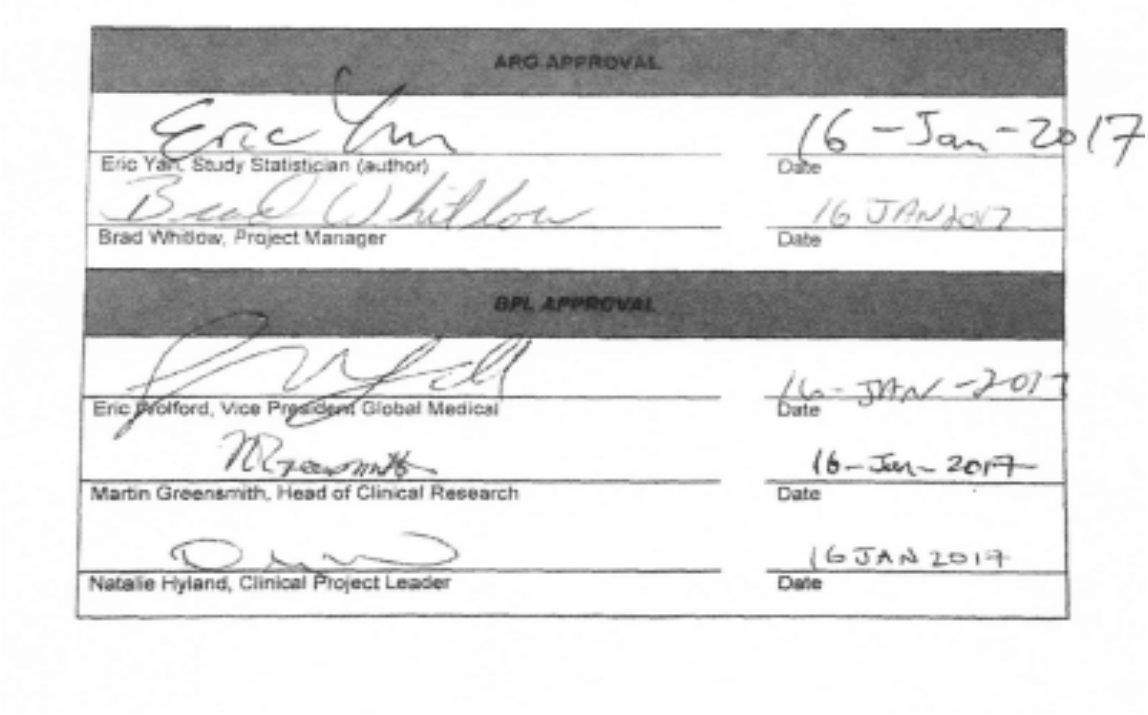
STATISTICAL ANALYSIS PLAN

A Phase III, Multicenter, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subgam®VF in Primary Immunodeficiency Diseases (PID)

Protocol Number	**SCIG03**
SAP Version	**1.0**
Date	**January 12, 2017**



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Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
BPL	Bio Products Laboratory Limited
Cl	Clearance
C_{max}	Maximum concentration
CRF	Case Report Form
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
EMA	European Medicines Agency
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	U.S. Food & Drug Administration
kg	Kilogram
K_{elim}	Elimination Rate Constant
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Immunoglobulin Intravenous
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
ITT	Intent–to-treat
LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRT	Mean Residence Time
PID	Primary Immunodeficiency
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI Units	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Time at which C_{max} first occurs
$t_{1/2}$	Half-life
TEAE	Treatment Emergent Adverse Event
Vd	Volume of Distribution
WHO-DD	World Health Organization-Drug Dictionary

1. Revision History

Version	Date	Document Owner	Revision Summary
1.0	12 January 2017	Eric Yan	Final

2. RELEVANT DOCUMENTS AND STANDARDS

2.1 Protocol, Amendments, CRF and SAP Version

Protocol Version 5.0 (28 April 2016)
Annotated CRF Version 1.0 (08 September 2015)

2.2 Applicable Standards

ICH Guidance on Statistical Principles for Clinical Trials (ICH E9)
ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3)
ICH Guidance for Good Clinical Practice (ICH E6)

3. PURPOSE OF THE ANALYSIS

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to support the completion of the Clinical Study Report (CSR) for protocol SCIG03. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR.

PK analyses are not included in this SAP but documented separately in PK Analysis Plan.

4. STUDY OBJECTIVES

4.1 Primary Objective

- To determine the PK profile of Subgam-VF and compare the AUC($_{0}$-τ) with historical AUC data (all standardized to one week at steady state) from Gammaplex 5% IGIV PID studies (GMX01 and GMX04).

4.2 Secondary Objectives

- To assess the safety of Subgam-VF, including the incidence of adverse events and site infusion reactions in subjects with PID.
- To refine the dose adjustment coefficient for Subgam-VF.

4.3 Exploratory Objective

- To explore PK modelling for alternative dosing schedules

5. STUDY METHODS

5.1 Overall Study Design

This will be a Phase III, multicenter, open-label, non-randomized study. Up to 50 subjects will be enrolled to ensure 30 evaluable subjects. At least 18 subjects will be adults* (aged 16-75 years) and 12 will be children split between the age groups 2 to 5 years (i.e. not reached their 6th birthday), 6 to 11 years (i.e. not reached their 12th birthday) and 12 to 15 years (i.e. not reached their 16th birthday).

**The definition of an adult as ≥ 16 years is as per the FDA guidance for PK studies. Note this does not affect the requirements for consent/assent, for which each site should follow their IRB guidelines.*

Subjects will receive 26 infusions (weeks) of Subgam-VF at a weekly dose equivalent to 1.37 of their IGIV dose (expressed as mg/kg/week). If the subject was already receiving a weekly SCIG IgG there will be no dose adjustment. Pharmacokinetics and safety of Subgam-VF will be assessed.

The schedule of assessments is given in Table 1.

All subjects will undergo a pharmacokinetic (PK) profile after the 21st infusion of Subgam-VF. Pharmacokinetic Assessment Schedule for Subgam-VF (Week 21 to Week 22) is given as outlined in Table 2.

Table 1 Schedule of Assessments

Assessment																		
(Wk)	**Screen**	**1[a]**	**2**	**3 to 4**	**5**	**6 to 8**	**9**	**10 to 12**	**13**	**14 to 16**	**17**	**18 to 20**	**21**	**22**	**23 to 25**	**26**	**27 FU[b]**	**30 Telephone FU[c]**
Clinic Visit No.	**1**	**2**	**3**		**4**		**5**		**6**		**7**		**8**	**9**		**10**	**11**	
Informed Consent	X																	
Inclusion /Exclusion Criteria / Eligibility	X	X																
Medical History	X																	
Physical Examination	X	X							X								X	
Weight	X	X	X		X		X		X		X		X	X		X	X	
Chest X-ray – if not available in previous 12 months		X																
Vital signs[d]	X	X	X		X		X		X		X		X	X		X	X	
Infusion with Subgam-VF		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Infusion Site Inspection for reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event reporting[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TEE examination [f]	X																X	
Hematology	X	X	X		X		X				X						X	
Biochemistry	X	X	X		X		X				X						X	
Urinalysis	X	X									X						X	
HCG urine pregnancy test	X																	
IgG trough levels	X	X	X		X		X		X		X		X	X		X	X	
IgA, IgM [g]	X																	
IgG subclasses	X																X	
Specific anti-bodies [h]	X																X	
Virology i	X																X	
Parvovirus B19 [j]		X	X														X	
Direct Coombs' Test [k]		X	X						X								X	

Assessment																		
(Wk)	**Screen**	**1[a]**	**2**	**3 to 4**	**5**	**6 to 8**	**9**	**10 to 12**	**13**	**14 to 16**	**17**	**18 to 20**	**21**	**22**	**23 to 25**	**26**	**27 FU[b]**	**30 Telephone FU[c]**
Clinic Visit No.	**1**	**2**	**3**		**4**		**5**		**6**		**7**		**8**	**9**		**10**	**11**	
Haptoglobin, plasma free hemoglobin, urine hemosiderin [l]		X	X						X								X	
PK assessment [m]													X	X				
Study Diary issue	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Reserve sample	X	X	X		X		X		X		X		X	X		X	X	
Archive: Store at –70°C for 15 years		X															X[n]	

[a] **Eligible subjects** return 7 days (+/- 1 day) for their first Subgam-VF dose. Infusion visits will be scheduled every 7 days. Individual infusions may be administered at ± 1 day of the planned schedule, if absolutely necessary (e.g. because of unavoidable conflicts, see section 7.2 for details)

[b] **Week 27** Follow-up visit will occur seven days (+/- 1 day) after the last Subgam-VF infusion. This visit must occur prior to administration of a new IgG product.

[c] **Week 30** Telephone follow-up will occur 28 days (+/- 1 day) after the last Subgam-VF infusion to check for AEs.

[d] **Vital signs** will be recorded once during the screening and follow up visits. During Subgam-VF infusion site visits vital signs will be collected 10 minutes before the start of each infusion (+/- 5 minutes) and 30 minutes after stopping the infusion (+/- 15 minutes).

e **AEs** will be documented from the date of consent until the last follow-up visit. AEs will be collected in subject diaries and by direct observation during each site visit. In addition there will be a telephone follow up by the site on day 3 after each infusion to check for any adverse reactions including infusion site reactions. The date of infusion is considered to be Day 0. If Day 3 is to fall on a weekend or public holiday then this telephone follow up call should be performed on the closest working day after Day 3 as possible.

[f] **Thromboembolic event (TEE)** monitoring to be performed at screening and at the follow-up visit- refer to section **7.8** for details

[g] **IgA, IgM -** testing for IgA and IgM will **only** occur in those subjects where results are not available for the previous 12 months

[h] **Specific anti-bodies** for *Streptococcus pneumoniae* and *Haemophilus influenzae* B will be measured at screening and FU visit. Anti-bodies for measles will be measured at FU visit (this visit must occur prior to administration of a new IgG product as a trough sample is required).

[i] **Virology -** Serological tests for HBsAg, HCV, HIV 1 & 2 performed at screening and Week 27 FU visit, NAT for HCV and HIV only performed at Week 27 FU visit.

[j] **Parvovirus B19** – PCR/NAT and serology

[k] **Direct Coombs' Test** and tests for hemolysis will be repeated for the subject at each subsequent clinic visit if the result is positive at any visit

[l] **Haptoglobin, plasma free hemoglobin, urine hemosiderin** – tests for hemolysis will be repeated for the subject at each subsequent clinic visit if the result is positive at any visit

[m] **PK sampling** will begin on Week 21 (prior to 21st infusion of Subgam-VF), with the last sample taken on Week 22 just before the next (22nd) infusion given at the site. Where possible, PK samples and assessments from Steady State Day 1 onwards could be conducted at the subject's home by an appropriately qualified member of the study team, or a Home Health Agency. See Table 3 for PK schedule. If the PK sampling cannot be completed at Week 21 (eg.. due to patients work/vacation schedule) then this can be delayed to start at Week 22, 23, 24 or 25; however, the patient should still visit the office/hospital for their week 21 infusion and complete the other assessments scheduled for Visit 8, if possible. Week 22 assessments (Visit 9) will normally coincide with the PK sampling Day 7. However, if PK sampling is delayed, Visit 9 will also be delayed.

[n] **Archive** sample should be collected before an infusion of another product

N.B. The non-shaded columns represent infusions that may be performed at the subject's home. After the Week 2 visit and if an appropriately qualified member of the study team or the subject's care giver is available, then arrangements may be made to conduct some of the visits at the subject's home to reduce the number of visits to the sites. Alternatively a Home Health Agency may be utilized. The subject would be required to sign an extra IRB/EC approved consent form to permit the site to share the subject's details with the agency in order for them to collect the samples/conduct the assessments.

Table 2 Pharmacokinetic Assessment Schedule for Subgam-VF (Week 21 to Week 22[a])

Evaluation	Before start of infusion Day 0	Time after end of infusion				
	Approx. -30 min	**1 day** (24 hours) ± 2 hours	**2 days** (48 hours) ± 4 hours	**3 days** (72 hours) ± 6 hours	**5 days** (120 hours) ± 8 hours	**7 days[b]** (168 hours) ± 12 hours
IgG	**X**	**X**	**X**	**X**	**X**	**X**
Reserve sample	**X**	**X**	**X**	**X**	**X**	**X**

a If the PK sampling cannot be completed at Week 21 (eg. due to patients work/vacation schedule) then this can be delayed to start at Week 22, 23, 24 or 25; however, the patient should still visit the office/hospital for their week 21 infusion and complete the other assessments scheduled for Visit 8, if possible. Week 22 assessments (Visit 9) will normally coincide with the PK sampling Day 7. However, if PK sampling is delayed, Visit 9 will also be delayed..

b The PK sample must be collected before the infusion scheduled for that day is started.

c In exceptional circumstances, and with prior Sponsor approval, if one of the following PK samples if lost, unevaluable, or not taken it may be taken at the same timepoint during the week following the PK assessment, as long as the same dose in mg/kg has been given:

- 1 day (24 hours ± 2 hours)
- 2 days (48 hours ± 4 hours)
- 3 days (72 hours ± 6 hours)
- 5 days (120 hours ± 8 hours).

5.2 Treatment Administration

Subgam-VF should only be infused subcutaneously using an infusion pump. Subgam-VF can be infused into the following sites: abdomen, thigh, upper arm and/or lateral hip.

The dose of Subgam-VF can be given into multiple infusion sites (although this should be no more than six sites, and eight sites for subjects ≥100 kg). If more sites are needed to achieve a full dose, then the sites can be used consecutively, but the infusions should be at least two inches apart.

Only one batch of Subgam-VF should be infused during any one infusion session.

Subgam-VF infusions will be administered in accordance with the table below, the maximum volumes and flow rates may be reduced according to tolerability.

Table 3 – Recommended infusion flow rates for Subgam-VF

	Volume	Rate
First infusion	20 mL/site	20 mL/hr/site
Maximum at subsequent infusions	Up to 30 mL/site	Up to 30 mL/hr/site

- Up to six infusion sites can be used simultaneously. Subjects weighing ≥100 kg may use up to eight sites if necessary. If more sites are required, these must be used consecutively (during the same infusion).
- Any increase in flow rate or number of sites should first be tried whilst the subject is in the clinic
- For young children or adults of below average weight lower flow rates may be used, depending on tolerability.

Details on how to prepare and administer the Subgam-VF infusion can be found in the Pharmacy Manual.

Full training must be provided to the subject prior to self-administration at home or other appropriate setting. It is aimed to start home-therapy at Week 3, however if the subject requires further training this will be provided (i.e. it is not mandatory that the infusions are performed at home from Week 3).

Lack of tolerance at any given rate must be recorded as an AE at that rate. If a subject has had the same treatment related AE at the same rate twice, and those AEs have been recorded, then subsequent infusion rate should be halted at the previously highest tolerated rate.

If any AE(s) occur, these will be documented as detailed in section 10.3 of the protocol. The infusion may then be resumed at a rate tolerated by the subject.

5.3 Randomization and Blinding

This is an open-label, non-randomized study.

5.4 Plasma Concentration Measurements

All subjects will undergo a PK assessment (see Table 1 and 2 for the sampling time points).

Where possible, samples from Steady State Day 1 (24 hours after the infusion at Week 21 or if delayed, up to Week 25) onwards may be collected at the subject's home by an appropriately qualified member of the study team. Alternatively a Home Health Agency may be utilized to take the PK samples outside of the investigational site. The subject would be required to sign an IRB/EC approved consent form to permit the site to share the subject's details with the agency in order for them to collect the sample.

The timing of the collection of blood samples for PK should be as per Table 1. The scheduling has been selected to ensure achievement of steady state of Subgam-VF.

A variation of <10% is allowed in the timing for samples as follows:
Steady State Day 1 (24 hours) ± 2 hours,
Steady State Day 2 (48 hours) ± 4 hours
Steady State Day 3 (72 hours) ± 6 hours
Steady State Day 5 (120 hours) ± 8 hours
Steady State Day 7 (168 hours) ± 12 hours.

All PK parameters will be calculated based on absolute (uncorrected) and baseline-adjusted (i.e. trough-adjusted at steady state) concentrations.

Details of the PK methods will be outlined in a PK Analysis Plan. The PK Analysis Plan will be finalized before database lock.

6. STUDY ENDPOINTS

6.1 Primary Efficacy Endpoint

As this is a pharmacokinetic and safety study, no formal efficacy analyses are planned.

6.2 Safety Endpoints

Safety endpoints include assessment of adverse events and adverse drug reactions, significant changes in vital signs, safety laboratory parameters (including kidney and liver function and Direct Coombs' test), virology, physical examination or medical history during the study.

The variables used to assess safety will be the following:

- Adverse Events
  - The number and percent of adverse events (AEs) including infusion site reactions.
  - The number and percent of infusions associated with one or more AEs that begin during the infusion, up to one hour, 24 hours, 48 hours or within 72 hours after completion of the infusion.
  - Adverse reactions, defined as any AE occurring during the infusions or within 72 hours of the infusion completion OR any AE classed as product related.
  - Thrombotic events
  - Nature, severity, and frequency of AEs (tolerability)
  - Suspected unexpected serious adverse reactions (SUSARs), if any
- Vital signs
- Clinical laboratory tests including tests for hemolysis
- Transmission of viruses
- Physical examination

6.3 Pharmacokinetic Endpoints

In addition to the PK variables determined as described in the PK plan, the following PK parameters will be determined:

- Trough serum IgG levels (measured before every infusion administered at the study site).
- Trough levels of serum IgG subclasses will be measured prior to certain infusions.
- Levels of specific antibodies (*Haemophilus influenzae* B, *Streptococcus pneumoniae, Measles*) will be measured prior to certain infusions.

7. INTERIM ANALYSIS

There is no planned interim analysis for this study, however after sufficient adult PK data has been collected, a review of the blood sampling schedules for children will be performed and the PK sampling will be optimized and reduced if possible.

8. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

This study will enroll up to 50 subjects to ensure 30 evaluable subjects. A sample size of approximately 18 adults (aged 16-75 years) and 12 children (aged between or equal to 2 and 15 years), has been decided as recommended by the FDA guidance for IGIV products[1]. For this study, the children will be enrolled across the age groups of 2 to 5 years, 6 to 11 years, and 12 to 15 years with a minimum of four in each age group. Data will be compared to historical data from previous Gammaplex IGIV studies. All the subjects will undergo a PK assessment.

Assuming no true difference exists in average exposure compared with the historical data, 30 evaluable subjects will give greater than 98% power of concluding equivalence assuming a between-subject coefficient of variation (CV) of 18.2 % (equivalently, a standard deviation of logged data of 0.181). If there is a true difference of 10%, power drops to 86%.

9. ANALYSIS POPULATIONS

9.1 Intent-to-treat (ITT) Population

All subjects who receive at least one infusion of Subgam-VF will be included in the intent-to-treat (ITT) population. The ITT population will be used for all safety analyses and summaries of demography.

10. GENERAL ISSUES FOR STATISTICAL ANALYSES

Subject listings of all data represented in the electronic CRF (eCRF) will be provided. Measurements from subjects excluded from the predefined analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the subject listings. In general, the subject listings will be sorted by subject number and assessment date (and time) if applicable.

Unless otherwise specified, descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.

All categorical/qualitative data will be presented using absolute counts and percentages. The total number of subjects in the treatment group overall (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

All analyses and summaries will be produced using SAS® version 9.2 (or higher).

10.1 Baseline Value

Unless otherwise specified, baseline is the last available observation before the start of the first infusion of study drug.

10.2 Methods for Withdrawals and Missing Data

Data from subjects who withdraw will be included, where possible, in all summaries and analyses. All summaries and analyses will be based on observed data. No imputation will be done for missing data.

10.3 Adverse Events

AEs will be documented from the date the informed consent form is signed until 28 days after the last dose of Subgam-VF is infused. All AEs will be coded by using MedDRA, Version 18.0.

Although all AEs will be listed, summary tables will be based on treatment emergent adverse events (TEAE), defined as those with onset date between first infusion date and 28 days after the last infusion.

10.4 Concomitant Medication

Concomitant medications will be coded by using the World Health Organization-Drug Dictionary (WHO-DD) Version March 1, 2015. Concomitant medications are defined as all medications (excluding study drug) taken while "on study". The on-study period is from the date of the first infusion of Subgam-VF up to and including the date of the last visit (the telephone follow-up at week 30).

If the start date of a concomitant medication is missing, then the start date will be estimated using the first infusion date. If the imputed start date is after the stop date, the start date will be set to the day prior to the stop date. If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing.

Other non-complete dates will use the same algorithm as above for TEAE.

10.5 Multicenter Considerations

Centers will not be pooled for analysis.

10.6 Multiple Comparisons and Multiplicity

No adjustments will be made for multiple comparisons.

10.7 Data Safety Monitoring Board (DSMB)

No DSMB is planned for this study.

10.8 Presentation by Age Group

All tables will present data for all adults, pediatrics, and all subjects. Selected tables, as identified in the relevant section, will be repeated for the pediatric age subgroups, in the following order:

- All subjects
- Adult subjects
- Pediatric subjects
- Pediatric subjects aged 2-5 years
- Pediatric subjects aged 6-11 years
- Pediatric subjects aged 12-15 years

11. SUBJECT DISPOSITION

The number of subjects enrolled, completing the study, and discontinuing the study will be presented in a summary table and a listing, along with the reason for discontinuation. The table will be based on the all subjects.

11.1 Protocol Deviations

All protocol deviations will be listed by subject for the ITT population.

11.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be presented in a summary table and a listing. The summary table will be based on the Intent-to-Treat population. Demographic variables will be age, gender, race and ethnicity. Baseline and disease characteristics are height, weight, BMI, the results of a chest x-ray, diagnosis and prior infections in the 6 months prior to screening. The following data will be listed only: prior IgA and IgM levels in the 12 months prior to screening or at screening, and results of pregnancy testing at screening.

Age will be summarized as both a continuous variable and using the categories:

- 2-5 years
- 6-11 years
- 12-15 years
- ≥ 16 years.

Age (years) will be calculated as (date of informed consent – date of birth)/365.25, rounded down to the nearest whole number.

11.3 Medical History and Chronic Conditions

Descriptions of medical history findings and chronic conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0. Medical history and chronic conditions will be summarized by the number and percent of subjects within each body system and preferred term. These summaries will be based on the Intent-to-Treat population.

11.4 Prior IGIV Therapy

Prior immunoglobulin G (IgG) therapy will be coded using WHO-DD (Version March 1, 2015). The number and percent of subjects who used different IgGs will be presented by ATC Levels 2 and 3, and the coded synonym.

11.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO-DD (Version March 1, 2015). Prior medications are defined as those with a start date before the date of the first Subgam-VF infusion.

The number and percent of subjects taking prior and concomitant medications will be summarized by classification according to preferred term and route. If a subject has taken a prior/concomitant medication more than once, the subject will be counted only once in the respective total.

The number and percent of subjects taking pre-medications during the study will also be summarized by preferred term. These will be identified by a review of the coded medications.

12. EFFICACY ANALYSES

As this is a pharmacokinetic and safety study, no formal efficacy analyses are planned.

13. SAFETY ANALYSES

Safety data will be presented using the Intent-to-Treat population.

The variables used to assess safety will be the following:

- Drug exposure
- Adverse Events
    - The number and percent of adverse events (AEs) including infusion site reactions.

- The number and percent of infusions associated with one or more AEs that begin during the infusion, up to one hour, 24 hours, 48 hours or within 72 hours after completion of the infusion.
- Adverse reactions, defined as any AE occurring during the infusions or within 72 hours of the infusion completion OR any AE classed as product related.
- Thrombotic events
- Nature, severity, and frequency of AEs (tolerability)
- Suspected unexpected serious adverse reactions (SUSARs), if any

- Vital signs
- Clinical laboratory tests including tests for hemolysis
- Transmission of viruses
- Physical examination

13.1 Extent of Exposure

The duration of exposure will be expressed as the time in days from the first infusion of Subgam-VF through to the Follow-up visit at week 27 (inclusive). Duration will also be expressed categorically in months, where a month is defined as a calendar month.

The actual dose in mg/kg, based on the total volume infused and body weight, will also be calculated at each infusion.

Duration of infusion will also be summarized for each infusion. A summary of the number of subjects exposed and the total duration of exposure across all subjects will also be presented by infusion dose category (categories to be defined following review of data), age group and gender, and race.

13.2 Adverse Events (AEs)

Although all AEs will be listed, summary tables will be based on treatment emergent adverse events (TEAE), defined as those with onset between first infusion date and 28 days after the last infusion.

An overall summary of TEAEs will show the number and percent of subjects who report any TEAE, any study drug related TEAE, any serious TEAE, any study drug related serious TEAE, and any TEAE leading to discontinuation. The 2-sided 95% exact confidence intervals for the incidence in each of the categories will be calculated and expressed as a percent. Tables will be presented for the pediatric subgroups in addition to all subjects, all adults and all pediatric subjects.

The number and percent of infusions associated with one or more AEs (irrespective of causality) that occur during the infusion or within 72 hours after completion of the infusion will be calculated. A 1-sided 95% upper confidence bound for this percent will be derived. If the upper bound is less than 40%, excluding local infusion site reactions, the incidence of infusion-related AEs associated with Subgam-VF will be considered acceptable. In addition, the number and percent of subjects who report any AEs and the number and percent of subjects who report any AEs at least possibly related to Subgam-VF will be calculated, and the upper bound of the 95% confidence interval for the percentages will be presented. Tables will be presented for the pediatric subgroups in addition to all subjects, all adults and all pediatric subjects.

The overall incidence of TEAEs (number and percent of subjects reporting an event, and the number of events) will be summarized by system organ class (SOC) and preferred term (PT). This summary will be repeated showing only events occurring in ≥5% of all subjects.

The number and percent of subjects with TEAEs at each infusion will be presented by the most recent infusion number for each infusion schedule. These summaries will be by SOC and PT and will summarize all events, all product related events and all events not product related. Events will be associated with an infusion if they begin during the infusion or within 72 hours after the completion of the

infusion. Product related events include all events that were possible, probable or very likely/certain related to study drug.

The number and percent of subjects with product related TEAEs, and the corresponding number of events, will be summarized by SOC and PT.

The number and percent of subjects with AEs that occur during an infusion will be summarized overall and by the infusion rate at which the AEs are reported. If necessary, the infusion rate will be grouped into different levels. The number and percent of subjects with AEs that occur during an infusion will also be summarized by the number of infusion sites, and by the location of infusion (home or clinic).

In addition, the number and percent of subjects with AEs occurring within 1, 24, 48, 72 and over 72 hours after infusion completion will also be summarized by SOC and PT. This summary will be repeated for product related events.

The number and percent of subjects with AEs will be summarized by maximum intensity and strongest study drug relationship. If more than 1 AE is recorded for a subject within any SOC or PT, the subject will be counted only once at the worst severity or strongest relationship.

The number and percent of subjects with serious TEAEs and product related serious TEAEs will be summarized by SOC and PT. In addition, non-serious, product related TEAEs will also be summarized. Tables will be presented for the pediatric subgroups in addition to all subjects, all adults and all pediatric subjects.

The number and percent of subjects with suspected unexpected serious adverse reactions (SUSARs) will be summarized by SOC and PT. To assess 'expectedness', all AE will be reviewed to determine whether event meets the definition of "unexpected," based on whether the event is listed in the Investigator's Brochure. Unexpected AE will be identified prior to database lock for data summarization.

Listings will be provided for all AEs, AEs temporally associated with infusion (events beginning during the infusion or within 72 hours after the completion of the infusion), SAEs, SUSARs and AEs resulting in discontinuation.

Infusion site reactions will be listed and summarized. The Investigator will determine if these should be recorded as AEs. Infusion site reactions will be recorded as AEs when the symptoms/signs lead to infusion stop, require concomitant medication, or have an impact on the general condition of the subject as judged by the Investigator.

FDA Specified AE Table: The AE table as specified below will also be presented.

Adverse reactions are defined as treatment emergent adverse events which meet any of the following criteria:

(a) adverse events which begin during an infusion of Subgam-VF or within 72 hours of the end of an infusion,

(b) adverse events considered by the investigator to be possibly, probable, or very likely/certain related to administration of Subgam-VF,

(c) adverse events for which the investigator's causality assessment was either missing or indeterminate. The above defined adverse reactions, sorted by preferred term based on Intent-to-Treat, will be summarized in two columns: 1) Number and percent of subjects experiencing the AE using total number of subject as denominator. 2) Number and percent of events using total number of infusion as denominator.

13.3 Vital Signs

Vital signs tables will show summaries for all ages combined, all pediatrics (2 to 15 years of age) and adults (16 years and over).

Descriptive statistics for vital signs (absolute values and change from baseline) will be presented for each study visit. Descriptive statistics for percent change from pre-infusion value will be presented at each of the post-infusion measurements for the following vital signs: blood pressure (diastolic and systolic), pulse rate, respiration rate and temperature. Since each subject has multiple infusions throughout the study,

the average change over all infusions for each subject will first be calculated, so that the descriptive statistics will summarize the mean change over all infusions for each subject. The pre-infusion value at each infusion will be the average of the measurements recorded at 10 minutes prior to infusion, and at infusion start.

13.4 Clinical Laboratory Evaluations, Tests for Markers of Hemolysis and Viral Transmission Tests

All summaries of laboratory data will be based on the Intent-to-Treat population. Tables will be subset for all pediatrics (2 to 15 years of age) and adults (16 years and over). Tables will also show summaries for all ages combined.

Descriptive statistics and change from baseline values will be provided for biochemistry and hematology results at each visit. The baseline value for each parameter is defined as the last result prior to the first infusion (usually collected on Day 1).

Summaries of urinalysis will be split by type of result: continuous or categorical. For categorical results (e.g., dipstick tests), the table will display the number and percent of subjects with the given result at the specified visit. Continuous results will be summarized as described above for biochemistry and hematology.

Results of tests for markers of hemolysis (Direct Coombs' test, haptoglobin, plasma free haemoglobin and urine hemoseridin) will be summarized by the number and percent of subjects with the given result at each visit. Percentages will be based on the number of subjects in the ITT population for the given infusion schedule. Two additional listings will be produced:

1) showing all the above values, and those for serum bilirubin and LDH, for visits in which at least one of the parameters is indicative of hemolysis.
2) showing absolute haemoglobin, change from baseline, and Direct Coombs' tests at each visit

Viral transmission test results will be summarized as described above for the markers of hemolysis test results. In addition, a shift table will show changes from baseline to end of study for each test. The shift table will be subset by age only and percentages will be calculated from the number of subjects with the given result at baseline.

13.5 Physical Examination

Physical examination tables will be subset for all pediatrics (2 to 15 years of age) and adults (16 years and over). Tables will also show summaries for all ages combined.

The number and percent of subjects with assessments of normal, abnormal or not done at screening will be displayed in a summary table for each body system. At each post screening assessment the number and percent of subjects with assessments of no change, normal, abnormal or not done will also be displayed in a summary table for each body system. Percents will be calculated out of the number of subjects with results at a given visit (including assessments indicated as not done).

The end of study assessment will be tabulated against the screening assessment for each body system in a shift table. Percentages will be calculated from the number of subjects with the given result at Screening.

Summary of physical examination results will be based on the Intent-to-Treat population.

13.6 Thromboembolic Events

Monitoring for thromboembolic events (TEEs) will be performed at screening (baseline) and at the Week 27 follow up visit (as well as when clinically indicated); TEEs will be listed.

14. PHARMACOKINETIC ANALYSES

PK analyses are not included in this SAP but documented separately in a PK Analysis Plan. Only the following listings and tables are included in this SAP:

- Listing of IgG levels (trough levels, serial IgG levels at the PK assessment), IgG subclasses, IgA, IgM and antibodies by subject.

- Trough levels of total IgG, IgG subclasses and IgG antibodies to specific antigens will be summarized descriptively for all the subjects in the ITT group. Tables will be presented for the pediatric subgroups in addition to all subjects, all adults and all pediatric subjects. Trough levels will be compared with those collected at the Screening visit.

15. DEVIATIONS FROM THE PROTOCOL SPECIFIED ANALYSIS

There are no deviations from the protocol specified analysis.

16. REFERENCES

[1] FDA guidance, Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (Jun 2008)

[2] EMEA Committee for Proprietary Medicinal Products. Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIG). London; 6 Feb 2009, CPMP/BPWG/388.95 rev. 2.