

CLINICAL STUDY PROTOCOL

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

Protocol Number	SCIG03
Date	22 March 2017
Version	6
Name of Investigational Product	Subgam-VF
Name and Address of Sponsor	Bio Products Laboratory Limited (Ltd.) Dagger Lane, Elstree Hertfordshire, WD6 3BX, UK.
IND No.	Tel: +44 (0) 20 8957 2200 15599

SIGNATURES

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

Protocol Number: SCIG03
IND No.: 15599
EudraCT Number: N/A

I have carefully read this protocol and I confirm that it contains all the necessary information to perform the study. This study is to be conducted in accordance with the protocol, ICH GCP and applicable regulatory requirements.

Sponsor's Representative

Eric Wolford
Vice President, Global Medical
Bio Products Laboratory Ltd
Dagger Lane,
Elstree
Hertfordshire,
WD6 3BX,
U.K.


Signature

28-3-2017
Date

SPONSOR'S RESPONSIBLE MEDICAL OFFICER

Name: Dr Elizabeth Holmes
Title: Chief Medical Officer
Address: Bio Products Laboratory Ltd,
Dagger Lane,
Elstree,
Hertfordshire
WD6 3BX, UK

VERSION HISTORY

Version	Date	Changes
Version 3	19 March 2015	First version approved by regulatory and IRBs (not implemented in any region)
Version 4	29 June 2015	Amendment to: <ul style="list-style-type: none"> • Add measles testing at follow up visit. • Clarify adverse event reporting for infusion site reactions (section 10.3).
Version 5	28 April 2016	<ul style="list-style-type: none"> • Correction to analysis of adverse events • Increase in maximum number of subjects, to allow flexibility in enrolment during the trial. • Clarification of the pharmacokinetic assessments to be performed. • Updates in line with protocol clarification letters • Updates or clarifications of study assessments / procedures • Allowance for a PK sample to be taken the week following the PK assessment if required • Minor changes to the safety analyses • Administrative changes
Version 6	22 March 2017	<ul style="list-style-type: none"> • Change in Chief Medical Officer at BPL • Number of pediatric subjects updated in line with updated Pediatric Study Plan. • Update to statistical analysis populations • Clarification of the definition of an adverse reaction • Update to the pharmacokinetic analysis Re-emphasis on infusion timing prior to PK sampling.

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Table 2 Schedule of Assessments

Table 3 Pharmacokinetic Assessment Schedule for Subgam-VF (Week 21 to Week 22)

Table 4 IRB Maximum Allowable Total Blood Draw Volumes (Clinical + Research)

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AEs	Adverse Events
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
Anti-D	Anti-D immunoglobulin
AST	Aspartate Transaminase
AUC	Area under the curve
AUC _(0-τ)	Area under the plasma concentration-time curve of the dosing interval
sAUC _(0-τ)	Area under the plasma concentration-time curve of the dosing interval standardized to one week
BMI	Body Mass Index
BPL	Bio Products Laboratory Limited (Ltd.) (the Sponsor and manufacturer)
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CL	Systemic clearance (PK)
C _{max}	Maximum concentration in plasma
CFR	Code of Federal Regulations
CRO	Contract Research Organization
Cryo-Store	Archive Facility for Laboratory Samples
CV	Coefficient of Variation
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food & Drug Administration
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Immunoglobulin Intravenous
IgM	Immunoglobulin M
IMP/IP	Investigational Medicinal Product / Investigational Product (EU / US)
IRB	Institutional Review Board
ITT	Intent-To-Treat (population)
IV	Intravenous
LDH	Lactate Dehydrogenase

MOsmol	MilliOsmolae
mL	Milliliter
NAT	Nucleic acid Amplification Test (PCR)
PA	Posterior-Anterior
PaO ₂	Partial pressure of Oxygen in arterial blood
PCR	Polymerase Chain Reaction
PID	Primary Immunodeficiency Diseases
PK	Pharmacokinetic
PVC	Polyvinyl Chloride
RNA	Ribosenucleic Acid
SAE	Serious Adverse Event
SC	Subcutaneous
SCIG	Subcutaneous IgG
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE(s)	Treatment-emergent Adverse Event(s)
TEE	Thrombo-embolic events
t _{max}	Time to reach the maximum concentration in plasma
UK	United Kingdom
US	United States

3. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Bio Products Laboratory Ltd. (BPL) Dagger Lane, Elstree Hertfordshire, WD6 3BX. UK.	Name of Manufacturer: Bio Products Laboratory Ltd. (BPL) Dagger Lane, Elstree Hertfordshire, WD6 3BX. UK.
Name of Finished Product: Subgam-VF	Protocol identification code: SCIG03
Name of Active Ingredient: Immune Globulin (Human)	Protocol Synopsis version and date: Version 6, 22 March 2017
Title of study: A Phase III, Multicenter, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subgam-VF in Primary Immunodeficiency Diseases (PID)	
Indication: Primary immunodeficiency diseases	
Study centers: This will be a multicenter study planned for the US, but depending upon the availability of suitable subjects may be extended into other countries.	
Development phase: III	
<p>Objectives:</p> <p>Primary Objective</p> <ul style="list-style-type: none"> To determine the PK profile of Subgam-VF and compare the $AUC_{(0-\tau)}$ with historical AUC data (all standardized to one week at steady state) from Gammalex 5% IGIV PID studies (GMX01 and GMX04). <p>Secondary Objectives</p> <ul style="list-style-type: none"> 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 <p>Exploratory Objective</p> <ul style="list-style-type: none"> To explore PK modelling for alternative dosing schedules. 	
<p>Study design:</p> <p>This will be a Phase III, multicenter, open-label, non-randomized study.</p> <ul style="list-style-type: none"> Following a screening period, eligible subjects will commence weekly Subgam-VF treatment; this is a 16% subcutaneous IgG product. Subjects will receive Subgam-VF for 26 weeks during which time safety will be assessed. After Week 21, PK sampling will commence to measure $AUC_{(0-\tau)}$. The patient populations will be as similar as possible to that of the historical studies (GMX01 and GMX04) as per similar inclusion/exclusion criteria. Comparable methods will be used to determine PK concentrations to that of the historical studies and the AUC measured will be at steady state. Follow-up visit (one week after the last Subgam-VF infusion, Week 27). All AEs will be monitored up to 28 days after the last Subgam-VF infusion by telephone contact (Week 30). The initial weekly dose of Subgam-VF administered will be calculated by taking the average weekly equivalent of the subject's IGIV dose (should be stable, as in same mg/kg +/- 5%), divided by the average dosing interval in weeks (i.e. 3 or 4), multiplied by 1.37, a dose adjustment coefficient based on other licensed subcutaneous IgG products. If the subject was already receiving a weekly SCIG IgG there will be no dose adjustment. Oral and parenteral steroids as concomitant medication are allowed if the average daily dose is < 0.15 mg of prednisone equivalent/kg body weight per day. 	

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<ul style="list-style-type: none"> • Routine premedication to reduce potential adverse effects associated with SCIG infusions are discouraged. Exceptions; <ul style="list-style-type: none"> • Premedication will be permitted if a subject has reported systemic adverse events on two Subgam-VF infusions. • Local anesthetics (e.g. an analgesic cream) can be used before Subgam-VF infusion to reduce the potential pain associated with needle insertion if required. • Subgam-VF will be administered subcutaneously using infusion pumps. • Subjects will be given diaries to record adverse event data as well as any infusions administered at home. In addition there will be a telephone follow up by an appropriately qualified site staff member on day 3 after each site administered and home administered infusion to check for any adverse reactions including infusion site reactions and remind subjects to document these in their subject study diary. 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. 	
<p>Screening/Baseline</p> <p>After informed consent/assent (as appropriate):</p> <p>Screening/baseline – subjects receive their usual dose of IGIV/SCIG and have all safety screening tests performed, including biochemistry, hematology, virology, vital signs and serum IgG trough levels.</p>	
<p>Treatment Period (Weeks 1 to 26)</p> <p>Eligible subjects return 7 days (+/- 1 day) after the Screening/Baseline visit for their first Subgam-VF dose (Week 1 visit). Weekly dosing with Subgam-VF will be administered for 26 weeks during which time safety will be assessed.</p> <p>Week 21 to Week 22: Subjects will undergo PK sampling between two treatment visits to measure $AUC_{(0-\tau)}$ (sample taken pre dose, then at 1, 2, 3, 5 and 7 days post dose, defined as Steady State Day 0, Steady State Day 1, Steady State Day 2, Steady State Day 3, Steady State Day 5, Steady State Day 7). 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.</p> <p>If the subject is not already receiving IgG via the subcutaneous route, it is planned that home infusion will begin on Week 3 (3rd infusion of Subgam-VF), following training by the site during the preceding Subgam-VF visits. However, if the subject requires further assistance this will be provided (i.e. it is not mandatory that the infusions are performed at home).</p> <p>The subject will return to the clinic every four weeks for a safety assessment (haematology, chemistry, pre and post dose vital signs and physical exam). Their regular Subgam-VF infusion will be given whilst the subject is at the clinic and additional Subgam-VF vials will be dispensed. Trough levels will also be measured at the clinic visits.</p>	
<p>Follow-up visit</p> <p>Final safety assessments will be carried out approximately seven days after the final study infusion. All AEs will be monitored up to 28 days after the last Subgam-VF infusion by telephone contact.</p>	

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Name of Finished Product: Subgam-VF	Protocol identification code: SCIG03
Name of Active Ingredient: Immune Globulin (Human)	Protocol Synopsis version and date: Version 6, 22 March 2017
<p>Number of subjects</p> <p>Plan to enroll up to 50 subjects to ensure 30 evaluable subjects. At least 18 enrolled subjects will be adults (16-75 years) and 12 enrolled subjects will be children with a minimum of four enrolled in each of the following age groups: 2-5 years, 6-11 years and 12 to 15 years. All subjects who receive at least one infusion of Subgam-VF will be included in the safety analysis.</p> <p>The total number of subjects (adults plus children) evaluable for PK analysis will be at least 30. Data will be compared to historical data from previous Gammaplex IGIV studies.</p> <p>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%.</p>	
<p>Study variables and criteria for evaluation:</p> <p>Pharmacokinetic Variables</p> <p>The following PK variables for total IgG levels will be determined for the PK population:</p> <ul style="list-style-type: none"> • $AUC_{(0-\tau)}$ - area under the plasma concentration-time curve of the dosing interval; • $sAUC_{(0-\tau)}$ - area under the plasma concentration-time curve of the dosing interval standardized to one week. This will be calculated for the historical data only • C_{max} - maximum concentration in plasma; • t_{max} - time to reach the maximum concentration in plasma; • CL - systemic clearance. <p>The following additional PK variables will also be determined for the ITT population:</p> <ul style="list-style-type: none"> • Trough serum IgG levels (measured before every infusion administered at the study site); • Trough levels of IgG, and IgG subclasses will be measured prior to certain infusions; • Levels of specific antibodies (<i>Haemophilus influenzae</i> B, <i>Streptococcus pneumoniae</i>, <i>Measles</i>) will be measured prior to certain infusions; <p>Safety Variables</p> <p>The variables used to assess safety will be the following: number and percent of adverse events (AEs); adverse reactions, vital signs; clinical laboratory tests and Direct Coombs' Test; markers of virus transmission; physical examination.</p>	
<p>Statistical Methodology:</p> <p>ITT Population:</p> <p>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 the safety analysis.</p> <p>PK Population:</p> <p>This comprises the Subgam PK population (subset of the ITT population) and Gammaplex PK population (from historical Gammaplex 5% IGIV PID studies). In addition, the PK Dose-Adjustment population is the subset of the PK population</p>	

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<p>which excludes subjects in the Subgam PK population who had prior treatment with another subcutaneous weekly IgG product.</p> <p>Safety: The number and percent of infusions with at least one adverse event (AE), irrespective of causality, that occurs 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%, <u>excluding local infusion site reactions</u>, 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. AEs occurring during the infusion and within 1, 24, 48 and 72 hours after the infusion completion will also be summarized.</p> <p>AEs that occur during an infusion will be summarized by the infusion rate at which the AEs are reported. If necessary, infusion rates will be grouped into different levels.</p> <p>Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be summarized with all AEs, and separate listings will be provided for SAEs and SUSARs.</p> <p>All other safety assessments will be summarized descriptively for each treatment group.</p> <p>An adverse reaction will be defined as any TEAE (irrespective of causality) that occurs during the infusion or within 72 hours after completion of the infusion, any AE classed as product related or any AE with unknown causality.</p>	
<p>Pharmacokinetics: The pharmacokinetics (PK) of Subgam-VF will be described by using a non-compartmental method. The trough levels of total IgG will be summarized descriptively for all the Intent-to-Treat (ITT) subjects and compared with historical data for Gammaplex 5%. Pharmacokinetic variables will be summarized descriptively. The primary PK parameter will be $sAUC_{(0-\tau)}$.</p> <p>All PK parameters will be calculated based on absolute (uncorrected) and baseline-adjusted (i.e. trough-adjusted at steady state) concentrations.</p>	
<p>IgG subclasses and IgG antibodies: The trough levels of IgG subclasses and IgG antibodies against specified antigens will be summarized descriptively for all the Intent-to-Treat (ITT) subjects.</p>	
<p>Primary Statistical Analysis Data will be pooled with historical data and a treatment variable defined (Subgam-VF or Gammaplex IGIV). Log transformed $sAUC_{(0-\tau)}$, ($AUC_{(0-\tau)}$ standardized to one week) will be analyzed using a mixed model fitted including treatment, and allowing for variability to be different between treatment groups. The mean difference (Subgam-VF or Gammaplex IGIV) between treatments with 90% Confidence Interval (CI) will be back transformed to give an estimate of the ratio (Subgam-VF/ Gammaplex IGIV) of $sAUC_{(0-\tau)}$. If the resulting 90% CI for the ratio lies within the equivalence limit of</p>	

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Name of Finished Product: Subgam-VF	Protocol identification code: SCIG03
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<p>(0.80, 1.25), it will be concluded that there is equivalence in $sAUC_{(0-\tau)}$ and thus the dosing factor of 1.37 for Subgam-VF (in addition to the adjustment for dosing interval) gives equivalent exposure at steady state to Gammalex IGIV.</p> <p>Secondary Statistical Analyses</p> <ol style="list-style-type: none"> The primary analysis method will be repeated with data derived from baseline-adjusted concentrations. A term for dosing interval within treatment will be included in the model described in the primary analysis so that ratios with 90% CI can be presented for Subgam-VF relative to both the 21 day and 28 day dosing interval regimens of Gammalex. The primary analysis model will be extended to include any significant (at the 10% level) covariates or covariate by treatment interactions. Covariates considered for inclusion will include age category, weight, BMI and sex. The effect of previous treatment (SCIG or IGIV) on $AUC_{(0-\tau)}$ in the Subgam PK population will be analysed. If the resulting 90% CI for the ratio lies within the equivalence limit of (0.80, 1.25), it will be concluded that the previous treatment does not affect exposure at steady state. If this is the case then the refined dose adjustment with 90% CI will be presented on the full PK population (in addition to on the PK Dose Adjustment population described below). In addition, the data from the current study will be restricted to a PK Dose Adjustment population and analysed as per the primary analysis. A refined dose adjustment will be estimated as 1.37/the ratio (Subgam-VF / Gammalex IGIV) of geometric means for $sAUC_{(0-\tau)}$ and presented with 90% CI. <p>Exploratory Analysis</p> <p>PK modelling will be performed to explore alternative dosing schedules.</p>	
<p>Subject selection criteria:</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> Aged between 2 and 75 years (at time of initial consent). Body Mass Index (BMI) < 46 for adults (aged 16 years and older), and BMI < 28 for children. Diagnosed with primary immunodeficiency disease e.g. common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinaemia, hyper-IgM syndrome, Wiskott-Aldrich syndrome. Currently receiving a licensed (or investigational stage III, IIIb) IGIV or SCIG and <ol style="list-style-type: none"> IGIV dose is between 300 and 800 mg/kg/month. SCIG dose is between 110 and 300 mg/kg/week; Dose is stable for at least the past three months (i.e. consistent mg/kg +/- 5%); The infusion interval is every 21 or 28 days for IGIV and seven days for SCIG; Has a documented trough level of ≥ 6 g/L (600 mg/dL) on current IgG therapy. If not available can be obtained at the screening visit, Visit 1 (Week 0). Female subjects who are (or become) sexually active must practice contraception by using a method of proven reliability for the duration of the study. Females of child-bearing potential, (defined from the onset of menstruation to one year post menopause), must have a negative result on a urine HCG-based pregnancy test. Willing to comply with all aspects of the protocol, including blood sampling, for the duration of the study. Signed an informed consent form. In the case of subjects under the legal age the parent/guardian will sign an informed consent form and where appropriate the subject will sign an assent form. 	

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Name of Finished Product: Subgam [®] VF	Protocol identification code: SCIG03
Name of Active Ingredient: Immune Globulin (Human)	Protocol Synopsis version and date: Version 6, 22 March 2017
<p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1) Has a history of any severe anaphylactic reaction to blood or any blood-derived product. 2) Has selective IgA deficiency or has a history of antibodies to IgA. 3) Has clinically significant impairment of cellular or innate immunity at the discretion of the Investigator 4) Has evidence of an active infection at the time of enrolment (i.e. on day of first infusion). Subjects who are asymptomatic but have not completed their course of antibiotics are eligible. 5) Has previously completed or withdrawn from this study. 6) Is currently receiving, or has received, any investigational agent within the prior three months, unless it is an investigational stage III, IIIb IGIV or SCIG. 7) Is pregnant (confirmed by a positive result on an HCG-based pregnancy test) or is nursing. 8) Is positive for any of the following at screening: <ul style="list-style-type: none"> • Serological test for HIV 1&2, HCV, or HBsAg 9) Has levels at screening greater than 2.5 times the upper limit of normal as defined at the central laboratory of any of the following: <ul style="list-style-type: none"> • Alanine transaminase (ALT) • Aspartate transaminase (AST) 10) Has severe renal impairment (defined as serum creatinine greater than two times the upper limit of normal or BUN greater than two times the upper limit of normal for the range of the laboratory doing the analysis); the subject is on dialysis; or has a history of acute renal failure. 11) Is known to abuse alcohol, opiates, psychotropic agents, or other chemicals or drugs, or has done so within the past 12 months. 12) Has a history of DVT, or thrombotic complications of IgG therapy, or a prior diagnosis of thrombophilia. 13) Suffers from any acute or chronic medical condition, (e.g. renal disease or predisposing conditions for renal disease, coronary artery disease, or protein losing state, proteinuria) that the Investigator feels may interfere with the conduct of the study. 14) Has an acquired medical condition, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (ANC < 1 x 10⁹/L). 15) Is receiving the following medication: <ul style="list-style-type: none"> • Steroids (long-term daily, ≥ 0.15 mg of prednisone equivalent/kg/day). Requirement for short or intermittent courses of > 0.15mg/kg/day would not exclude a subject. • Immunosuppressive drugs • Immunomodulatory drugs 16) If ≥ 18 years of age, has non-controlled arterial hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg). For younger subjects refer to current guidelines for diagnosis of blood pressure¹. 17) Has anemia (hemoglobin < 10 g/dL) at screening. 18) Has severe dermatitis that would preclude sites for safe product administration. <p>1. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004 Aug;114 (Suppl 2:) 555-76.</p>	
<p>Test product, dose/mode of administration, batch number(s)</p> <p>Subgam-VF is a 16% IgG and will be administered weekly, by subcutaneous infusion:</p> <ul style="list-style-type: none"> • The initial weekly dose of Subgam-VF administered will be calculated by taking the average weekly equivalent of 	

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<p>the subject's IGIV dose (should be stable, as in same mg/kg +/- 5%), multiplied by 1.37, a dose adjustment coefficient based on other licensed subcutaneous IgG products. If the subject was already receiving a weekly SCIG IgG there will be no dose adjustment.</p> <p>It is planned to use one batch of Subgam-VF in this study. Additional batches may be used if required. The following infusion rates will be followed.</p> <p>Subgam-VF infusions will be administered in accordance with the table below:</p>										
<p>Table 1 Volume and Rate of Subgam-VF infusions</p> <table border="1"> <thead> <tr> <th></th> <th>Volume</th> <th>Rate</th> </tr> </thead> <tbody> <tr> <td>First infusion</td> <td>20 mL/site</td> <td>20 mL/hr/site</td> </tr> <tr> <td>Maximum at subsequent infusions</td> <td>Up to 30 mL/site</td> <td>Up to 30 mL/hr/site</td> </tr> </tbody> </table>			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
	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								
<ul style="list-style-type: none"> Up to 6 infusion sites can be used simultaneously. Subjects weighing ≥ 100 kg may use up to 8 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. However, the infusions must be administered at the volume and rate outlined in Table 1 throughout the entire infusion. Titration during the infusion is not allowed. For young children or adults of below average weight, lower flow rates may be used, depending on tolerability. 										
<p>Duration of treatment: The total duration of treatment will be for 26 weeks.</p>										
<p>Compliance Statement This trial will be conducted in accordance with the protocol, EU Clinical Trial Directives 2001/20/EC and 2005/28/EC and applicable local regulatory requirements.</p> <p>The study will be performed in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and in accordance with ICH GCP guidelines, European Union (EU) Directives 2001/20/EC, 2005/28/EC and United States Title 21 Code of Federal Regulations (CFR) as well as the demands of national drug and data protection laws, other applicable regulatory requirements, and any new directives or regulations that become enforceable during the course of the study.</p>										

4. INTRODUCTION

4.1. Background

The primary immunodeficiency diseases are a heterogeneous group of disorders in which there is an intrinsic defect in the tissues, cells, and/or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinemia and/or defective antibody production and, as a consequence, increased susceptibility to infection.

Replacement therapy with immunoglobulin G (IgG) purified from pools of plasma from multiple donors has been used since the early 1950s. The initial products were administered intramuscularly, but were of limited efficacy because of the relatively small quantities that could be administered by that route. Beginning in the 1980s, intravenous immunoglobulin (IGIV) became available in the United States (US) and had become the main choice of treatment in the US^{3,4,5}.

Subgam-VF is a newly developed, highly purified, unmodified human immunoglobulin G (IgG) product intended for subcutaneous (SC) administration, and is manufactured by Bio Products Laboratory Ltd., (BPL), UK. The target indication is the treatment of primary immunodeficiency states, such as congenital agammaglobulinemia, common variable immunodeficiency, and X-linked agammaglobulinemia.

Subgam-VF is manufactured from plasma from healthy US donors who are subjected to medical examinations, laboratory tests, and a review of their medical history before being allowed to donate plasma by apheresis. Each donation must be non-reactive for hepatitis B surface antigen (HBsAg), anti-HIV-1 and HIV-2 antibodies, and anti-HCV antibodies. Furthermore, plasma minipools (512 donations per pool) undergo nucleic acid amplification (NAT) testing for HIV, HBV, HCV, HAV, and parvovirus B19. Manufacturing pools are tested for HBsAg and HIV antibodies; HIV, HBV, HCV, HAV and parvovirus B19 are also tested using NAT.

Subgam-VF is a ready-prepared solution for SC administration that contains per mL 0.16 g IgG⁶. Immunoglobulin G purity reaches 100%, the pH is typically 6.6 to 6.8 but in the range of 6.4 to 7.2, and osmolality is not less than 240 mOsmol/kg. The immunoglobulins present are virtually 100% IgG, and the distribution of the four IgG subclasses is approximately 64% IgG₁, 30% IgG₂, 5% IgG₃, and 1% IgG₄. The content of IgA is lower than 50 µg/mL. The Anti-A, Anti-B and Anti-D content of the final product is monitored and controlled to specification.

Subgam-VF was developed from BPL's SCIG product, Subgam[®], and introduces a 20nm virus filtration processing stage common to BPL's IGIV product, Gammalex[®], which was licensed in the UK and US in 2009. Subgam[®] is also licensed in Cyprus since 2007 and Columbia from 2009. Subgam-VF is manufactured by using an identical process to that for Gammalex, apart from an increase in IgG concentration at the end of processing to allow for subcutaneous administration. Subgam-VF contains the same active protein as the licensed IgG product, Gammalex, but differs in terms of concentration (16% and 5% respectively). In addition Subgam-VF is glycine based compared with Gammalex which is sorbitol based. The efficacy of Gammalex has been investigated in prior studies therefore a PK and safety study will be performed with Subgam-VF and compared with historical Gammalex data, as the two products are essentially identical apart from their relative concentrations, excipients and route of delivery.

4.2. Clinical trial data

Subgam[®], the precursor non-virus filtered product to Subgam-VF, has been evaluated in a Phase III efficacy study involving 50 pediatric and adult subjects with Primary Immunodeficiency Disease. The primary efficacy outcome to achieve target IgG trough levels over a minimum of 12 months was met; 85% of adults/teenagers and 93% of children achieved target serum IgG levels at all observation time points. Subgam[®] was safe and well tolerated during the study. There were 82 reports of infusion site reactions in 25 of the 50 patients. The most common product-related adverse events were headache (8 reports in 7 patients), pruritus (7 reports in 2 patients) and vomiting (5 reports in 3 patients). There were no withdrawals due to adverse events or safety considerations and no product-related SAEs⁶.

Since licensure in the UK 2004 till 31 May 2014 BPL has received a total of 34 spontaneous reports of product-related adverse events (20 non-serious and 14 serious). There have been no reports of virus transmission.

There is no clinical trial data currently available on Subgam-VF.

4.3. Benefit / Risk Statement

Published data has shown that subcutaneous IgG (SCIG) use in subjects with PID provides protection which is comparable to that found with IGIV therapy^{7,8,9,10}.

Infusions of IgGs given subcutaneously (SCIG) were initially used in patients who were unable to tolerate IgG administered either through intravenous (IV) or intramuscular (IM) routes¹⁰. SCIG has the advantage in that it can be self-administered at a time and location more suitable to the individual and without the need for assistance from a trained professional (other than during the initial training period). This convenience has been associated with an improvement in quality of life^{11,12}.

This form of infusion requires no venous access. Unlike IGIV which is infused directly into the intravascular compartment, SCIG must diffuse first into the lymphatic system and is then

subsequently carried into the blood stream via the thoracic duct^{8,13,14,15}, therefore with SCIG the intravascular concentration of IgG increases more gradually, peaking at 48-72 hours. The rate IgG enters the circulation appears to be the main driver of systemic tolerability and as such the incidence of systemic adverse events appears to be much lower with SCIG therapy¹³ than with IV infusion. Also division of the dose into weekly fractions produces more consistent IgG levels without the peaks and troughs experienced with monthly IGIV infusions. However, with SCIG therapy because some of the IgG is already equilibrating into the extracellular fluid before all of the IgG has entered the bloodstream; and also due to binding and/or degradation of the IgG in subcutaneous tissue, the maximum serum concentration of IgG can be on average 61% of the level achieved with IGIV^{16,17,18}.

As with any blood product, viral safety is a concern. Subgam-VF undergoes a stringent multi-step process, including solvent/detergent treatment, nanofiltration, and a terminal low pH incubation of the finished product, to reduce the risk of potential viral contaminants and enhance the safety of the product.

5. STUDY OBJECTIVES

5.1. *Primary Objective*

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

5.2. *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

5.3. *Exploratory Objective*

- To explore PK modelling for alternative dosing schedules.

6. STUDY POPULATION

6.1. *Inclusion Criteria*

In order to qualify for entrance into the study, each subject must satisfy all criteria listed below:

1. Aged between 2 and 75 years old (at time of initial consent)
2. Body Mass Index (BMI) < 46 for adults (aged 16 years and older), and BMI < 28 for children.
3. Diagnosed with primary immunodeficiency disease e.g. common variable immunodeficiency, X-linked and autosomal forms of agammaglobulinaemia, hyper-IgM syndrome, Wiskott-Aldrich syndrome.

4. Currently receiving a licensed (or investigational stage III, IIIb) IGIV or SCIG and
 - a. IGIV dose is between 300 and 800 mg/kg/month. SCIG dose is between 110 and 300 mg/kg/week;
 - b. Dose is stable for at least the past three months (i.e. consistent mg/kg +/- 5%);
 - c. The infusion interval is every 21 or 28 days for IGIV and seven days for SCIG;
 - d. Has a documented trough level of ≥ 6 g/L (600 mg/dL) on current IgG therapy. If not available can be obtained at the screening visit, Visit 1 (Week 0).
5. Female subjects who are (or become) sexually active must practice contraception by using a method of proven reliability for the duration of the study
6. Females of child-bearing potential, (defined from the onset of menstruation to one year post menopause), must have a negative result on a urine HCG-based pregnancy test
7. Willing to comply with all aspects of the protocol, including blood sampling, for the duration of the study
8. Signed an informed consent form. In the case of subjects under the legal age the parent/guardian will sign an informed consent form and where appropriate the subject will sign an assent form.

6.2. Exclusion Criteria

Subjects will be excluded if any of the following exclusion criteria are met:

1. Has a history of any severe anaphylactic reaction to blood or any blood-derived product.
2. Has selective IgA deficiency or has a history of antibodies to IgA.
3. Has clinically significant impairment of cellular or innate immunity at the discretion of the Investigator.
4. Has evidence of an active infection at the time of enrolment (i.e. on day of first infusion). Subjects who are asymptomatic but have not completed their course of antibiotics are eligible.
5. Has previously completed or withdrawn from this study.
6. Is currently receiving, or has received, any investigational agent within the prior three months unless it is an investigational stage III, IIIb IGIV or SCIG.
7. Is pregnant (confirmed by a positive result on an HCG-based pregnancy test) or is nursing.
8. Is positive for any of the following at screening:

- Serological test for HIV 1&2, HCV, or HBsAg
9. Has levels at screening greater than 2.5 times the upper limit of normal as defined at the central laboratory of any of the following:
 - Alanine transaminase (ALT)
 - Aspartate transaminase (AST)
 10. Has severe renal impairment (defined as serum creatinine greater than two times the upper limit of normal or BUN greater than two times the upper limit of normal for the range of the laboratory doing the analysis); the subject is on dialysis or has a history of acute renal failure.
 11. Is known to abuse alcohol, opiates, psychotropic agents, or other chemicals or drugs, or has done so within the past 12 months.
 12. Has a history of DVT, or thrombotic complications of immunoglobulin therapy, or a diagnosis of thrombophilia.
 13. Suffers from any acute or chronic medical condition (e.g. renal disease or predisposing conditions for renal disease, coronary artery disease, or protein losing state, proteinuria) that the Investigator feels may interfere with the conduct of the study.
 14. Has an acquired medical condition, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia ($ANC < 1 \times 10^9/L$).
 15. Is receiving the following medication:
 - Steroids (long-term daily, ≥ 0.15 mg of prednisone equivalent/kg/day). Requirement for short or intermittent courses of > 0.15 mg/kg/day would not exclude a subject.
 - Immunosuppressive drugs
 - Immunomodulatory drugs
 16. If ≥ 18 years of age, has non-controlled arterial hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg). For younger subjects refer to current guidelines for diagnosis of blood pressure¹.
 17. Has anemia (hemoglobin < 10 g/dL) at screening.
 18. Has severe dermatitis that would preclude sites for safe product administration.

1. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004 Aug;114 (Suppl 2): 555-76.

7. STUDY DESIGN AND PLAN

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 adults¹ (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), with a minimum of 4 in each age group.

All children who receive at least one infusion of Subgam-VF will be included in the safety analysis. Due to the potential for early withdrawals, PK data may not be available on all 12 children and there may be fewer than 12 evaluable children in the PK analysis. The total number of subjects (adults plus children) evaluable for PK analysis will be at least 30.

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.

All subjects will undergo a pharmacokinetic (PK) profile after the 21st infusion of Subgam-VF (see PK Assessment Schedule, Table 3). Where an appropriately qualified member of the study team is available, arrangements will be made to collect the PK samples from Steady State Day 1 (24 hours post-infusion) onwards at the subject's home to reduce the number of visits to the sites. 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 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 sample.

In the case of younger children it is important not to exceed the maximum blood withdrawal volumes stated in Appendix V. Therefore smaller volumes of blood will be taken. See the Laboratory Manual for details.

- Following a screening period, eligible subjects will commence weekly Subgam-VF treatment; this is a 16% subcutaneous IgG product.
- Subjects will receive Subgam-VF for 26 weeks during which time safety will be assessed

¹ *The definition of an adult as ≥ 16 years is as per the FDA guidance for PK studies². Note this does not affect the requirements for consent/assent, for which each site should follow their IRB guidelines.*

- After Week 21, PK sampling will commence to measure $AUC_{(0-\tau)}$ over 7 days.
- The patient populations will be as similar as possible to that of the historical studies (GMX01 and GMX04) as per similar inclusion/exclusion criteria.
- Comparable methods will be used to determine PK concentrations to that of the historical studies and the AUC measured will be at steady state.
- Follow-up visit Week 27 (one week after the last Subgam-VF infusion).
- Follow-up telephone call Week 30 (four weeks after the last Subgam-VF infusion).
- The initial weekly dose of Subgam-VF administered will be calculated by taking the average weekly equivalent of the subject's IGIV dose (should be stable, as in same mg/kg +/- 5%), multiplied by 1.37, a dose adjustment coefficient based on historical data for other subcutaneous IgG products. If the subject was already receiving a weekly SCIG IgG there will be no dose adjustment.
- Oral and parenteral steroids as concomitant medication are allowed if the average daily dose is < 0.15 mg prednisone equivalent/kg body weight per day. Short or intermittent courses of > 0.15 mg/kg/day are allowed if required.
- Routine premedication to reduce potential adverse effects associated with SCIG infusion are discouraged. Exceptions:
 - Premedication will be permitted if a subject has reported systemic adverse events on two Subgam-VF infusions.
 - Local anesthetics (e.g. an analgesic cream) can be used before any Subgam-VF infusion to reduce the potential pain associated with needle insertion if required.
- Subgam-VF will be administered subcutaneously using infusion pumps.
- Subjects will be given diaries to record adverse event data as well as any infusions administered at home.

7.1. Study Visits

For details of which procedure will be performed at any specific visit, see the schedule of assessments (Table 2) in Appendix IV.

Screening/Baseline

After informed consent/assent (as appropriate):

- Screening/baseline – subjects receive their usual dose of IGIV/SCIG and have all safety screening tests performed, including biochemistry, hematology, virology, vital signs and serum IgG trough levels.

Treatment Period (Weeks 1 to 26)

- Eligible subjects then return seven days (+/- 1 day) after the Screening/Baseline visit for their first Subgam-VF dose (Week 1 visit). Weekly dosing will be administered for 26 weeks during which time safety will be assessed. Site visits (Weeks 1, 2, 5, 9,

13, 17, 21, 22 and 26) – subjects will attend the clinic at specific points and they will receive their Subgam-VF infusion at the clinic. There will also be routine safety assessments, which will include blood sampling. After the Week 2 visit and if an appropriately qualified member of the study team or the subject's carer 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 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.

- If the subject is not already receiving IgG via the subcutaneous route, following training by the site during the preceding Subgam-VF visits it is planned that home infusions will begin on Week 3 (3rd infusion of Subgam-VF). For home infusions, subjects (or care givers) will infuse Subgam-VF themselves and will record any concomitant medications, date and time of any adverse events (including inspecting the infusion site for reactions) and record details of their Subgam-VF dose. If the subject requires further assistance this will be provided (i.e. it is not mandatory that these infusions are performed at home).
- There will be a telephone follow up by an appropriately qualified site staff member on day 3 after each site administered and home administered infusion to check for any adverse reactions including infusion site reactions and remind subjects to document these in their subject study diary. 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.
- The subject will return to the clinic every four weeks for a safety assessment (hematology, chemistry, pre and post dose vital signs and physical exam). Their regular Subgam-VF infusion will be given whilst the subject is at the clinic and additional Subgam-VF vials will be dispensed. IgG trough levels will also be measured at the clinic visit every four weeks.
- PK sampling – This will occur on Week 21 (defined as Steady State Day 0 to 7), and will continue over the subsequent seven days to allow calculation of AUC (see the PK schedule, Table 3, Appendix IV). 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. All PK blood samples will be taken at the study site. However, if an appropriately qualified member of the study team is available, arrangements to collect the remaining PK samples from Steady State Day 1 onwards at the subject's home could be made, to help reduce the number of visits to the sites. Alternatively a Home Health Agency may be utilized to take the PK samples outside of the investigational site.

- In exceptional circumstances, and with prior Sponsor approval, if one of the following PK samples is 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 \pm 2 hours)
 - 2 days (48 hours \pm 4 hours)
 - 3 days (72 hours \pm 6 hours)
 - 5 days (120 hours \pm 8 hours).

Follow-up visit and end of study

- Follow-up visit (Week 27) – A follow up visit will occur seven days (+/- 1 day) after the last Subgam-VF infusion has been completed, to carry out assessments for safety. Blood samples will be taken at this visit. This visit must occur prior to administration of a new IgG product.
- Telephone follow-up (Week 30) – 28 days (+/- 1 day) after the last Subgam-VF infusion the subject will be contacted by the site via the telephone to check for any AEs.

It is expected that any given subject will complete all treatments and follow-up assessments within approximately 30 weeks, (26 weeks on Subgam-VF, plus four weeks follow-up). The end of the trial will be after the last subject's last visit (which will be the telephone follow-up (Week 30) visit for the last subject).

7.2. Infusions

Subjects will receive 26 infusions of Subgam-VF subcutaneously on a weekly schedule using the supplied infusion pumps.

Rescheduling of Infusions (visit windows)

If absolutely necessary (e.g. because of unavoidable conflicts) Subgam-VF infusions can be rescheduled +/- 1 days. The reason why this visit was rescheduled should be recorded in the eCRF. If there is a deviation from the scheduled visit/ visit windows, the study monitor should be contacted, and the deviation must be documented appropriately. These circumstances must not become routine. If an infusion is rescheduled the other planned study assessments should also be rescheduled so that these are performed on the day of infusion.

If the infusion just prior to PK sampling has to be rescheduled, then the PK sampling should be postponed to ensure that the PK samples are collected seven days after the last Subgam-VF infusion and the sampling times in Table 3 are adhered to.

7.3. *Pharmacokinetics*

All subjects will participate in the pharmacokinetic (PK) segment of the study (if blood withdrawal volumes allow), see Appendix IV, Table 3. In the case of younger subjects, pediatric blood volumes will need to be taken to ensure the maximum blood withdrawal volumes specified in Appendix V are adhered to (see Laboratory Manual for more details).

- In exceptional circumstances, and with prior Sponsor approval, if one of the following PK samples is 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 \pm 2 hours)
 - 2 days (48 hours \pm 4 hours)
 - 3 days (72 hours \pm 6 hours)
 - 5 days (120 hours \pm 8 hours).

Where possible, arrangements to collect PK samples at the subject's home, from Steady State Day 1 onwards, by a suitably qualified member of the study may be made.

IMPORTANT: If the infusion just prior to PK sampling has to be rescheduled, then the PK sampling should be postponed to ensure that the PK samples are collected seven days after the last Subgam-VF infusion and the sampling times in Table 3 are adhered to.

7.4. *Clinical Laboratory Tests*

All blood samples collected for the study will be processed by a central laboratory. Once the results are made available, eligibility should be checked by the Investigator and eligible subjects may be enrolled into the study.

Samples for clinical laboratory testing should be taken before certain infusions, unless otherwise indicated, as per the Schedule of Assessments (Appendix IV Table 2) and will include:

- Biochemistry –including: alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), sodium, potassium, total bilirubin, alkaline phosphatase, glucose and gamma-glutamyl transpeptidase (GGT).
- Hematology - Complete Blood Count (CBC) with differential – including: hematocrit, hemoglobin, red blood cells (RBC), platelet count and white blood cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).
- Tests for hemolysis

- Direct Coombs' Test (Direct Antiglobulin test – DAT)
- Haptoglobin
- Plasma free hemoglobin
- Urine hemosiderin

Tests for bilirubin and serum LDH in the standard biochemistry panel is also considered a test for hemolysis.

- Specific antibody function to test for antibodies against the following antigens:
 - *Haemophilus influenzae* B
 - *Streptococcus pneumoniae*.
 - Measles
- Virology testing
 - Serological tests for HBsAg, HCV, HIV 1 & 2 at screening for eligibility and at Week 27 Follow up visit
 - Nucleic Acid Testing (NAT) for HCV, HIV at Week 27 Follow up only
 - Parvovirus B19 NAT and serology at Infusion 1, 2 and Week 27 Follow up visit.
- Urinalysis – that will include microscopic examination.
- Pregnancy testing - all females of child-bearing potential will receive a urine-based, human chorionic gonadotropin (HCG) pregnancy test regardless of claimed inability to conceive (including patients who have undergone surgical sterilization).

7.4.1. Effects on Hepatic, Renal, and Hematologic Function

If the results of any blood test demonstrate a rise to 2.5 times the upper limit of normal in AST, ALT, or bilirubin, these laboratory results will be documented as an AE.

A blood test demonstrating a change in renal or hematologic function will be documented as an AE if considered clinically significant by the Investigator.

7.4.2. Direct Coombs' Test

Blood samples for Direct Coombs' Tests and tests for hemolysis (bilirubin, haptoglobin, serum LDH, plasma free hemoglobin and urine hemosiderin) will be drawn at various times during the study (as detailed in Appendix IV, Table 2). Tests for bilirubin and LDH are included in the biochemistry panel.

In the event that a Direct Coombs' Test result is positive, the following procedures should be followed:

- The laboratory will notify the Investigator and the designated CRO within two business days of receiving the abnormal result.

- Subjects with a positive result will be flagged by the laboratory, and those subjects will have a Direct Coombs' Test and other tests for hemolysis (as detailed above) before every subsequent infusion given during a clinic visit and at the follow-up visit.
- Upon receiving a first report of a positive direct Coombs' test on any subject, the Investigator will contact the subject to return for additional laboratory testing for haptoglobin, serum LDH, plasma free hemoglobin bilirubin, and urine hemosiderin as soon as practically possible (generally within three business days) and will assess the subject in order to determine if there is any clinically significant hemolysis. Thereafter, further tests for hemolysis may be done if clinically indicated and at the discretion of the investigator.
- All positive Direct Coombs' tests will be reported as adverse events.

Other criteria for hemolysis:

- If the Direct Coombs' Test is negative, but other hemolysis tests are indicative of hemolysis, the Investigator should conduct further tests to confirm hemolysis as clinically indicated and at the discretion of the Investigator. This may include repeat Direct Coombs' Test, haptoglobin, serum LDH, plasma free hemoglobin, bilirubin and urine hemosiderin.
- A drop in hemoglobin of 2 g/dL or greater, in conjunction with both a drop in serum haptoglobin to below the lower limit of normal and a rise in serum LDH from baseline, would suggest intravascular hemolysis:
 - Investigator should review all results with reference to above criteria, and in conjunction with patient medical history to determine if there is clinically significant hemolysis. Investigator should conduct further tests as clinically indicated and at the discretion of the Investigator. This may include repeat Direct Coombs' Test, haptoglobin, serum LDH, plasma free hemoglobin, bilirubin and urine hemosiderin.
- Clinically significant hemolysis should be diagnosed taking into account the above criteria (drop in hemoglobin of 2 g/dL or greater, in conjunction with both a drop in serum haptoglobin to below the lower limit of normal and a rise in serum LDH from baseline) and any additional tests, as applicable.
- Clinically significant hemolysis will be reported as an adverse event. Subjects with clinically significant hemolysis should have a Direct Coombs' test and other tests for hemolysis (as detailed above) before every subsequent infusion at the clinic.

7.4.3. Virology Testing

If the tests for HBV, HCV, HIV, or Parvovirus B19 suggest a change in viral status of the subject, the tests will be repeated by the central laboratory. If a change in viral status is confirmed by a second independent test, the reserve sample taken before the first infusion of Subgam-VF will be retested in the same laboratory in the same batch as a retest of the suspect

sample. The central laboratory will inform the Sponsor and the designated CRO within one business day of a confirmed report of a change in viral status.

7.4.4. Reserve Samples

Reserve plasma and serum samples will be collected at all relevant time points, for reanalysis if needed, e.g. if an original sample is spoiled or if results are discrepant. Where necessary an additional blood sample will be collected; at other time points plasma or serum aliquots will be split so that a reserve plasma or serum sample can be retained at site. See Appendix IV and Laboratory Manual.

Reserve samples should be sent to the central laboratory within one month of collection where they will be stored at -70°C for the duration of the study. Reserve samples may be kept until the licence for Subgam-VF is granted by the relevant regulatory authorities and will be used, if required, for repeat assays at the request of a regulatory agency. For full details, please see separate Laboratory Manual.

Table 4 (Appendix V) displays the suggested maximum blood withdrawal for children. If the volume of blood withdrawn within 30 days is expected to exceed that specified on Table 4, then the Sponsor/Contract Research Organization (CRO) should be contacted to discuss order of priority for blood sampling. In these cases it will likely be the reserve samples that will not be taken so as to not exceed the maximum blood volumes allowed. The deviation must be documented appropriately on the eCRF.

7.4.5. Archive Sample

A blood sample will be collected from each subject immediately before the first infusion of Subgam-VF and at the follow-up (week 27) visit before another IgG product is given and sent at the end of the study (after all subjects have completed) to the central laboratory for onward dispatch to Cryo-store for long-term storage. Serum will be stored in tubes at -70°C for a minimum of 15 years after the trial is complete¹⁹. Samples will be used for serology and NAT testing if required in the future. The handling and shipping of these samples will be coordinated by the central laboratory.

7.5. Informed Consent

Written informed consent (and assent when appropriate) must be obtained from the subject and where appropriate by the subject's parent/legal guardian and signed by a suitable qualified and trained person, first in the protocol and the legal and ethical requirements of the study, before any study procedures are carried out (see Appendix II, Section 2).

7.6. Medical History

A complete medical history of the subject including demographics will be taken at Screening and an interval medical history (adverse events) will be taken at subsequent clinic visits.

Special attention should be paid to any aspect of the medical history or any clinical/laboratory feature that may serve to exclude the subject from participation.

Chronic infections and conditions that may require intermittent or continuous treatment during the study and/or could potentially change in frequency or severity during the study such as: cough, chronic bronchitis, chronic sinusitis, and arthritis and the type and frequency of treatment required should also be assessed and recorded so that symptoms of these conditions can be distinguished from treatment emergent adverse events (TEAEs) as the study progresses.

Any elective procedures that are planned for pre-existing conditions should be recorded.

Previous immunologic data that document the specific immunologic diagnosis will be recorded.

The medical history must include the use of prior IGIV and SCIG treatments received and how they were tolerated if available. The previous use of an IGIV and SCIG product must be documented in the subject's eCRF.

7.7. Physical Examination

Physical examination will be performed by an appropriately qualified member of staff at the study site. The physical examination is also a safety variable.

Elements of the examination should include:

- General appearance
- Head, eyes, ears, nose, throat
- Cardiovascular
- Respiratory
- Skin

Other body systems examined should be specified in the eCRF.

Height will be measured at screening and weight will be measured at screening and at every clinic visit.

Any clinically significant change from baseline in any system will be recorded as an AE (Appendix I).

7.8. Monitoring for thromboembolic events (TEE)

Monitoring for thromboembolic events (TEE) will be performed at screening (baseline) and at the Week 27 follow up visit (as well as when clinically indicated); this will include assessment of lower extremities for pain, swelling, tenderness or redness, also a respiratory

examination for any sudden onset of shortness of breath and any associated signs or symptoms of pulmonary embolus.

Assessment is particularly important in patients at high risk of TEE including prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors.

Subjects will be educated about the risk of TEE events and the signs and symptoms that they should look out for. This information will be included in the written instructions for home infusions. Subjects will be instructed to contact the site immediately should they experience any symptoms of concern.

Any clinically significant change from baseline in any system will be recorded as an AE (see Appendix I).

7.9. Concomitant Medication

All concomitant prescription and non-prescription medications received by the subject should be documented in the source notes, eCRF and study diary (when away from the site).

The following concomitant medications are excluded during the study:

- Steroids (long term daily, ≥ 0.15 mg of prednisone equivalent/kg/day). Requirement for short or intermittent courses of steroids would not exclude a subject.
- Immunosuppressive drugs.
- Immunomodulatory drugs.
- Vaccination with live attenuated virus vaccines during the trial (ie. until final follow up visit).

7.10. Chest X-Ray

A baseline chest X-ray (posterior-anterior and lateral) will be obtained on all subjects unless a chest X-ray taken within the previous 12 months is available to be used as a baseline.

7.11. Vital Signs

Vital signs assessed by qualified personnel will be entered on the eCRF. The vital signs to be observed will be:

- diastolic blood pressure (mmHg)
- systolic blood pressure (mmHg)
- pulse rate (beats/min)
- respiration rate (breaths/min)
- temperature ($^{\circ}$ C)

The subject must be in the same position each time vital signs are obtained. Temperature must be recorded using the same method every time e.g. orally, under the arm or via another common method.

Any clinically significant changes in vital signs will be reported as AEs as described in Section 10.2.

Clinically significant hypotension and/or anaphylactic reactions (significant hypotension with generalized hives/angioedema or bronchospasm) warrant discontinuation of the infusion and administration of appropriate supportive care as deemed necessary by the investigator (this may include: epinephrine, antihistamine, corticosteroids, supplemental oxygen, expansion of the plasma volume as necessary, etc.). These occurrences must be recorded on the eCRF as AEs. At the discretion of the investigator, the subject may be withdrawn from the study, but will complete the follow-up visits.

If a subject has been assessed as being dehydrated and is given intravenous fluids before beginning the subcutaneous study infusion, the baseline vital signs will be taken after the re-hydration fluids have been given but before infusion of investigational product.

Vital signs will be recorded once during the screening and follow up visits.

Vital signs will be recorded during site visits at the following times:

- 10 minutes before the start of each Subgam-VF infusion (+/- 5 minutes)
- 30 minutes after stopping the Subgam-VF infusion (+/- 15 minutes)

Vital signs are also an important safety variable.

If any AE of moderate or severe intensity occurs, the rate of the infusion at which this AE occurred will be recorded, and the infusion rate will be reduced appropriately, depending upon the severity of the AE symptoms. The infusion may then be resumed at a rate tolerated by the subject. Also see the most current Subgam-VF Investigator Brochure (IB) for a list of common product-related AEs⁶.

Before listing changes in vital signs as AEs, each change should be assessed for clinical relevance.

7.12. IgG - Blood Levels of the Previous IgG Preparation

As screening is likely to be performed during the same visit where the subject will receive their regularly scheduled infusion of a licensed (or investigational stage III, IIIb) IGIV or SCIG), the sample to determine trough IgG levels must be drawn before the infusion is started. Trough IgG levels must be documented to demonstrate that the subject is in a steady state. The minimum target trough level of IgG is 600 mg/dL. In addition, the dose, treatment interval, method of administration (IV/SC) and trade name or investigational reference of their current preparation must be recorded.

Samples will also be collected as per the Schedule of Assessments (Appendix IV, Table 2), and should always be taken before administration of the product.

7.13. IgG Subclasses-Blood Levels of the Previous IgG Preparation

Samples will also be collected as per the Schedule of Assessments (Appendix IV, Table 2) to determine the survival of the IgG subclasses during treatment with Subgam-VF. Samples should always be taken before administration of the product.

7.14. Specific Antibody Function

A sample will be taken prior to certain infusions (see Appendix IV, Table 2) to test for antibodies against the following antigens:

- *Haemophilus influenzae* B (screening and follow up [Week27])
- *Streptococcus pneumoniae* (screening and follow up [Week27])
- *Measles* (follow up [Week27])

7.15. IgA and IgM Levels

If levels of IgA and IgM in serum measured within the previous 12 months are not available, blood samples for IgA and IgM levels will be obtained. Samples should be taken at screening only.

7.16. Routine Pre-medications

Routine premedication to reduce potential adverse effects associated with the SCIG infusion are discouraged. Exceptions:

- Premedication will be permitted if a subject has reported systemic adverse events on two Subgam-VF infusions.
- If required, local anesthesia (for example Emla cream) is also allowed before any infusion to reduce the pain associated with needle insertion.

The routine long-term use of corticosteroids is not allowed. Oral and parenteral steroids are allowed if the average daily dose is < 0.15 mg prednisone equivalent/kg/day. Short or intermittent courses of > 0.15 mg/kg/day are allowed if required.

If a subject who previously required premedication before infusion with a licensed or experimental (Phase III or IIIb) IgG product is enrolled, their previous use of premedication, as well as associated side-effects must be recorded on the eCRF.

7.17. Data Recording

All data from the study collected at site will be entered into the eCRF. Subjects will record the data listed in 7.18 directly into the study diary, which will be reviewed by the study site at each visit. All key data must be entered into the subjects' medical record before they are entered into the eCRF (also see Appendix II, section 12.4). Subject diary data will not be transcribed but will be used as source data for home infusions, adverse events and concomitant medication.

7.18. Subject Study Diary

The subject or parent/guardian will complete a study diary daily between visits, starting after the Screening Visit. The data from the study diary will be reviewed at each site visit by qualified site personnel. The data to be recorded in the study diary are as follows:

- AEs (including time [24 hour clock] and date of onset/stop date and any AEs following infusion site inspection).
- Concomitant medication, especially antibiotics
- Subgam-VF infusion details including:
 - Batch number
 - Date of infusion
 - Start and stop times of the infusion
 - Volume of Subgam-VF infused and number of vials used
 - Infusion rate
 - Infusion sites used and any associated infusion site reactions.

For children and adolescents the parent/legal guardian is required to oversee that the diary is completed accurately and legibly.

The study staff will review the data from the subject study diary at each visit, to ensure the diary is completed correctly. If there is any discrepancies or missing data this will be discussed with the subject and then if required corrected by the subject. These discussions will be documented in the subject's medical notes.

7.19. Subject Withdrawal

If more than five subjects withdraw prematurely from the study then a sufficient number of subjects will be replaced to ensure data for 30 evaluable subjects.

Subjects can be withdrawn from the study for any of the following reasons:

- The subject or parent/legal guardian withdraws consent for the study.

- The subject or parent/legal guardian is uncooperative and non-compliant (defined as the subject missing two consecutive or three overall study visits) with respect to provisions of the protocol.
- The subject misses two scheduled infusions
- The subject has a serious AE (SAE) while participating in the study and, at the discretion of the site investigator, is withdrawn.
- The subject becomes pregnant while participating in the study (the pregnancy will not be recorded as an SAE, but will be captured on a Pregnancy Report Form and followed through until delivery or elective/spontaneous termination).
- The subject requires treatment with any of the medications listed in the exclusion criteria.

Investigators may withdraw subjects at any time if they feel it is not in the subject's best interests to continue. Reasonable efforts will be made to contact the parent/legal guardian and subject. If the subject is lost to follow-up, this will be documented in the subject's medical records.

In exceptional circumstances relating to safety, the sponsor may withdraw subjects at any time.

Data and samples collected up until a subject's withdrawal from the study will be used in the analysis. Subjects who have completed the study and subjects who have withdrawn cannot participate in the study for a second time.

7.19.1. Evaluations at Early Withdrawal

If a subject withdraws from the study or is dropped from the study for any reason, all tests identified for the end of study follow-up visit will be performed. If subjects have stopped Subgam-VF treatment and started another product, this will be taken into consideration in the analysis of the data.

7.20. Study Termination

Conditions for early termination are detailed in Appendix II, section 8.

8. DESCRIPTION OF TREATMENT ADMINISTERED

8.1. Investigational Product

8.1.1. Identification and Batch Numbers

It is planned to use one batch of Subgam-VF in this study. Additional batches may be used if required. The batch number(s) of Subgam-VF will be documented in the Certificate of Analysis that will be filed in the Trial Master File. The actual batch number will be

documented in the eCRF for each infusion. A list of all batches used and the subjects who received them will be included in the final study report.

8.1.2. Packaging and Labeling

Subgam-VF will be manufactured, packed, and labeled by BPL. The product will be supplied in glass vials (10 mL per vials containing 1600 mg of IgG = 16%) and each vial will be packed in a carton. The vials and the cartons will be labelled with identifying and contact information for BPL. The label will also include the identity, total quantity and volume, concentration, batch number, expiry date, and storage requirements of the product.

8.1.3. Conditions for Storage and Use

Subgam-VF should be stored in a refrigerator in a safe area of limited access or a Pharmacy. The product must be protected from light and maintained at a temperature of 36°F to 46°F (2°C to 8°C). Product that has been stored out of a fridge for one period of up to one week at temperatures up to 77°F (25°C) may be returned to the fridge with no change to the expiry date. Subgam-VF must not be frozen (inadvertently or on purpose). A log of daily temperatures in the Pharmacy storage area must be maintained to demonstrate that the product has been stored under the specified conditions.

Once fully trained, subjects will be issued with Subgam-VF for home use. The study staff will ensure that all subjects and parents/guardians are familiar with the correct storage conditions and provided with written storage instructions before any product is dispensed.

8.2. Investigational Treatment

8.2.1. Dosing Schedule and Rationale

Subgam-VF is a 16% subcutaneous IgG product. The weekly dose of Subgam-VF administered will be calculated by taking the weekly equivalent of the subject's stable IGIV dose, multiplied by 1.37, a dose adjustment coefficient based on other licensed subcutaneous IgG products. If the subject was already receiving a weekly SCIG IgG there will be no dose adjustment. The Subgam-VF dose should remain the same throughout the study, if a subject's weight changes by >5% compared with baseline (screening) or the previous visit, the dose should be adjusted accordingly with the aim of maintaining a stable dose in terms of mg/kg. If the dosage needs to be increased to achieve the required trough IgG level, then this should first be discussed with the CRO Medical Monitor, who will, if needed, discuss with the Sponsor.

8.2.2. Product Preparation

Before use, all vials must be inspected visually for discoloration, particles and fibers; if the contents of a vial is cloudy or contain particulate material, the vial must not be used. Subgam-VF is to be infused at room temperature (vial not cold when touched).

8.2.3. Method of 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 1 – 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. However, the infusions must be administered at the volume and rate outlined in Table 1 throughout the entire infusion. **Titration during the infusion is not allowed.**
- 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 Patient Medication Guide.

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. The infusion may then be resumed at a rate tolerated by the subject.

8.2.4. Product Accountability

The Investigator is responsible for the accountability of all used and unused product utilized in the study. Product accountability must be maintained as detailed in the Pharmacy Manual.

An IP accountability log for Subgam-VF must be kept current by the site.

The Pharmacy Manual will contain further information on IP accountability during the study, including disposal.

Subgam-VF must not be used outside of this protocol and must not be used for subjects who are not in this study.

8.3. Treatment Compliance

Subgam-VF will be administered subcutaneously both at the study site and also by self-administration at home. Subjects will be required to keep diaries and records of Subgam-VF usage. Site staff will check at each study site visit that the product is being stored appropriately, administered correctly and safely and the correct volume infused.

9. ASSESSMENT OF EFFICACY

9.1. Primary Efficacy Variables

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

10. ASSESSMENT OF SAFETY AND TOLERABILITY

10.1. Safety Variables

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.
 - An adverse reaction will be defined as any TEAE (irrespective of causality) that occurs during the infusion or within 72 hours after completion of the infusion, any AE classed as product related or any AE with unknown causality.
 - 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

10.2. Adverse Events

- The definitions and procedures for reporting AEs is detailed in Appendix I. AEs will be documented from the date the Informed Consent Form or Assent Form is signed until the follow-up visit and then monitored up to 28 days after the last dose of Subgam-VF is infused. AEs will be reviewed and documented by collecting the diaries at each visit and by direct observation during each infusion. In addition there will be a telephone follow up by an appropriately qualified site staff member on day 3 after each site administered and home administered infusion to check for any adverse reactions including infusion site reactions and remind subjects to document these in their subject study diary. 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.

The investigator will attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. It is the diagnosis that should be documented as the AE and not the individual symptoms.

An adverse reaction will be defined as any TEAE (irrespective of causality) that occurs during the infusion or within 72 hours after completion of the infusion, any AE classed as product

related or any AE with unknown causality.. Also see the most current Subgam-VF Investigator's Brochure listing common product-related AEs⁶.

10.3. Infusion Site Reactions

Infusion site reactions will be assessed during the study site infusion visits by the investigator or delegated study staff, but also rated by the subjects during home infusions and recorded in the subject diaries.

Subjects will inspect infusion sites and record any infusion site reactions (including date and time) into their study diary. Subjects will use the following criteria to grade all infusion site reactions in their study diary:

Mild: no limitation to normal activities

Moderate: some limitation to normal activities

Severe: inability to carry out normal activity.

All Infusion site reactions will be recorded in the eCRF. However 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. The Investigator will also use their judgment to record the severity of the AE and may use the subjects diary grading to aid that decision.

11. ASSESSMENT OF PHARMACOKINETICS

11.1. Pharmacokinetics of Subgam-VF for Total IgG Levels

All subjects will undergo a PK assessment (see Appendix IV, Table 2 and 3 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 following PK variables for total IgG levels will be determined for the PK population:

- $AUC_{(0-\tau)}$ - area under the plasma concentration-time curve of the dosing interval.
- $sAUC_{(0-\tau)}$ - area under the plasma concentration-time curve of the dosing interval standardized to one week. This will be calculated for the historical data only.

- C_{max} – maximum concentration in plasma.
- t_{max} – time to reach the maximum concentration in plasma.
- CL – systemic clearance.

The timing of the collection of blood samples for PK should be as per Table 2. 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) \pm 2 hours,
Steady State Day 2 (48 hours) \pm 4 hours
Steady State Day 3 (72 hours) \pm 6 hours
Steady State Day 5 (120 hours) \pm 8 hours
Steady State Day 7 (168 hours) \pm 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.

11.2. Other Pharmacokinetic Parameters

The following PK parameters will be listed and summarized descriptively for the ITT population:

- 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. The measles assay is for research purposes only and will not be reported to the investigational site.

12. 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.

13. STATISTICAL METHODS

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

13.1. Sample Size Determination

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 products². 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. All children who receive at least one infusion of Subgam-VF will be included in the safety analysis. Due to the potential for early withdrawals, PK data may not be available on all 12 children and there may be less than 12 evaluable children in the PK analysis. The total number of subjects (adults plus children) evaluable for PK analysis will be at least 30.

Data will be compared to historical data from previous Gammplex 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%.

13.2. Analysis Population

13.2.1. 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, summaries of demography and the following PK parameters: trough serum IgG levels, IgG subclasses and specific antibodies.

13.2.2. PK population

The PK population will comprise of subjects in the Subgam PK population and subjects in the Gammplex PK population as described below.

13.2.2.1. Subgam PK population

All subjects in the ITT population who have a pre-dose sample at steady state and at least four post-dose samples at steady state, one of them should be the Steady State Day 7 PK sample. In the case of a subject who provides IgG levels at the PK assessment but does not meet the criteria for inclusion in the Subgam PK population, data will be listed only.

13.2.2.2. Gammplex PK population

All subjects from Gammplex 5% IGIV PID studies (GMX01 and GMX04) who had an evaluable $AUC_{0-\tau}$.

13.2.2.3. PK Dose-Adjustment population

The PK Dose-Adjustment population is the subset of the PK population which excludes subjects in the Subgam PK population who had prior treatment with another subcutaneous weekly IgG product. Thus the PK Dose-Adjustment population includes all the Gammaplex PK population and those in the Subgam PK population who had previous treatment with IGIV. This population is analysed to estimate a refined dose adjustment factor.

13.3. Efficacy Analyses

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

13.4. Safety Analysis

13.4.1. Adverse Events

Summaries of AEs will be based on treatment-emergent AEs (TEAEs), defined as those events with onset date between the first infusion date and 28 days after the last infusion.

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. AEs occurring during the infusion and within 1, 24, 48 and 72 hours after the infusion completion will also be summarized.

An adverse reaction will be defined as any AE occurring during the infusion and within 72 hours after the infusion completion OR any AE classed as product-related or with unknown causality.

AEs that occur during an infusion will be summarized by the infusion rate at which the AEs are reported. If necessary, infusion rates will be grouped into different levels.

SAEs and SUSARs will be summarized with all AEs, and separate listings will be provided for SAEs and SUSARs.

All other safety assessments will be summarized descriptively for each treatment group.

Further summaries of AEs will be detailed in the Statistical Analysis Plan.

13.4.2. Other Safety Analyses

All other safety assessments will be summarized descriptively.

13.5. *IgG subclasses and IgG antibodies*

The trough levels of IgG subclasses and IgG antibodies against specified antigens will be summarized descriptively for all the Intent-to-Treat (ITT) subjects. This analysis will be conducted for subjects 2 to 5 years of age, 6 to 11 years of age, 12 to 15 years of age, all pediatric subjects (2 to 15 years of age), all adult subjects (aged 16 years and over), then for all subjects.

13.6. *Pharmacokinetic Analyses*

The pharmacokinetics of Subgam-VF will be based on absolute and baseline-adjusted (trough adjusted at steady state) values and will be described using a non-compartmental method. Actual sample times rather than nominal times will be used to calculate pharmacokinetic parameters.

The following PK parameters will be calculated for the Subgam PK population: The maximum observed concentration (C_{max}), the time at which C_{max} was apparent (t_{max}), the area under the concentration versus time curve within a dosing interval ($AUC_{0-\tau}$) and the systemic clearance (CL).

Pharmacokinetic variables will be summarized descriptively. This analysis will be conducted for subjects 2 to 5 years of age, 6 to 11 years of age, 12 to 15 years of age, all pediatric subjects (2 to 15 years of age), all adult subjects (aged 16 years and over), then for all subjects.

For the Gammaplex PK population, $sAUC_{0-\tau}$ will be calculated as the area under the concentration versus time curve within a dosing interval (21 or 28 days), standardized to one week i.e. $AUC_{0-\tau}(21 \text{ day})/3$ or $AUC_{0-\tau}(28 \text{ day})/4$. For the Subgam PK population, $sAUC_{0-\tau}$ is equivalent to $AUC_{0-\tau}$ (i.e. no standardization required as dosing is weekly).

All PK data collected on all subjects in the Subgam PK population will be listed. The PK population i.e. Subgam PK population combined with the Gammaplex PK population (historical data following administration of Gammaplex 5% IGIV) will be used for the primary and secondary statistical PK analyses.

The trough levels of total IgG will be summarized descriptively for all the subjects in the ITT population. Trough levels in the ITT population will be compared with those from the Gammaplex PK population.

13.6.1. Primary Statistical Analysis

Data will be pooled with historical data and a treatment variable defined (Subgam-VF or Gammaplex IGIV). Log transformed $sAUC_{(0-\tau)}$, ($AUC_{(0-\tau)}$ standardized to one week) will be analyzed using a mixed model fitted including treatment, and allowing for variability to be different between treatment groups. The mean difference (Subgam-VF or Gammaplex IGIV) between treatments with 90% Confidence Interval (CI) will be back transformed to give an estimate of the ratio (Subgam-VF/ Gammaplex IGIV) of $sAUC_{(0-\tau)}$. If the resulting 90% CI for the ratio lies within the equivalence limit of (0.80, 1.25), it will be concluded that there is equivalence in $sAUC_{(0-\tau)}$ and thus the dosing factor of 1.37 for Subgam-VF (in addition to the adjustment for dosing interval) gives equivalent exposure at steady state to Gammaplex IGIV.

13.6.2. Secondary Statistical Analyses

- i. The primary analysis method will be repeated with data derived from baseline-adjusted concentrations.
- ii. A term for dosing interval within treatment will be included in the model described in the primary analysis so that ratios with 90% CI can be presented for Subgam-VF relative to both the 21 day and 28 day dosing interval regimens of Gammaplex.
- iii. The primary analysis model will be extended to include any significant (at the 10% level) covariates or covariate by treatment interactions. Covariates considered for inclusion will include age category, weight, BMI and sex.
- iv. The effect of previous treatment (SCIG or IGIV) on $AUC_{(0-\tau)}$ in the Subgam PK population will be analysed. If the resulting 90% CI for the ratio lies within the equivalence limit of (0.80, 1.25), it will be concluded that the previous treatment does not affect exposure at steady state. If this is the case then the refined dose adjustment with 90% CI will be presented on the full PK population (in addition to on the PK Dose Adjustment population described below).
- v. In addition, the data from the current study will be restricted to a PK Dose Adjustment population and analysed as per the primary analysis. A refined dose adjustment will be estimated as 1.37/the ratio (Subgam-VF / Gammaplex IGIV) of geometric means for $sAUC_{(0-\tau)}$ and presented with 90% CI.

13.6.3. Exploratory Analysis

PK modelling will be performed to explore alternative dosing schedules. For example; PK modelling and simulation will be carried out to compare weekly administration to a biweekly schedule at double the weekly dose and assess IgG exposure.

Full details of the PK and associated statistical methods will be described in a PK Analysis Plan.

14. PROVISION OF ADDITIONAL INFORMATION

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the subject's confidentiality is protected in accordance with applicable regulations.

15. INVESTIGATOR AGREEMENT

A Phase III, Multicenter, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subgam-VF in Primary Immunodeficiency Diseases (Protocol Number SCIG03)

I have been adequately informed about the development of the investigational product to date and agree that this study protocol contains all the information required to conduct the study.

I will provide copies of the study protocol and all product information relating to prior product experience furnished to me by the Sponsor/CRO to all staff responsible to me who participate in this study. I will discuss this material with them to ensure that they are fully informed regarding the product and the conduct of the study.

The information contained in this document is CONFIDENTIAL and, except to the extent necessary to obtain informed consent, may not be disclosed, unless such disclosure is required by government regulation or applicable laws. Persons to whom the information is disclosed must be informed that the information is CONFIDENTIAL and cannot be disclosed by them.

By my signature below I agree to conduct this clinical trial in accordance with the protocol, ICH Good Clinical Practice, the Declaration of Helsinki and relevant/applicable national drug laws regulations.

I agree to ensure the confidentiality of the subjects enrolled under my care; however, I agree to make their medical records available to authorized representatives of the CRO; authorized representatives of Bio Products Laboratory Ltd., the Sponsor of this clinical trial; and relevant regulatory authorities.

I have read the Investigator's Brochure (IB) and protocol, and I am aware of my responsibilities as Investigator as stated on FDA Form 1572.

Site Investigator:

Investigator name: _____ Site Name: _____

Signature: _____ Date: _____

16. REFERENCES

1. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics* 2004 Aug;114 (Suppl 2:) 555-76.
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APPENDIX I: ADVERSE EVENT DEFINITIONS AND REPORTING

ABBREVIATIONS

AE	Adverse Event
BPL	Bio Products Laboratory Limited
CRF	Case Report Form
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	US Food and Drug Administration
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP/IP	Investigational Medicinal Product/Investigational Product
IRB	Institutional Review Board
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Definitions of Adverse Events

1.1 Adverse Events

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

All AEs, whether or not considered by the Investigator to be related to the IMP (test product, comparator or placebo), must be described and recorded on the appropriate Adverse Event forms in the case report form (CRF)/electronic case report form (eCRF). Where possible, a diagnosis should be made. Anticipated fluctuations of preexisting conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Infusion-Related Adverse Events

All AEs that occur from the start of the infusion until 72 hours from the end of the infusion will be recorded as temporally related to the infusion.

Clinical Laboratory and Other Adverse Events

A laboratory result that is considered by the Investigator to be clinically significant or have a clinically significant pathological change from baseline should be recorded as an AE.

Other abnormal results (e.g. x-rays, scans, physical examination findings) that worsen from baseline and/or are considered clinically significant should also be recorded as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Reporting

Adverse events should be reported and documented in accordance with the procedures outlined in this section. All AEs occurring during the study must be documented on the relevant CRF/eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

Pregnancy

Subjects will be instructed that a known or suspected pregnancy occurring during the study should be reported to the Investigator. The Investigator should also be notified of a pregnancy occurring during the study but confirmed after completion of the study. If a subject is found to be pregnant after inclusion in the study, the subject must be withdrawn from the study. Any pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Full details of any pregnancy will be recorded on the AE page of the CRF/eCRF, and a Pregnancy Report Form will be completed. A copy of the Pregnancy Report Form must be faxed to the CRO within 24 hours.

At the end of the study, it is expected that subjects will continue treatment with other immunoglobulin products. Any adverse events which occur after last study visit are more likely related to the continued treatment with non-study immunoglobulin products and therefore extended use of contraception and follow-up of pregnancies occurring after end of study visit are not appropriate in this study. Subjects of child bearing potential should

be advised of the risks of pregnancy in accordance with the relevant product information for their ongoing therapy.

1.2 Suspected Adverse Reaction

Definition: Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

The following are examples of types of evidence that would suggest a causal relationship between the drug and the adverse event to determine *Reasonable possibility*.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the Sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

1.3 Adverse Reaction

Definition: An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

1.4 Serious Adverse Event or Suspected Adverse Reaction

Definition: An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death,**
- **A life-threatening adverse event, [See Section 1.5]**
- **Inpatient hospitalization or prolongation of existing hospitalization,**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,**
- **A congenital anomaly/birth defect.**
- **Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.**

Hospitalization does not include hospitalizations for elective procedures for pre-existing conditions that did not worsen from baseline)

If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

The following events of special interest will always be regarded as serious::

- Anaphylaxis or anaphylactoid reaction
- Myocardial infarction
- Stroke
- Pulmonary embolism
- Any thromboembolic event (TEE)
- Laboratory documented infection with blood borne virus
- Acute renal failure
- Any transmissible spongiform encephalopathy

In general, information that might materially affect the risk-benefit assessment of a medicinal product or that would suggest changes in the way it is to be administered or to the way a clinical investigation should be conducted should be reported in an expedited manner. Examples include the following:

- Single case reports of an expected adverse reaction with an unexpected outcome (e.g. fatal outcome)
- For an expected serious adverse reaction, an increase in the rate of occurrence that is judged to be clinically important
- A significant hazard to the patient population, such as lack of efficacy in treating life-threatening diseases or an event which is significant enough to lead to

important changes in the way a medicine is developed (e.g. change in dose, monitoring, consent forms).

- A major new safety finding from a newly completed animal study
- An SAE associated with a study procedure that could modify the conduct of the trial

1.5. Life-Threatening

Definition: *An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.*

As with the definition of *serious*, the determination of whether an adverse event is life-threatening can be based on the opinion of either the investigator or Sponsor. Thus, if either believes that it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes

1.6 Unexpected Adverse Event or Suspected Adverse Reaction

Definition: *An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.*

1.7 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

The Sponsor must report any suspected adverse reaction to study treatment (i.e. including active comparators) that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three of the definitions:

- *Suspected adverse reaction*
- *Serious*
- *Unexpected*

The Sponsor (or designated Contract Research Organization [CRO]) shall ensure that all relevant information about a SUSAR is reported to the Competent Authorities and to the independent ethics committees (IECs)/institutional review boards (IRBs) concerned.

2. Detecting Adverse Events

Subjects will be carefully monitored for adverse events that occur after the Informed Consent Form (ICF) has been signed until the 28 days after the last infusion of study medication. At site visits, the Investigator or delegate will question the subjects about AEs using a nonleading question such as “How are you feeling?” The Investigator will also record AEs reported spontaneously by the subjects, including AEs recorded in the patient diary. Clinically significant changes in the findings of physical examination and clinically significant abnormalities in the result of objective tests (e.g. laboratory variables, ECG) should be recorded as AEs.

2.1 Causality (Assessment of Relationship)

All AEs will be recorded in the CRF/eCRF, whether considered to be related or unrelated to the treatment. The record will include the following: a brief description of event (preferably a diagnosis), date and time started and stopped, severity, outcome, actions taken, and classification of the AE. The Investigator should also evaluate the probability of a causal relationship of the AE to the study medication according to the following criteria:

- **Unrelated:** Clinical event with an incompatible time relationship to IMP administration, or that could be explained by underlying disease or other drugs or chemicals, or is incontrovertibly not related to the IMP
- **Unlikely:** Clinical event whose time relationship to IMP administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals
- **Possible:** Clinical event with a reasonable time relationship to IMP administration, but that could also be explained by concurrent disease or other drugs or chemicals
- **Probable:** Clinical event with a reasonable time relationship to IMP administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals
- **Very likely/certain:** Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals

Study medication is defined as those investigational compounds or their controls used in a study.

It will be assumed that for all AEs classified as having a “possible”, “probable” or “very likely/certain” relationship to the study medication, there is reasonable likelihood that the

AE was causally related to the product. All such AEs will be regarded as “causally related” to the study medication.

2.2 Outcome of Adverse Events

The outcome of the AE should be documented as:

1. Recovered / resolved
2. Recovering / resolving
3. Not recovered / not resolved
4. Recovered / resolved with sequelae
5. Fatal
6. Unknown

2.3 Action Taken

The action taken by the Investigator or study staff should be documented as:

1. Drug withdrawn
2. Dose reduced
3. Dose increased
4. Dose not changed
5. Unknown
6. Not applicable

2.4 Severity of Adverse Event

Severity refers to the grading of adverse events to assess the severity of symptoms as evaluated by the Investigator or as experienced by the subject. The severity grading is independent of seriousness; in other words, a severe event is not necessarily serious. The Investigator will make an assessment of severity (e.g. mild, moderate, severe) for each AE and SAE reported during the study in accordance with the following definitions:

Mild: A non-serious adverse drug experience that is usually transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: A non-serious adverse drug experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. This includes laboratory test alterations indicating injury, but without long-term risk.

Severe: A non-serious adverse drug experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization is required for treatment, it becomes a serious adverse event.

3. Adverse Event Follow-up

All adverse events will be followed:

- To resolution; or

- Until an underlying condition has been diagnosed; or
- Until the patient's condition has stabilized; or
- For a period of 28 days following the last administration of the study drug.

Any new or unresolved AEs noted at the last study visit will be followed up for a further 28 days unless they fulfil the above criteria.

If the subject becomes pregnant while participating in the study, the pregnancy will not be recorded as an SAE, but will be captured on the AE page of the CRF/eCRF and in a Pregnancy Report Form and followed through until delivery or elective/spontaneous termination. Any birth defects will be reported as in the procedures for SAEs (see Sections 1 and 4).

4. Reporting Serious Adverse Events

When an AE occurs that fulfils the definition of serious (see Section 1.3), the Investigator must:

Complete and sign the Serious Adverse Event Form and send it to the CRO within 24 hours. The CRO will then inform the Sponsor within 24 hours of receiving the SAE notification.

SAE FAX

1 866 851 9318

Medical coverage for urgent queries relating to AEs will be provided on a 24-hour/7-day a week basis by contacting the safety office at the following number and the call will be routed to the Medical Monitor:

Telephone Number

1 888 619 3216

The Investigator is responsible for expedited reporting of all Serious Adverse Events immediately to the CRO. This reporting requirement covers any SAEs that develop at any point between the date when a subject provides Informed Consent and up to 28 days after the last administration of the investigational medicinal product. The Investigator is also responsible for reporting to the CRO any SAEs with an onset date more than 28 days after the last administration of the product if he/she judges the SAE to be possibly, probably or very likely/certainly related to the product.

The immediate report should contain the following as a minimum:

1. Suspected investigational medicinal product
2. Study subject number
3. Details of the serious adverse event
4. Classification of SAE
5. Causality of SAE (if available)

The immediate SAE form should be followed by a detailed, complete SAE form as soon as possible. The immediate report and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to the evaluation of safety must be reported to the designated CRO by the Investigator according to the reporting requirements within the time periods specified in this protocol.

The Investigator must not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of IMP administration and linked by the Investigator to this study should be reported to the designated CRO/Sponsor.

The Sponsor or designated CRO will promptly notify all relevant Investigators and regulatory authorities of findings that could adversely affect the safety of patients, affect the conduct of the study, or alter the approval/favorable opinion of the study by the IEC/IRB. In addition, the Sponsor (or designated CRO) will expedite the reporting of all AEs that are serious, unexpected, and, in the opinion of the Investigator, related to the IMP to all concerned Investigators, the IEC/IRB, where required, and the regulatory authorities.

The Investigator will comply with local requirements related to the reporting of SAEs, IND Safety Notification Letters, and other safety information related to the trial to their local IRB.

For reported deaths of a subject, the Investigator shall supply BPL or designated CRO and the Research Ethics Committee with any additional information requested.

Completing Serious Adverse Event Forms

Serious Adverse Event (SAE) forms must be completed in a timely manner and contain the following information:

- Subject number, sex, age, study center, trial code
- Description of event (where possible a diagnosis should be made rather than just listing symptoms)
- Study drug, indication for use, batch number, dose, route, date and time of last dose
- Date and time of adverse event

- **All** concomitant medication
- Causal relationship to study medication (as in Section 2.1)
- Outcome (as in Section 2.2)
- Action taken and treatment given (as in Section 2.3)
- Severity (as in Section 2.4)
- Classification of serious adverse event (as in Section 1.4)

The SAE form must be signed and dated by the person reporting the SAE. The final report must be signed and dated by the Principal Investigator from the site.

5. Sponsor's Responsibilities

The Sponsor and/or the designated CRO will be responsible for reporting all relevant safety information (including a listing of all SUSARs) to the regulatory authorities and to the IRBs/IECs concerned. Safety reports will be issued in accordance with local relevant procedures (as a minimum on an annual basis).

The Sponsor and/or the designated CRO will inform the relevant Competent Authority(ies), in line with regulatory guidelines, of AEs occurring during the trial. The Investigator retains the right to inform the relevant Competent Authority(ies) if he/she so desires but must inform the Sponsor and/or designated CRO so that duplicate reports to the Competent Authority(ies) can be highlighted.

The Sponsor and/or designated CRO will inform all Investigators of all SUSARs occurring during the study or findings that could adversely affect the safety of subjects.

6. Summary of Investigator and Sponsor Reporting Responsibilities¹

Term	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious (or life-threatening)	Yes (Investigator must report all serious adverse events to the Sponsor immediately)	Yes	An event is considered serious or life-threatening, based on <i>either</i> the Investigator's or Sponsor's opinion.
Unexpected	No (No requirement to assess "expectedness")	Yes	The Sponsor is responsible for determining whether event meets the definition of "unexpected," based on whether the event is listed in the Investigator's Brochure; or if an Investigator's Brochure is not required or available, is

			not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.
Suspected Adverse Reaction – (causality assessment standard - “reasonable possibility”)	Yes (Investigator must provide Sponsor with an assessment of causality)	Yes (Sponsor’s assessment determines reportability, regardless of Investigator’s assessment)	The <i>Sponsor</i> is responsible for determining whether there is a reasonable possibility that the drug caused the adverse event, taking into consideration the Investigator’s assessment

7. Reference

1. Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies. U.S. Department of Health and Human Services. Food and Drug Administration, December 2012.

APPENDIX II - ADMINISTRATIVE REQUIREMENTS

ABBREVIATIONS AND DEFINITIONS

ARSAC	- Administration of Radioactive Substances Committee
BPL	- Bio Products Laboratory Limited (Ltd.)
CA	- Competent Authority
CI	- Chief Investigator
COI	- Coordinating Investigator
CRA	- Clinical Research Associate
CRO	- Contract Research Organization
CFR	- Code of Federal regulation
CV	- Curriculum Vitae
DQF	- Data Query Form
eCRF	- Electronic Case Record Form
EU	- European Union
FDA	- Food and Drug Administration
GCP	- Good Clinical Practice
GMC	- General Medical Council
ICH	- International Conference on Harmonisation
ID	- Identification
IEC	- Independent Ethics Committee
IMP/IP	- Investigational Medicinal Product
IRB	- Institutional Review Board
PI	- Principal Investigator
R&D	- Research and Development
SOP	- Standard Operating Procedure
USA	- United States of America

CA – ‘Competent Authority’, synonymous with ‘Regulatory Authority’: the Government body that has the power to regulate. In the context of ICH GCP, the term ‘Competent Authority’ includes the authorities that review submitted clinical data and those that conduct inspections.

CI – ‘Chief Investigator’: in relation to a clinical trial conducted at a single trial site, the Investigator for that site. In relation to a clinical trial conducted at more than one trial site, the authorized health care professional, whether or not he/she is an Investigator at any particular site, who takes primary responsibility for the conduct of the trial.

COI – ‘Coordinating Investigator’: an investigator assigned the responsibility for the coordination of investigations at different centers participating in a multicenter trial.

PI - ‘Principal Investigator’: a doctor or person following a profession for investigations because of the scientific background and the experience in subject care it requires. The Principal Investigator is responsible for the conduct of the trial at the trial site. If a trial is conducted by a team of individuals at a trial site, the Principal Investigator is the leader responsible for the team.

IEC – ‘Independent Ethics Committee’: a review board or a committee, institutional, regional, national or supranational, constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IRB – ‘Institutional Review Board’: an independent body constituted of medical, scientific and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial by, among other things, reviewing, approving and providing continuing review of the trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IMP – ‘Investigational Medicinal Product’: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

1. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and in accordance with GCP guidelines (ICH), EU Directives 2001/20/EC¹, 2005/28/EC² and FDA’s Code of Federal Regulations (CFR)³ as well as the demands of national drug and data protection laws, other applicable regulatory requirements and any new directives or regulations which become enforceable during the course of the study.

Before the study can begin the Investigator must have submitted to an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) the study protocol, Investigator’s Brochure, subject information leaflet, parent/guardian information sheets, assent form, consent form (and any updates), subject recruitment procedures and any other relevant study documentation as outlined in the guidance document (‘Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal

products for human use', ENTR/CT 2) for EU Directive 2001/20/EC¹ and FDA's Code of Federal Regulations (CFR)³. Written approval of the study must be obtained before the study center can be initiated or the investigational medicinal product (IMP) can be released to the Investigator. Any necessary extensions or renewals of IEC / IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IEC / IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC / IRB annually, or more frequently if requested by the IEC / IRB, in accordance with local regulatory requirements. On completion of the study, the Sponsor and /or designated CRO will notify the IEC/IRB that the study has ended.

2. INFORMED CONSENT

No study-related procedures will be performed prior to the subject's and subject's parent/legal guardian's (if applicable) signed consent to participate in the study being obtained. Before the decision to participate, the Investigator or a duly authorized deputy will provide both an oral and a written full explanation of the study and the subject's rights. The written consent must be given by the subject and the parent/legal guardian (if applicable) of the subject, after detailed information about the study has been given as outlined above in EU Directive 2001/20/EC¹, FDA's Code of Federal Regulations (CFR)³ and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

For subjects not qualified to give legal consent, written consent must be obtained from the subject's parent/legal guardian. If appropriate, children old enough to understand the risks and benefits of the study (generally for children above 6 years of age) should also be informed and provide their written assent. In addition, the subject/subject's parent or legal guardian will sign a consent and child's assent form authorizing release of the subject's HIV test results to appropriate authorities. All consent and assent forms must be approved in advance by the IRB/IEC.

If the legal guardian is unable to read, an impartial witness should be present during the entire informed consent discussion. After the informed consent form and any other written information is provided, read, and explained to the subject or their legal guardian, and after oral consent has been obtained, if capable of doing so, the subject's legal guardian should sign and date the informed consent form, and where appropriate written assent should be obtained from the subject. The witness should also sign and date the consent form. In addition, the subject's legal guardian should, if possible, sign an additional form confirming that the

materials provided have been read and explained to them. The witness should also sign and date this additional form.

The Investigator or designated personnel will inform the subject and parents/guardians of the subject about the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject and parent/legal guardian (if applicable) must be given every opportunity to clarify any points they do not understand and, if necessary, to ask for more information. At the end of the interview, the subject and parent/legal guardian (if applicable) will be given time to consider the study if this is required, or if they request more time. Subjects and parents/legal guardians (if applicable) will be required to sign and date the informed consent form. After signatures are obtained, the informed consent forms will be kept and archived by the Investigator in the Investigator's Study File for possible inspection by regulatory authorities, the IEC or IRB, BPL or BPL's representative's personnel, auditors. The subject will keep an identical signed copy. A letter will be sent to the subject's primary care physician informing him/her that the subject is to participate in the study, as appropriate.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who withdraw consent should not continue in the study, but will be asked to attend an end-of-study visit, if possible.

Should the study require the completion of a subject study diary, for subjects under the age of 18, the parent/legal guardian will oversee that the diary is completed accurately and legibly.

The IEC / IRB will review and approve the subject information sheet and informed consent form. If the Investigator intends to use his/her own information leaflet (for non-interventional studies only) he/she must ensure that it contains all the information outlined in Section 4.8 of the ICH-GCP guidelines.

3. CONFIDENTIALITY

The Investigator will ensure that the subject's anonymity is preserved.

In order to protect the subject's identity, identification codes will be used in lieu of subject's name. Personal information will be treated as confidential but may need to be reviewed by BPL or BPL's representatives such as the CRA or auditor, or by representatives of IEC / IRBs or regulatory authorities. The subject's consent to direct access to their personal notes must be obtained prior to participation in the trial. Each subject's Primary Care Physician will be informed of the nature and timing of the study, as appropriate.

All unpublished documents including the protocol, the electronic case record form (eCRF) and the Investigator's Brochure are confidential. Those documents cannot be disclosed to a third party without the written consent of BPL. However, submission of those documents to the IEC / IRB is expressly permitted.

4. COMPENSATION/INDEMNITY

Compensation will be paid by BPL according to the Guidelines drawn up by the Association of the British Pharmaceutical Industry if a subject is injured as a result of being in this study.

Compensation will not be provided for injury or medical conditions that are unrelated to this study.

BPL will indemnify the Institute and the Investigator with respect to any claim for personal injury or death brought against it resulting from the administration to subjects, of source materials supplied by BPL, provided that the protocol and Investigator Agreement have been adhered to, and the event has not been occasioned by malpractice or negligence. BPL will take out private insurance in respect of its liability.

5. PROTOCOL ADHERENCE

Adherence to the protocol is a fundamental part of the conduct of the study. Deviations from the protocol, including deviations from the inclusion / exclusion criteria, might erode the scientific and ethical value of the protocol and its authorization and might have an impact on the processes put in place for the care and safety of the study subjects.

Deviations from the protocol must not be made without the **prior written approval** of BPL and the IEC / IRB and the CA except where there are logistical or administrative changes (non-substantial amendments), or where they are implemented to eliminate an immediate threat or hazard to health or safety of the subject. Where a deviation has been made to eliminate an immediate hazard the Investigator must submit a report of the implemented deviation and the reasons for it to the IEC / IRB and must notify relevant members of the **Medical Department of BPL or designated Contract Research Organization (CRO)**. All deviations must be adequately documented.

6. PROTOCOL AMENDMENTS

A decision will first be made by BPL as to whether a protocol amendment is 'Substantial' or 'Non-substantial'. Amendments to the protocol are regarded as 'Substantial' where they are likely to have significant impact on:

- The safety or physical or mental integrity of the subjects
- The scientific value of the trial
- The conduct or management of the trial
or
- The quality or safety of any investigational medicinal product (IMP) used in the trial

Competent Authority (CA) and IEC / IRB written approval (if applicable) will be obtained prior to any protocol amendment being adopted.

When a Sponsor and/or Investigator must take urgent safety measures to protect the trial subjects from immediate hazard BPL (or designated CRO) must be notified within 24 hours and the IEC / IRB and CA must be notified within 3 calendar days after appropriate safety measures have been taken. For any period during which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health, the IEC/IRB and CA should be informed as soon as possible. Where the amendment affects the risk/benefit ratio of continued participation for subjects already enrolled in the study, informed consent should be obtained again from such subjects using the new information leaflet/consent form. The updated version of the information leaflet/consent form should be used for all new subjects recruited on to the trial.

7. SERIOUS BREACHES

Reporting of Serious Breaches is not applicable as the study is not planned to be conducted in the UK.

8. TRIAL TERMINATION

BPL reserve the right to stop the trial if:

- Recruitment is too slow to allow accrual of an adequate number of subjects within a reasonable length of time
- Evidence is gained that the subjects are being exposed to an unacceptable risk
- For any reason, it is not possible to continue to supply trial material
- An advancement in knowledge makes the trial redundant

If the study is terminated, BPL, the CRO and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

9. MONITORING VISITS

The designated Clinical Research Associate (CRA) or representative CRA will monitor the study by telephone, correspondence, and regular visits to the investigational sites. In accordance with ICH-GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate, to carry out drug accountability and to ensure all documentation and study procedures comply with the protocol and with ICH-GCP.

The frequency of monitoring visits will be determined by the rate of subject recruitment.

The CRA will ensure that:

- The facilities remain adequate
- The Investigator adheres to the protocol and ethical responsibilities
- Source documents are legible and agree with entries in the eCRF
- Adverse events are adequately documented and reported
- Investigational medicinal product is properly stored and accountability is being maintained
- Laboratory samples are identified, handled and stored appropriately

The Investigator must permit the CRA, the IEC / IRB, BPL appointed auditors and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs. The Investigator will agree to make himself/herself available to correct or discuss any discrepancies. Subject confidentiality will be protected at all times.

A "Site Delegation List and Signature Log" will be completed and signed by the responsible Investigator. In accordance with this authority log, study site staff (e.g. co-Investigators and nurses) will be authorized to enter data into the eCRF. The monitor will visit the study centers as required.

10. AUDIT/INSPECTION

Access to documentation and facilities used during the study may be required by BPL appointed auditors or by regulatory authorities.

In the event that the regulatory authorities schedule an audit the Investigator must notify BPL (or the designated CRO) immediately. BPL will in turn notify the Investigator if they are informed of an audit at an Investigator's site.

The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the investigational product have been reported to the Sponsor.

The verification of the eCRF data may be performed by direct inspection of source documents, after the Investigator has protected all confidential personal subject information not related to the study, in accord with local regulations.

11. REQUIRED PRE-STUDY DOCUMENTATION

Before the start of the study, BPL will require, as a minimum, the following documentation:

1. A signed copy of the protocol and signed amendments approved by the IEC/IRB
2. A signed Clinical Trial Agreement, including any host R&D approval
3. Other signed financial agreements (e.g. laboratory, pharmacy)
4. Signed Confidentiality Agreements for study team
5. A signed Secrecy Agreement (if applicable)
6. A completed Investigator Financial Disclosure / Certification Statement and a Statement of Investigator (Form FDA 1572), if applicable
7. An Indemnity Form signed and dated by both parties unless indemnity is covered by other signed agreements for the study
8. Insurance policy or statement that this is not required.
9. IEC / IRB written approval
10. Assurance that the IEC / IRB is organized and operates according to GCP and the applicable laws and regulations
11. ARSAC approval (if applicable)
12. CA Approval
13. Signed CVs of Investigators and sub-Investigators showing current position and GMC registration number, as appropriate
14. Normal Ranges for:
 - Laboratory parameters
 - Medical or technical procedures
 - Tests included in the protocol
15. Evidence of validation of procedures/tests to be performed e.g.:
 - Accreditation
 - Certification
 - SOPs for specialized tests
16. IEC / IRB approved subject information sheet and consent forms, identified with version number and date, plus any other written information given to subjects
17. Investigator's Brochure, the edition clearly identified plus any updates
18. Master randomization list (if appropriate)
19. Decoding procedures for blinded trials
20. Sample case record form

If any of these documents are issued in a language other than English then verified translations are required.

12. COMPLETION AND RETURN OF CASE RECORD FORMS AND DATA QUERY FORMS

12.1 Recording data in Case Record Forms (eCRF) and Data Query Forms (DQFs)

All study data will be recorded on eCRF provided by BPL or designated CRO. These must be completed by the Investigator or a duly authorized assistant.

Electronic CRF

In the case of eCRF, errors occurring in the eCRFs will be corrected directly in the data field of the eCRF. An audit trail capturing the original entry, the new entry, the user ID of the entry personnel, and the date and time of each action will be maintained in the data capture system. Likewise, the interchange of queries between the CRO and the site, as well as query replies, will be maintained within the audit trail of the data capture system. Any changes to the data in the data capture system that occur after the Investigator or authorized co-Investigator have electronically signed the eCRF will require that the Investigator or authorized co-Investigator review and re-sign the eCRF.

12.2. Signing off eCRFs/DQFs and return to BPL or designated CRO

The Investigator must:

- Sign the completed eCRF/DQFs to confirm the validity of the data
- Return the completed eCRF/DQFs as instructed
- Retain a copy in the Investigator File

In the case of eCRF for each subject enrolled, eCRFs will be completed and signed electronically by the Investigator or an authorized co-Investigator. All paper source documents will be filled out using an indelible pen, and must be legible.

12.3. Handling of Clinical Trial Data

All clinical trial data will be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, whilst maintaining the confidentiality of the subjects' records.

12.4. Source Documents

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written in original records or consisting of certified copies of original records. The Investigator will permit trial-related monitoring, audit(s), IRB review(s) and regulatory inspection(s).

Source documents or data to be entered directly into the Case Record Form will be defined prior to study start in an appropriate plan e.g. definition of source data document.

13. MAINTENANCE AND ARCHIVING OF STUDY RECORDS

13.1. Investigator Site File

The Investigator will be supplied with an Investigator Site File by BPL, or the designated CRO, at the start of the study, containing copies of required pre-study essential documents. It is the responsibility of the Investigator and study team members at site to maintain these essential documents and ensure their secure storage. The Investigator file will comprise the following documentation, although certain sections may be kept in a separate file with certain study team members e.g. laboratory or pharmacy staff:

1. Agreements
 - Signed Confidentiality Agreements for study team
 - Signed Clinical Trial Agreement, including any host R&D approval (and submission documentation where applicable) detailing versions of documents approved
 - Other signed financial agreements specific to the site (e.g. laboratory, pharmacy)
 - Indemnity Form (if used) signed and dated by both parties, unless indemnity is covered by other signed agreements for the study
 - Insurance statement if applicable
 - A completed Investigator Financial Disclosure / Certification Statement and a Statement of Investigator (Form FDA 1572), if applicable
2. Protocol
 - A signed copy of the protocol and signed amendments approved by the IEC/IRB
3. Product Information
 - Investigator's Brochure, the edition clearly identified plus any updates
 - Supporting publications and information
 - Safety updates from BPL, including any aggregated line listings of SUSARs and summary safety reports, in accordance with local regulatory requirements
4. e-CRF and Supporting Information
 - Sample case record form
 - Other blank forms used in the study e.g. study diary
 - Data transmittal forms
5. CVs

- Signed CVs of Investigators and sub-Investigators showing current position and registration number, as appropriate
 - Case Record Form Signature and Study Duties Log
 - Reference to training records of study site personnel
6. Ethics Committee
- IEC / IRB written approval
 - CA Approval
 - ARSAC approval (if applicable)
 - Relevant correspondence with IEC/IRB
 - Copies of progress reports to IEC/IRB
 - Copies of annual safety reports to IEC/IRB, in accordance with local regulatory requirements
 - Copies of IEC/IRB approved consent forms
 - Copies of IEC/IRB approved information leaflets
 - Final letter and report to IEC/IRB documenting study completion
7. Laboratory Details
- Central laboratory manual, if applicable
 - Local laboratory normal ranges both current and previous if changed during study, if applicable
 - Local laboratory certification / accreditation both current and any updates, if applicable
 - Local laboratory validation or SOPs for specialized tests both current and any updates, if applicable
 - Sample storage log
 - Local sample handling procedures, unless included in a central laboratory manual
 - Laboratory parameters
 - Medical or technical procedures
 - Tests included in the protocol
8. Subject Details
- Master randomization list (if appropriate).
 - Subject screening log (if appropriate)
 - Subject enrolment log (if appropriate)
 - Signed informed consent forms; informed consent checklist, if used
 - Template of letter to primary physician
 - If applicable, completed subject identification code list for randomized studies (at study completion)
9. Adverse Events
- Reports of Serious Adverse Events and SUSARs
 - Correspondence relating to SAEs and SUSARs
 - Notification of SUSARs to IEC/IRB
10. General Correspondence
11. Investigational Medicinal Product

- IMP receipt forms.
 - Procedure for temperature monitoring
 - Certificates of Analysis, if requested
 - IMP accountability records
 - Instructions for handling IMP
 - Example prescription form (if applicable)
 - Documentation of destruction of IMP
 - Randomization code location (if not kept in Investigator Site File)
12. Monitoring
- Pre-study and Initiation Site Visit Report forms
 - Case Record Form correction notes
 - Data query forms
13. Reports
- Any interim clinical study report
 - The final clinical study report. A synopsis will suffice
14. Completed eCRFs
- Copies of completed eCRFs or reference if stored separately
 - Copy of any eCRF and data query tracking and acknowledgement forms
15. Meetings
- Minutes of meetings, agenda and correspondence relating to meetings
16. Publications
- Any publications of trial results available before site closure

If any of these documents are issued in a language other than English then verified translations are required.

13.2. Subject Notes

The Investigator must maintain adequate records of subject participation for the duration of the study. These records must be available for inspection upon reasonable request by the Sponsor, members of the regulatory authorities or other authorized individuals. The Investigator must detail in the subject notes that the subject is eligible for the study prior to enrolment. The Investigator must also ensure that worksheets provided for the study that form part of the source data must always be included in the subject notes.

13.3. Availability of Data for Inspection

The Investigator is obliged to provide BPL, or BPL's representative, with complete test results and all data and reports within the timeframe agreed by both parties.

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives.

13.4. Archiving Study Documentation

The Investigator must make proper provision for archiving study documentation. Essential documents must be retained in accordance with ICH-GCP. Essential documents must be retained for two years after the last marketing approval in an ICH region or until at least two years have elapsed since the discontinuation of clinical development of the IMP. It is BPL's responsibility to inform the Investigator or Institute as to when these documents no longer need to be retained. It is the Investigator's responsibility to notify BPL, or BPL's representative, in writing if they are unable to make suitable provisions for archiving study documents at the study center. Prior to archive, subject ID codes should be kept in a suitable place to enable easy access at the Investigator site. Subject ID codes must be retained for a period of at least 15 years after issue of the final study report. Subject consent forms and other study related documentation must be retained for a maximum period of time permitted by the hospital, institution or private practice

Essential documents from trials which are not to be used in regulatory submissions should be retained for at least five years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with BPL.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified.

14. REPORT AND PUBLICATION

BPL's standard report and publication policy is detailed below. In the case of the agreement between BPL and the Investigator differing from this policy, what is stated in the agreement will override what is stated below.

BPL recognizes that the Investigator might wish to publish the results of the study. The Investigator and members of the Investigator's team engaged in the study shall not be permitted to present at symposia and professional meetings or to publish journals, theses or dissertations, or otherwise of their choosing, methods and results of the Study (all of which hereinafter referred to as "the Publication") without the consent of BPL.

In the case that the Investigator or members of the Investigator's team engaged in the study wish to pursue the Publication, the Investigator shall furnish BPL with copies of the Publication at least two months in advance of the intended date of whichever is the earliest submission of the Publication or presentation of the Publication or publication of the Publication or the making of a commitment to do any of the foregoing. The Investigator agrees, if BPL requests a meeting between the Investigator and BPL, to discuss in good faith the comments.

BPL shall have two months, after receipt of said copies, to object to such proposed Publication on reasonable grounds. For the avoidance of doubt the grounds that the subject matter is patentable or commercially sensitive shall constitute reasonable grounds.

Authorship should reflect work done by the Investigators and BPL personnel, in accordance with generally recognized principles of scientific collaboration.

15. REFERENCES

1. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
2. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.
3. FDA guidelines CFR 21 (www.fda.gov) which dictates the regulations and principles for conducting clinical trials in the USA, detailed guidelines are also provided.

APPENDIX III - LOCAL INVESTIGATOR'S RESPONSIBILITIES BASED ON THE ICH GUIDELINES FOR GOOD CLINICAL PRACTICE

1. LOCAL INVESTIGATOR

1.1 Investigator's Qualifications and Agreements

- 1.1.1 The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the IRB/EC, and/or the regulatory authority(ies).
- 1.1.2 The Investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the Sponsor.
- 1.1.3 The Investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- 1.1.4 The Investigator should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies).
- 1.1.5 The Investigator should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related duties.

1.2 Adequate Resources

- 1.2.1 The Investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- 1.2.2 The Investigator should have sufficient time to properly conduct and complete the study within the agreed study period.
- 1.2.3 The Investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.
- 1.2.4 The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.

1.3 Medical Care of Study Subjects

- 1.3.1 A qualified physician (or dentist, when appropriate), who is an Investigator or a sub-Investigator for the study, should be responsible for all study-related medical (or dental) decisions.
- 1.3.2 During and following a subject's participation in a study, the Investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study. The Investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.
- 1.3.3 It is recommended that the Investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.
- 1.3.4 Although a subject and their Parent(s)/Guardian(s) are not obliged to give their reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

1.4 Communication with IRB/EC

- 1.4.1 Before initiating a study, the Investigator should have written and dated approval/favorable opinion from the IRB/EC for the study protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information to be provided to subjects.
- 1.4.2 During the study the Investigator should provide to the IRB/EC all documents subject to review.

1.5 Compliance with Protocol

- 1.5.1 The Investigator should conduct the study in compliance with the protocol agreed by the Sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/EC. The Investigator and the Sponsor should sign the protocol, or an alternative contract, to confirm agreement.
- 1.5.2 The Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)).
- 1.5.3 The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

- 1.5.4 The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/EC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted.
- a) to the IRB/EC for review and approval/favorable opinion,
 - b) to the Sponsor for agreement and, if required,
 - a) to the regulatory authority(ies).

1.6 Investigational Product(s)

- 1.6.1 Responsibility for investigational product(s) accountability at the study site(s) rests with the Investigator.
- 1.6.2 Where allowed/required, the Investigator may/should assign some or all of the Investigator's duties for investigational product(s) accountability at the study site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator.
- 1.6.3 The Investigator and/or a pharmacist or other appropriate individual, who is designated by the Investigator, should maintain records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the Sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and study subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the Sponsor.
- 1.6.4 The investigational product(s) should be stored as specified by the Sponsor and in accordance with applicable regulatory requirement(s).
- 1.6.5 The Investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
- 1.6.6 The Investigator, or a person designated by the Investigator, should explain the correct use of the investigational product(s) to each subject/Parent(s)/Guardian(s) and should check, at intervals appropriate for the study, that each subject/Parent(s)/Guardian(s) are following the instructions properly.

1.7 Randomization Procedures and Unblinding

The Investigator should follow the study's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the study is blinded, the Investigator should promptly document and explain to the Sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

1.8 Informed Consent of Study Subjects

- 1.8.1 In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the Investigator should have the IRB/EC written approval/favorable opinion of the written informed consent form and any other written information to be provided to subject/Parent(s)/Guardian(s).
- 1.8.2 The written informed consent form and any other written information to be provided to subjects/Parent(s)/Guardian(s) should be revised whenever important new information becomes available that may be relevant to the subject's/Parent(s)/Guardian(s)' consent. Any revised written informed consent form, and written information should receive the IRB/EC approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's/Parent(s)/Guardian(s)' willingness to continue participation in the study. The communication of this information should be documented.
- 1.8.3 Neither the Investigator, nor the study staff, should coerce or unduly influence a subject/Parent(s)/Guardian(s) to participate or to continue to participate in a study.
- 1.8.4 None of the oral and written information concerning the study, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the Investigator, the institution, the Sponsor, or their agents from liability for negligence.
- 1.8.5 The Investigator, or a person designated by the Investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the study including the written information given approval/favorable opinion by the IRB.
- 1.8.6 The language used in the oral and written information about the study, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
- 1.8.7 Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- 1.8.8 Prior to a subject's participation in the study, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

- 1.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
- 1.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
- a) That the study involves research.
 - b) The purpose of the study.
 - c) The study treatment(s) and the probability for random assignment to each treatment.
 - d) The study procedures to be followed, including all invasive procedures.
 - e) The subject's/Parent(s)/Guardian(s)' responsibilities.
 - f) Those aspects of the study which are experimental.
 - g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
 - h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject/Parent(s)/Guardian(s) should be made aware of this.
 - i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
 - j) The compensation and/or treatment available to the subject/Parent(s)/Guardian(s) in the event of study-related injury.
 - k) The anticipated prorated payment, if any, to the subject/Parent(s)/Guardian(s) for participating in the study.
 - l) The anticipated expenses, if any, to the subject/Parent(s)/Guardian(s) for participating in the study.
 - m) That the subject's participation in the study is voluntarily through its Parent(s)/Guardian(s) and that the subject/Parent(s)/Guardian(s) may refuse to

participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject/Parent(s)/Guardian(s) are otherwise entitled.

- n) That the monitor(s), the auditor(s), IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
 - o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
 - p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
 - q) The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.
 - r) The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
 - s) The expected duration of the subject's participation in the study.
 - t) The approximate number of subjects involved in the study.
- 1.8.11 Prior to participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- 1.8.12 When a clinical study (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
- 1.8.13 Except as described in 1.8.14, a non-therapeutic study (i.e. a study in which there is not anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.
- 1.8.14 Non-therapeutic studies may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- a) The objectives of the study cannot be met by means of a study in subjects who can give informed consent personally.
- b) The foreseeable risks to the subjects are low.
- c) The negative impact on the subject's well-being is minimized and low.
- d) The study is not prohibited by law.
- e) The approval/favorable opinion of the IRB/EC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such studies, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

- 1.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/EC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the study as soon as possible and consent to continue and other consent as appropriate (see 1.8.10) should be requested.

1.9 Records and Reports

- 1.9.1 The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- 1.9.2 Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.
- 1.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained): this applies to both written and electronic changes or corrections (see 1.18.4 (n)). Sponsors should provide guidance to Investigators and/or the Investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by Sponsor's designated representatives are documented, are necessary, and are endorsed by the Investigator. The Investigator should retain records of the changes and corrections.
- 1.9.4 The Investigator should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Study and as required by the applicable regulatory requirement(s). The Investigator should take measures to prevent accidental or premature destruction of these documents.

- 1.9.5 Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained.
- 1.9.6 The financial aspects of the study should be documented in an agreement between the Sponsor and the Investigator.
- 1.9.7 Upon request of the monitor, auditor, IRB, or regulatory authority, the Investigator should make available for direct access all requested study-related records.

1.10 Progress Reports

- 1.10.1 The Investigator should submit written summaries of the study status to the IRB/EC annually, or more frequently, if requested by the IRB/EC.
- 1.10.2 The Investigator should promptly provide written reports to the Sponsor, the IRB/EC and, where applicable, the institution on any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects.

1.11 Safety Reporting

- 1.11.1 All serious adverse events (SAEs) should be reported immediately to the Sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the study subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The Investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/EC.
- 1.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the Sponsor according to the reporting requirements and within the time periods specified by the Sponsor in the protocol.
- 1.11.3 For reported deaths, the Investigator should supply the Sponsor and the IRB/EC with any additional requested information (e.g. autopsy reports and terminal medical reports).

1.12 Premature Termination or Suspension of a Study

If the study is prematurely terminated or suspended for any reason, the Investigator should promptly inform the study subjects/Parent(s)/Guardian(s), should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

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- 1.12.1 If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator should promptly inform the Sponsor and the IRB/EC, and should provide the Sponsor and the IRB/EC a detailed written explanation of the termination or suspension.
- 1.12.2 If the Sponsor terminates or suspends a study, the Investigator should promptly inform the institution where applicable and the Investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.
- 1.12.3 If the IRB/EC terminates or suspends its approval/favorable opinion of a study, the Investigator should inform the institution where applicable and the Investigator should promptly notify the Sponsor and provide the Sponsor with a detailed written explanation of the termination or suspension.

1.13 Final Report(s) by Investigator

Upon completion of the study, the Investigator, where applicable, should inform the institution: the Investigator should provide the IRB/EC with a summary of the study's outcome, and the regulatory authority(ies) with any reports required.

APPENDIX IV- VISIT SCHEDULE

Table 2 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

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	
Virology ⁱ	X																X	
Parvovirus B19 ^j		X	X														X	
Direct Coombs' Test ^k		X	X						X								X	
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 3 Pharmacokinetic Assessment Schedule for Subgam-VF (Week 21 to Week 22^{a, b, d})

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 ^c (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 If the infusion just prior to PK sampling has to be rescheduled, then the PK sampling should be postponed to ensure that the PK samples are collected seven days after the last Subgam-VF infusion and the sampling times in Table 3 are adhered to.

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

d In exceptional circumstances, and with prior Sponsor approval, if one of the following PK samples is 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).

APPENDIX V- MAXIMUM BLOOD WITHDRAWAL VOLUMES**Table 4 IRB Maximum Allowable Total Blood Draw Volumes (Clinical + Research)**

Body Wt (Kg)	Body Wt (lbs)	Total blood volume (mL)	Maximum allowable volume (mL) in one blood draw (= 2.5% of total blood volume)	Total volume (clinical + research) maximum volume (mL) drawn in a <u>30-day period</u>	Minimum Hgb required at time of blood draw	Minimum Hgb required at time of blood draw if subject has respiratory/CV compromise
1	2.2	100	2.5	5	7.0	9.0 -10.0
2	4.4	200	5	10	7.0	9.0-10.0
3	6.3	240	6	12	7.0	9.0-10.0
4	8.8	320	8	16	7.0	9.0-10.0
5	11	400	10	20	7.0	9.0-10.0
6	13.2	480	12	24	7.0	9.0-10.0
7	15.4	560	14	28	7.0	9.0-10.0
8	17.6	640	16	32	7.0	9.0-10.0
9	19.8	720	18	36	7.0	9.0-10.0
10	22	800	20	40	7.0	9.0-10.0
11-15	24-33	880-1200	22-30	44-60	7.0	9.0-10.0
16-20	35-44	1280-1600	32-40	64-80	7.0	9.0-10.0
21-25	46-55	1680-2000	42-50	64-100	7.0	9.0-10.0
26-30	57-66	2080-2400	52-60	104-120	7.0	9.0-10.0
31-35	68-77	2480-2800	62-70	124-140	7.0	9.0-10.0
36-40	79-88	2880-3200	72-80	144-160	7.0	9.0-10.0
41-45	90-99	3280-3600	82-90	164-180	7.0	9.0-10.0
46-50	101-110	3680-4000	92-100	184-200	7.0	9.0-10.0
51-55	112-121	4080-4400	102-110	204-220	7.0	9.0-10.0
56-60	123-132	4480-4800	112-120	224-240	7.0	9.0-10.0
61-65	134-143	4880-5200	122-130	244-260	7.0	9.0-10.0
68-70	145-154	5280-5600	132-140	264-280	7.0	9.0-10.0
71-75	156-185	5680-6000	142-150	284-300	7.0	9.0-10.0
76-80	167-176	6080-6400	152-160	304-360	7.0	9.0-10.0
81-85	178-187	6480-6800	162-170	324-340	7.0	9.0-10.0
86-90	189-198	6880-7200	172-180	344-360	7.0	9.0-10.0
91-95	200-209	7280-7600	182-190	364-380	7.0	9.0-10.0
96-100	211-220	7680-8000	192-200	384-400	7.0	9.0-10.0

Source: Tables used by the Committee on Clinical Investigations, Children's Hospital in Los Angeles, CA; Baylor College of Medicine, Dallas, TX; and Cincinnati Children's Hospital Institutional Review Board, OH

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