.4°C)
- 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

Data listings will also be provided.

Additionally, efficacy endpoints measured during both the CP Treatment Period and the IMP Treatment Period will be summarized side-by-side using the appropriate descriptive statistics using all treated population. For the CP Treatment Period, the summary descriptive statistics will be aggregated over all commercially licensed products.

11. EVALUATION OF SAFETY PARAMETERS

Evaluation of safety includes the analysis of treatment-emergent adverse events (TEAEs) and the analysis of laboratory investigations.

All TEAEs experienced will be recorded during the study and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. Details to be collected include TEAE diagnosis, date and time of onset and resolution, whether the event is ongoing, whether the event is serious, frequency, severity, outcome status, action taken and relationship to study drug (IMP or CP).

Safety endpoints measured during both the CP Treatment Period and the IMP Treatment Period will be summarized side-by-side using the appropriate descriptive statistics.

11.1. Temporally Associated TEAEs (TAAEs)

The FDA recommends that for a novel IGIV formulation, a study should demonstrate a TA rate of not more than 40 TAAEs associated with the study drug per 100 administrations. A TAAE should be established as related to the infusion of study drug by implicating temporal association.

For the purpose of this study, TAAEs 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. The overall TAAE rate considered temporally associated with the study drug infusion and the rate of at least possibly related TAAEs considered temporally associated with the study drug infusion will be considered. A one-sided 95% upper confidence boundary for this percentage will be calculated by using the normal approximation.

The proportion of infusions with a TAAE will be analyzed using a non-inferiority test, with the objective of demonstrating that the percentage of infusions with one or more infusional TAAE is less than 40%. This will be achieved by calculating the percentage of affected infusions for each subject, and then calculating a (weighted) mean of these percentages, with a 95% (one-sided) confidence interval. A suitable transformation will be used if appropriate. The upper limit of this confidence interval should be below 40% in order to demonstrate non-inferiority. Weighting will be based on the number of IMP infusions for which data are available. This method of calculation of the confidence interval takes proper account of the observed intra-subject correlation because it is based on a single summary data point for each subject.

The following SAS code can be used in the analysis.

```
proc genmod data=xxxxx descending ;
class x1 x2 …label/ ;
model resp_dur = / cl dist = bin link = logit alpha=0.1 ;
repeated subject = xxx / type=exch ;
run;
```

TAAE will be summarized by:

- during the infusion (i.e., infusional TEAEs)
- within 1 hour of infusion
- within 4 hours of infusion
- within 24 hours of infusion
- within 72 hours of infusion

A summary of descriptive statistics will be provided for the IMP subjects in the safety population.

The following observations will be summarized using the standard set of summary statistics.

- Summary of TAAEs by infusion rate;
- Total number of TAAEs and infusional TEAEs;
- The number and proportion of infusions with which one or more TAAEs and infusional TEAEs are associated;
- The number of temporally associated TAAEs and infusional TEAEs per infusion;
- Number of infusions/subject where infusion rate was decreased due to an AE, and
- Subjects with at least one infusion where rate was decreased due to an AE

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.

11.2. Treatment-Emergent Adverse Events

An overall summary table of TEAEs, including subjects experiencing at least one TEAE, at least one TEAE related to study drug, at least one TAAE, at least one infusional TEAE, at least one adverse reaction, at least one TEAE leading to study discontinuation, and at least one TEAE leading to death will be presented.

TEAEs including TAAEs, infusional TEAEs, and adverse reactions will be summarized by SOC and PT, showing the number and percentage of subjects experiencing a given event. In addition, TEAEs and TAAEs will be summarized by SOC, PT and worst severity; TEAEs will also be summarized by SOC, PT and relationship to study drug.

TESAEs will be similarly summarized. The number and proportion of subjects who have one or more TESAEs, and who have one or more serious TAAEs, will be presented. TEAEs will also be tabulated for the minimum of 30 subjects who received the highest average dose of IMP.

A subject will be counted only once for each preferred term when multiple AEs are coded to the same preferred term. If a subject experiences multiple AEs coded to the same preferred term, the maximum toxicity grade will be used for the summary.

11.3. Death

Subjects whose AE outcome is death will be listed.

11.4. Study Discontinuation due to a TEAE

Incidence of TEAEs and related TEAEs leading to study discontinuation will be summarized by SOC and PT. Additionally, subjects who discontinued from the study due to TEAEs will be listed. Subject discontinuation will be determined from the evaluation (where reason for termination is AE) and the specific AE will be determined from the AE CRF page (where action taken is discontinuation of study drug).

11.5. Clinical Laboratory Evaluations

11.5.1. Hemolysis Data

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 lactic dehydrogenase (LDH), low haptoglobin, increased bilirubin, increased plasma free hemoglobin, increased urine hemosiderin.

Data on potential IGIV-associated hemolysis will be summarized by cohorts and age groups for the CP and IMP Treatment Periods.

Additionally, as requested by FDA, a listing of hemolysis-related analytes across time for subject with >1 g/dL fall in hemoglobin from the mean of Screening and pre-IMP baseline values will be provided. Hemolysis analytes include urine hemosiderin, serum haptoglobin, plasma free hemoglobin, direct coombs test, LDH, and bilirubin.

11.5.2. Clinical Signs of Thrombosis Data

The clinical signs of thrombosis data will be summarized by post dose hours evaluated. Twenty-four hours post infusion, subjects will be contacted by phone calls. The results of thrombosis testing results will be summarized when a full work-up is necessary. The clinical signs of thrombosis data will also be listed.

11.5.3. Clinical Signs of Hemolysis Data

The clinical signs of hemolysis data will be summarized by post dose hours evaluated. Twenty-four hours post infusion, subjects will be contacted by phone calls. The results of hemolysis testing results will be summarized when a full work-up is necessary. The clinical signs of hemolysis data will also be listed.

11.5.4. β2GPI and to β2GPI-DI Antibody Data

Data on formation of antibodies to β2GPI (IgG and IgM) and to β2GPI-DI (IgG) will be tabulated and listed.

11.5.5. Safety Laboratory Data

Safety laboratory parameters will be graded according to FDA guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and summarized using descriptive statistics at baseline and at each subsequent time points. Those lab parameters that are not defined in the FDA guidance will be summarized descriptively.

All laboratory results will be tabulated for the safety population.

All laboratory results will be provided as a listing, and any values that lie outside the normal range or are clinically significant will be flagged.

11.6. Prior and Concomitant Medications

Prior and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHO Drug) version September 1, 2014, and will be summarized by drug class and generic name. In addition, prior treatment concomitant medications will be listed.

11.7. Physical Examination and Vital Signs

All vital signs (weight, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature) will be graded according to FDA guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and summarized descriptively by infusion rate and time points. The vital signs data will also be listed with any values that lie outside the normal range or are clinically significant will be flagged.

11.8. Pregnancy Tests

All pregnancy test data will be listed.

11.9. Viral Tests

Virology data will be summarized descriptively. Means, SD, median, minimum and maximum will be included for continuous results such as B19 IgG, and count and percentages will be reported for categorical results. Virology testing data will be listed with normal ranges and flags of abnormality.

11.10. Subject Diary

Subject diary data will be used to derive the following secondary efficacy endpoints:

- Episodes of fever (≥ 100.4°C)

- 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

The subject diary data will be tabulated and listed.

12. SUBGROUP ANALYSIS

Subgroup analyses of the efficacy and safety endpoints may be performed based on gender.

13. PHARMACOKINETIC ANALYSIS

For all subjects in the PK sub-study, blood samples will be collected for the assessment of serum concentrations of total IgG 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 following time points:

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)

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)

The actual times of sampling as recorded on the eCRF will be used in the PK analysis.

Total IgG concentration will be determined as defined in a laboratory plan. All concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such and ignored in the PK analysis. IgG concentration will be baseline-corrected using the trough level obtained immediately prior to infusion as baseline. Baseline-corrected concentration equal or lower than 0 will not be used in the PK analysis.

The following PK parameters will be determined by non-compartmental analysis (NCA) using Phoenix® WinNonlin 7.0 (Pharsight) for each subject:

- Area under the concentration-time curve over 1 dosing interval (AUC_{0-t})
- 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 ($t_{1/2}$)

Additional PK parameters might be determined by compartmental analysis.

PK concentration profiles will be summarized over time in tabular and graphical formats. Arithmetic [and/or geometric] [mean/median] ± SD concentration-time plots will be produced by cohort, and dosing frequency.

Descriptive statistics of PK parameters and concentrations will include mean, SD, percent coefficient of variation (CV%), minimum, median and maximum. When a geometric mean is presented, it will be labeled as such.

14. SCHEDULE OF ASSESSMENTS

14.1. Schedule of Assessments and Study Events for the CP Treatment Period

	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	CP2	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.

14.2. Schedule of Assessments and Study Events for the IMP Treatment Period

	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 [s]		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 $\geq$ 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)

15. REVISION HISTORY

SAP Version	SAP Version Date	Associated Protocol Version	Reason for Revision
V0.1	07Jan15	v.1.0 dated 21Nov2014	
V0.2	07Jan16	v. 3 dated 24Sept2015	
V0.3	07Mar16	v.3.1 dated 27Oct2015	Addressed comments from Diane Trybul and Karen Thibaudeau
V 0.4	11Jul16	v.4 Dated 14Jun2016	Protocol amendment
V.1.0	24Jan17	v5 Dated 22Dec2016	Protocol amendment
V2.0	12Sept2018	V5 dated 22Dec2016	Revised based on the final planned analyses.