

**A Prospective, Open-Label, Multicenter Study of the Efficacy, Safety,  
Tolerability, and Pharmacokinetics of Therapure PlasmaCap IG in Adults  
and Children with Primary Immune Deficiency Diseases**

|                                          |                                                                                            |
|------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>PROTOCOL NUMBER</b>                   | TBI-001-IGIV                                                                               |
| <b>NCT NUMBER</b>                        | NCT03238079                                                                                |
| <b>SPONSOR</b>                           | Therapure Biopharma Inc.<br>2585 Meadowpine Boulevard<br>Mississauga, ON L5N 8H9<br>Canada |
| <b>INVESTIGATIONAL MEDICINAL PRODUCT</b> | 10% Immunoglobulin Intravenous (IGIV)                                                      |
| <b>VERSION, DATE</b>                     | Version 5, 06 June 2018                                                                    |

Protocol Number: TBI-001-IGIV

A Prospective, Open-Label, Multicenter Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Therapure PlasmaCap IG in Adults and Children with Primary Immune Deficiency Diseases

|                                   |                                                                                            |
|-----------------------------------|--------------------------------------------------------------------------------------------|
| SPONSOR                           | Therapure Biopharma Inc.<br>2585 Meadowpine Boulevard<br>Mississauga, ON L5N 8H9<br>Canada |
| CRO RESPONSIBLE FOR MONITORING    | [REDACTED]                                                                                 |
| SPONSOR'S SAFETY OFFICER          | [REDACTED]                                                                                 |
| INVESTIGATIONAL MEDICINAL PRODUCT | 10% Immunoglobulin Intravenous (IGIV)                                                      |
| VERSION, DATE                     | [REDACTED]                                                                                 |

[REDACTED]

ECC5CD881EF8460

Name/Signature

[REDACTED]

Date

[REDACTED]

[REDACTED]

Name/Signature

Contract Research Organization's Representative

Date

CONFIDENTIALITY STATEMENT

The information contained in this protocol is provided to you in confidence for review by you, your staff, and any applicable regulatory authorities or Institutional Review Boards/Independent Ethics Committees/Research Ethics Boards. It is understood that this information may not be disclosed to any other party other than those directly involved in the study and listed on your Delegation of Duties Log and/or Form FDA 1572, in any form, without prior authorization from the sponsor, except to the extent necessary to obtain informed consent from the persons who may be administered investigational product.

Therapure Biopharma Inc.

Confidential

**SIGNATURE PAGE**

I, \_\_\_\_\_ have received from the CRO a copy of the protocol number  
*Investigator's Name*

TBI-001-IGIV, entitled:

**"A Prospective, Open-Label, Multicenter Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Therapure PlasmaCap IG in Adults and Children with Primary Immune Deficiency Diseases"**

\_\_\_\_\_ I agree to the conditions as set out in this protocol and fully accept that any change requires prior approval from the sponsor.

I agree to carry out all terms of this protocol in accordance with ICH Guidelines, and the Code of Federal Regulations 21 CFR Parts 11, 50, 54, 56, 312, and 314, Health Canada, the EU Clinical Trials Directive, and any other applicable requirements. I/we will ensure that the investigational medicinal product will be used only as described in this protocol.

\_\_\_\_\_  
\_\_\_\_\_

The information contained in this protocol is provided to me in confidence for review only by myself, the Institutional Review Board/Research Ethics Board authorized to review and approve the study at this study site, and designated research staff participating in this clinical study as listed on the FDA Form 1572 and Delegation of Duties Log.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorization from the sponsor, except to the extent necessary to obtain informed consent from potential study participants.

\_\_\_\_\_  
*Name /Signature*  
*Investigator*

\_\_\_\_\_  
*Date*

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## 1. STUDY SYNOPSIS

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                      | A Prospective, Open-Label, Multicenter Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Therapure PlasmaCap IG in Adults and Children with Primary Immune Deficiency Diseases                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Indication</b>                 | PlasmaCap IG is an immune globulin infusion (human) replacement therapy for primary immune deficiency diseases (PIDD) in adult and pediatric patients two years of age or older.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Study sites &amp; location</b> | Approximately [REDACTED] sites in the United States and Canada                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Phase</b>                      | Phase 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Population</b>                 | <p>Approximately [REDACTED] 2 to 70 years of age will be enrolled to achieve [REDACTED]. Two groups (Group 1 for adults and Group 2 for children and adolescents, 2 to &lt; 17 years of age) will ensure an appropriate number of subjects in each age demographic. A pharmacokinetic (PK) sub-study will also be conducted within both age groups. At least [REDACTED] in Group 1 will receive IMP for a minimum of three infusions before any pediatric subjects in Group 2 may begin the trial.</p> <p><b>Adults</b><br/> <u>Group 1</u> will enroll approximately [REDACTED] 17 to 70 years of age to obtain [REDACTED].<br/> <u>Within Group 1</u>, a PK subset (<b>Group 1b</b>) will enroll approximately [REDACTED] 17 to 70 years of age to [REDACTED].<br/> Group 1 subjects who are not in Group 1b will be designated as <b>Group 1a</b> (Non-PK).</p> <p><b>Children</b><br/> <u>Group 2</u> will enroll approximately [REDACTED]. [REDACTED]<br/> Group 2 will enroll up to [REDACTED] 2 to &lt;6 years of age, at least [REDACTED] 6 to &lt;12 years of age, and up to [REDACTED] 12 to &lt; 17 years of age (at time of screening).<br/> <u>Within Group 2</u>, a PK subset (<b>Group 2b</b>) will enroll approximately [REDACTED]. [REDACTED]<br/> Group 2b will enroll up to [REDACTED] 2 to &lt;6 years of age, at least [REDACTED] 6 to &lt;12 years of age, and up to [REDACTED] 12 to &lt;17 years of age (at time of screening).<br/> Group 2 subjects who are not in Group 2b will be designated as <b>Group 2a</b> (Non-PK).</p> |

|                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Investigational Medicinal Product</b> | 10% liquid formulation of Therapure Biopharma PlasmaCap IG, human immunoglobulin for intravenous (iv) use.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Duration</b>                          | The duration of the study will be approximately 41 months in total. Approximately 4 months are needed for study set-up and to obtain IRB/REB approval at all sites. Approximately 7-20 months are needed to meet the recruitment of [REDACTED] in all groups. Each subject must receive infusions for 12 months so it will take approximately 34 months from screening, enrollment and participation to completion for all subjects. Approximately 3 months are needed for final data reconciliation and closeout of all sites.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Purpose and Objectives</b>            | <p><b>Purpose</b></p> <p>The purpose of this study is to investigate the efficacy, safety, tolerability, and PK profile of the investigational medicinal product (IMP) and to determine, based on historical control data, how it compares with other 10% intravenous immunoglobulin (IGIV) products currently licensed in North America for the treatment of subjects with PIDD.</p> <p><b>Efficacy Objectives</b></p> <ul style="list-style-type: none"> <li>The primary efficacy objective of the study is to demonstrate the efficacy of the IMP by determining that the mean annual acute serious bacterial infection (SBI) rate (as defined in <a href="#">Appendix 20.1</a>) is statistically significantly lower than one infection per subject per year.</li> </ul> <p>The secondary efficacy objectives of the study are to assess:</p> <ul style="list-style-type: none"> <li>Average serum total IgG trough concentrations prior to each infusion;</li> <li>Number of infection episodes (serious and non-serious)</li> <li>Number of days out of work/school/daycare or;</li> <li>Number of days unable to perform normal daily activities due to infections;</li> <li>Ability of the IMP to maintain stable, therapeutic IgG levels;</li> <li>Episodes of fever;</li> <li>Number of days subjects are hospitalized due to infections;</li> <li>Use of antibiotics to treat infection and for short-term prophylaxis prior to and following surgical and dental procedures.</li> </ul> <p><b>Safety Objectives</b></p> <ul style="list-style-type: none"> <li>To examine the safety and tolerability of IMP by monitoring Adverse Events (AEs) after consent has been given through the Safety Follow-up Visit (SFV);</li> </ul> |

|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                           | <ul style="list-style-type: none"> <li>To examine temporally associated AEs (within 72 hours after infusion of the IMP), regardless of their relationship to IMP; <ul style="list-style-type: none"> <li>To monitor viral safety;</li> <li>To monitor for hemolysis and thromboembolic events.</li> <li>To observe the number and proportion of subjects who experience one or more suspected <u>serious</u> adverse reactions or adverse reactions, as well as the sum total of such reactions.</li> <li>To observe the number and proportion of subjects who experience one or more suspected adverse events or adverse events, as well as the sum total of such events.</li> </ul> </li> </ul> <p><b>Pharmacokinetic Objectives</b></p> <ul style="list-style-type: none"> <li>To determine the PK profiles based on the plasma concentration-time curve; half life (<math>t_{1/2}</math>) for each of the phases of this curve (the number of phases will be dictated by the data); area under the curve (AUC) including both AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>; volume of distribution at steady state (<math>V_{ss}</math>); clearance (Cl); mean residence time (MRT); elimination rate constants and maximum plasma concentration (<math>C_{max}</math>) for total IgG, IgG subclasses, and specific antibodies following administration of IMP;</li> <li>To determine the serum concentrations of total IgG, IgG subclasses (IgG1, IgG2, IgG3, and IgG4), and specific antibodies against <i>Streptococcus pneumoniae</i>.</li> </ul> |
| <b>Inclusion Criteria</b> | <ol style="list-style-type: none"> <li>Subject has a confirmed clinical diagnosis of a Primary Immune Deficiency Disease (PIDD), which requires treatment with IGIV. Documented hypogammaglobulinemia in the setting of PIDD is required in one of the following PIDDs: <ul style="list-style-type: none"> <li>Agammaglobulinemia</li> <li>Common Variable Immune Deficiency (CVID)</li> <li>Hyper-IgM Syndrome (HIGM), with documented IgG levels &lt;500 mg/dL</li> <li>Hypogammaglobulinemia, with documented IgG levels &lt;500 mg/dL and demonstration of specific deficiency of antibody production when available.</li> <li>Severe combined immunodeficiency (SCID) status post hematopoietic stem cell transplantation (HSCT) with normal T cell function and deficient antibody production with documented IgG levels &lt;500 mg/dL</li> <li>Adenosine deaminase deficiency resulting in severe combined immunodeficiency (ADA-SCID) receiving Adagen with normal</li> </ul> </li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           | <p>T cell function and deficient antibody production with documented IgG levels &lt;500 mg/dL</p> <ol style="list-style-type: none"> <li>2. Subject/guardian has provided written informed consent (and assent, as applicable).</li> <li>3. Subject is between 2 and 70 years of age.</li> <li>4. Subject has received IGIV therapy at 21- or 28-day (<math>\pm</math> 4 days) intervals for at least three consecutive months (12 weeks) [REDACTED] (without having a <math>\geq</math>25% change in dose) prior to Screening or;</li> <li>5. Subject has received commercial subcutaneous immunoglobulin (SCIG) [REDACTED] (without having a <math>\geq</math>25% change in dose) at any dosing schedule for at least 4 consecutive weeks prior to Screening. Subjects on SCIG must have documentation that they have received and tolerated IGIV treatment prior to SCIG treatment.</li> <li>6. Subject has a documented trough of [REDACTED] in the 6 months prior to and including Screening.</li> <li>7. Females of childbearing potential must be willing to use an effective form of birth control (eg, oral contraceptives) for the duration of the study, per IRB/REB guidelines.</li> <li>8. Subject agrees to comply with the requirements of the protocol.</li> </ol> |
| <b>Exclusion Criteria</b> | <ol style="list-style-type: none"> <li>1. Subject has had a documented bacterial or viral infection within seven days prior to the Baseline Visit or is receiving antibiotic treatment (Note: Subjects who have been asymptomatic for seven days but have not completed treatment or use a topical antibacterial, that is minimally absorbed systemically, when necessary (PRN) are not excluded).</li> <li>2. Subject has secondary immunodeficiency.</li> <li>3. Subject has been diagnosed with specific antibody deficiency or IgG subclass deficiency.</li> <li>4. Subject has a history of thrombotic events, such as deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism, etc. within the year prior to Screening.</li> <li>5. Subject has had an immune globulin associated arterial or venous thrombotic/thrombo-embolic event (TEE) within 7 days of an IgG infusion or a TEE that is not associated with an immune globulin within one year of Screening.</li> </ol>                                                                                                                                                                                                                                                              |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|  | <ol style="list-style-type: none"> <li>6. Subject has received any IMP under investigation within the past 30 days (<math>\pm</math> 2 days) at the time of the Baseline Visit.</li> <li>7. Subject has received blood products (except for IGIV, SCIG, or albumin) within six months of Screening.</li> <li>8. Subject's lab results show evidence of infection with a positive nucleic acid test (NAT) test of human immunodeficiency virus (HIV)-1 and HIV-2, hepatitis B virus (HBV), or hepatitis C virus (HCV).</li> <li>9. Subject has anemia (<math>\leq</math>8.5 g/dL).</li> <li>10. Subject has levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <math>&gt;</math>3.0 times the upper limit of normal (ULN).</li> <li>11. Subject has severe neutropenia (<math>\leq</math>1000 neutrophils per <math>\text{mm}^3</math>).</li> <li>12. Subject has creatinine concentration <math>&gt;</math>1.5 times the ULN and eGFR as calculated by the comprehensive metabolic panel (CMP) as <math>&lt;</math>60mL/min/1.73 <math>\text{m}^2</math>.</li> <li>13. Subject is receiving other immunosuppressive or immunomodulatory drugs or chemotherapy.</li> <li>14. Subject is taking or has taken, within the four weeks prior to Screening, prednisone at <math>\geq</math>0.15 mg/kg/day for more than 10 days. (Note: Topical agents, inhaled corticosteroids, and dermatologics are not excluded.)</li> <li>15. Subject has ever had a severe anaphylactic reaction to a blood or IgG product in the opinion of the PI.</li> <li>16. Subject has lymphoid malignancy, leukemia, or any other history of malignancy within the past five years, except squamous cell and basal cell carcinoma of the skin (not melanoma).</li> <li>17. Subject has hypoalbuminemia, protein-losing enteropathy, or proteinuria greater than 300 mg/24 hours except for subjects with documented orthostatic proteinuria.</li> <li>18. Subject has immunoglobulin A (IgA) deficiency with known antibodies to IgA.</li> <li>19. Female who is pregnant, breastfeeding, or planning a pregnancy during the course of the study (women who become pregnant during the study will be withdrawn from the study).</li> <li>20. Any condition that is likely to interfere with evaluation of IMP or satisfactory conduct of the trial in the Principal Investigator (PI) or designee's opinion.</li> </ol> |
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|                                                            | 21. Subjects who may not be compliant or have a history of non-compliance in the opinion of the PI.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Clinical Study Design, Description, and Methodology</b> | <p><b>Screening Visit</b></p> <p>All subjects will sign the informed consent form (ICF) for the main study and for the optional PK study as appropriate and applicable for their age. After the applicable written consent is provided, subjects will undergo the Screening Visit testing to obtain all data needed in order to confirm their eligibility for participation in the study.</p> <p>Subjects will provide their complete medical history to include past surgeries dating back two years. Any available documentation of immunoglobulin treatment for the past 3 months will be captured, including the current treatment regimen dose. Documentation will need to be provided to demonstrate 3 months of a stable mg/kg/infusion dose.</p> <p>Prior medications will be captured for the 4 weeks prior to Screening.</p> <p>Serious bacterial infections (SBIs) will be documented for the past ten years.</p> <p>Subjects will undergo a physical exam, which will include review of any x-rays within the past six months, as well as an assessment of clinical signs and symptoms of pulmonary infiltrates at the time of Screening. A screening chest x-ray will be performed if a normal, or “not clinically significant” one, is not available within the past six months.</p> <p>Subjects receiving SCIG must have tolerated prior IGIV use on a 21- or 28-day regimen and will return to their most recent IGIV regimen for the duration of the study, unless the Investigator deems it necessary for the subject’s safety to change the regimen.</p> <p>Blood samples will be collected for assessments of hematology, serum chemistry, virology, urinalysis, pregnancy, and IgG trough level. Retention samples for potential additional infectious agents and IgG testing will also be collected.</p> <p><b>Baseline Visit</b></p> <p>Baseline Visit will be scheduled based on the current IgG treatment regimen (21 days [<math>\pm 2</math> days] or 28 days [<math>\pm 2</math> days]) from their last infusion at the time of Screening. For subjects receiving SCIG, the Baseline Visit will take place the equivalent number of days (7, 14, 21, or 28 days) (<math>\pm 2</math> days), based on their standard dosing regimen, after the last dose of SCIG. Any changes in medical history and use of medication since the Screening Visit will be noted, and eligibility will be reconfirmed.</p> |

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|  | <p>Subjects will undergo a physical exam including weight, and vital signs.</p> <p>Blood samples will be collected for assessments of hematology, serum chemistry, virology, hemolysis, urinalysis, pregnancy, and IgG trough level. Retention samples for potential additional infectious agents and IgG testing will be collected.</p> <p>Subjects will be issued subject diaries and trained on their proper maintenance (ie, complete, accurate, and timely entries of adverse events that occur, days of work/school that are missed, and medications that are taken between study visits). Subjects will be instructed to bring their diaries to each visit to be collected by and reviewed with the PI or designee (ie, physician, physician's assistant or nurse practitioner) for accuracy and completeness.</p> <p>Infusion 1 of IMP will be administered at the Baseline Visit.</p> <p>Vital signs will be taken in accordance with the following directions at Baseline Visit and at all other infusions:</p> <ul style="list-style-type: none"><li>• ≤ 30 minutes pre-infusion;</li><li>• 10 minutes (± 5 minutes) after the start of infusion</li><li>• 10 minutes (± 5 minutes) after each rate change;</li><li>• 30 minutes (± 5 minutes) after the final rate change and then hourly (± 10 minutes) after that;</li><li>• 30 minutes post-infusion (± 5 minutes); and</li><li>• 60 minutes post-infusion (± 15 minutes).</li></ul> <p>Prior to each infusion, ensure the subject is properly hydrated, per site's standard of care. During all infusions, the subject will be monitored for AEs at each time point that vital signs are measured, and the infusion site will be examined if the subjects report pain at the site. Infusion rates and volumes of IMP will be carefully documented throughout all infusions. Subjects will be monitored in the clinic for one hour after all infusions, then all efforts will be made to monitor infusion-related AEs occurring within 24 and 72 hours after all infusions (by calling or texting the subject at home 24 and 72 hours post infusion).</p> <p>Concomitant medications will be recorded throughout the study period, and subjects will be reminded to document these in their subject diary.</p> <p>All AEs will be recorded from the signing of the ICF through the Safety Follow-up Visit (SFV).</p> <p>For all visits, an SBI will be confirmed according to testing and parameters stipulated in the Diagnostic Criteria for Serious Infection Types (see <a href="#">Section 20.1</a>).</p> |
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|  | <p><b>Visit 2 – Visit 16 (21-Day Regimen Subjects)</b></p> <p><b>Visit 2 – Visit 12 (28-Day Regimen Subjects)</b></p> <p>All subjects will receive 12 months of regular IMP infusions per protocol.</p> <p>Subjects on a 21-day regimen will receive one infusion at Visit 1, one infusion at visits 2 through 16, and one infusion at Visit 17 (Final Treatment and Termination Visit [FTTV]), totaling 17 infusions.</p> <p>Subjects on a 28-day regimen will receive one infusion at Visit 1, one infusion at visits 2 through 12, and one infusion at Visit 13 (FTTV), totaling 13 infusions.</p> <p>Vital signs will be taken according to the schedule outlined above.</p> <p>Hematology, serum chemistry and urinalysis will be obtained at Visits 0, 1, 2, 5, 8, 11, 14, 17/FTTV, and SFV for subjects on a 21-day regimen; and for subjects on a 28-day regimen, hematology, serum chemistry and urinalysis will be obtained at Visits 0, 1, 2, 5, 8, 11, 13/FTTV, and SFV.</p> <p>Testing for hemolysis and pregnancy will be performed at all visits. An IgG trough level, including a backup serum sample, will be obtained prior to infusion at all visits. Subjects will be asked about their use of concomitant medications and the occurrence of AEs. The subject diary will be collected by and reviewed with the PI or designee for accuracy and completeness (special care should be taken to monitor AEs occurring within 72 hours post infusion), and a new subject diary will be issued. Vital signs will be taken according to the schedule outlined above under Baseline Visit.</p> <p><b>Final Treatment and Termination Visit (FTTV) – Visit 17 or Visit 13</b></p> <p>The FTTV will occur as Visit 17 for subjects on a 21-day regimen or Visit 13 for subjects on a 28-day regimen. During the FTTV, last IMP infusion will be performed for both regimens. Subjects will be asked about their use of concomitant medications and the occurrence of AEs as well as any absences from school or work and treatments with antibiotics.</p> <p>The subject diary will be collected by and reviewed with the PI or designee for accuracy and completeness and a new subject diary will be issued. Vital signs will be taken according to the schedule outlined above under Baseline Visit. A physical exam will be performed, and blood samples will be collected for hematology, serum chemistry, hemolysis, urinalysis (including pregnancy testing), and IgG trough level including a retention serum sample. The subject will receive his or her last infusion, after which, the subject will be monitored by direct observation for one hour post infusion and by calling or texting the subject at home 24 and 72 hours post infusion.</p> |
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|  | <p><b>Early Termination Subjects (FTTV)</b></p> <p>If the subject terminates treatment prior to Visit 17 (21-day regimen) or Visit 13 (28-day regimen), all procedures for the FTTV should be added to the procedures for the scheduled visit. In addition, if the subject is terminating early from the study and cannot return for the SFV, the procedures for the SFV should also be completed.</p> <p><b>Safety Follow-up Visit (SFV) – Visit 18 or Visit 14</b></p> <p>The Safety Follow-up Visit (SFV) will occur as Visit 18 for subjects on a 21-day regimen or Visit 14 for subjects on a 28-day regimen. Blood and urine samples will be collected in support of hematology, serum chemistry, hemolysis, urinalysis (including pregnancy testing), IgG trough level, and NAT and serology viral safety testing (with the exclusion of tests that are positive at baseline). Retention samples for potential additional infectious agents and IgG testing will be collected. <b>During SFV, all blood samples should be collected prior to infusion of subject's standard IgG treatment.</b></p> <p>Vital signs will also be taken prior to infusion of subject's standard IgG treatment, as described above.</p> <p>Subjects will be asked about their use of concomitant medications and the occurrence of AEs as well as any absence from school/work and antibiotic use. The final subject diary will be collected by and reviewed with the PI or designee for accuracy and completeness (special care should be taken to monitor AEs occurring within 72 hours post infusion). Subjects on the 21-day regimen will return for SFV 21 days (<math>\pm 2</math> days) after Visit 17, and subjects on the 28-day regimen will return for SFV 28 days (<math>\pm 2</math> days) after Visit 13.</p> <p><b>PK Study – Group 1b and Group 2b</b></p> <p>Samples for the PK study will be taken at Infusion 6, Visit 7 (21-day regimen subjects) or Infusion 5, Visit 6 (28-day regimen subjects). Samples will be obtained from at least [REDACTED] in Group 1b and at least [REDACTED] in Group 2b. Note that vitals should be taken at least 5 minutes prior to any PK sampling.</p> <p>Additional samples for PK pre-dose baseline analysis will be obtained between <math>\geq 15</math> and <math>\leq 30</math> minutes prior to the infusion for Group 1b and Group 2b and then as follows:</p> <p><b><u>Group 1b:</u></b></p> <ul style="list-style-type: none"> <li>• 15 minutes (<math>\pm 5</math> minutes) after the end of the infusion;</li> <li>• 1 hour (<math>\pm 10</math> minutes) after the end of the infusion;</li> <li>• 4 hours (<math>\pm 15</math> minutes) after the end of the infusion;</li> <li>• 24 hours (<math>\pm 1</math> hour) after the end of the infusion;</li> <li>• 7 days (<math>\pm 1</math> day) after the end of the infusion;</li> </ul> |
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|  | <ul style="list-style-type: none"> <li>• 14 days (<math>\pm</math> 1 day) after the end of the infusion;</li> <li>• 21 days (<math>\pm</math> 2 days) after the end of the infusion (only for subjects on a 21-day cycle);</li> <li>• 28 days (<math>\pm</math> 2 days) after the end of the infusion (only for subjects on a 28-day cycle).</li> </ul> <p><b><u>Group 2b:</u></b></p> <ul style="list-style-type: none"> <li>• 15 minutes (<math>\pm</math> 5 minutes) after the end of the infusion;</li> <li>• 4 hours (<math>\pm</math> 15 minutes) after the end of the infusion;</li> <li>• 24 hours (<math>\pm</math> 1 hour) after the end of the infusion;</li> <li>• 7 days (<math>\pm</math> 1 day) after the end of the infusion;</li> <li>• 14 days (<math>\pm</math> 1 day) after the end of the infusion;</li> <li>• 21 days (<math>\pm</math> 2 days) after the end of the infusion (only for subjects on a 21-day cycle);</li> <li>• 28 days (<math>\pm</math> 2 days) after the end of the infusion (only for subjects on a 28-day cycle).</li> </ul> <p><b>Clinical Assessments</b></p> <p>During the physical infusion, or while the subject is in the clinic, specific attention will be paid for signs and symptoms of hemolysis and thrombosis.</p> <ul style="list-style-type: none"> <li>• <b>Follow up calls/texts:</b> If during the 24- and/or 72-hour post infusion phone calls/text message follow-ups the subject reports any symptoms of hemolysis or thrombosis, the subject will be asked to return to the site immediately for examination and full panel of testing per the site's standard of care and the PI's discretion.</li> <li>• Note: The subjects will be asked about any AE's during the 24- and 72-hour post infusion phone/text message follow-ups.</li> </ul> <p><b>The following are some of the common symptoms of Hemolysis and Thrombosis:</b></p> <ul style="list-style-type: none"> <li>• <b>Hemolysis:</b> Abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, enlargement of the spleen and liver, tachycardia, and heart murmur.</li> <li>• <b>Thrombosis:</b> Tenderness and pain along line of femoral or popliteal veins, entire limb swelling, pitting edema, lower leg pain. Systemic signs of thrombosis include dyspnea, cough, hemoptysis, diaphoresis or sudden chest pain that worsens with deep inspiration, sweating, anxiety and fatigue.</li> </ul> |
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|  | <p><b>Laboratory Assessments</b></p> <p>Serum trough IgG levels will be measured at all visits prior to administration. Total IgG levels for PK subjects (including Subclasses and Antibodies for adults and children &gt; 12 years of age) will be done after administration of IMP at visits 5 or 6 according to the timepoints in <a href="#">Section 7.7</a>.</p> <p>IgG subclasses (IgG1, IgG2, IgG3, and IgG4) and specific antibodies against <i>Streptococcus pneumoniae</i> will be measured at visits 5 or 6 for the PK subjects &gt; 12 years of age.</p> <p>Viral testing consists of NAT and serology testing for HAV, HBV, HCV, HIV-1, HIV-2, and PVB19. Testing is conducted at Screening (excluding HAV and PVB19), baseline, and prior to the first infusion of regular IgG treatment at the SFV (excluding any tests with positive results at baseline). Additional samples collected from each subject at Screening, Baseline, and the SFV will be retained for possible future testing of additional infectious agents.</p> <p>Safety testing samples as outlined below will be obtained at Screening, Baseline, and Visit 2, 5, 8, 11, 13/FTTV, and SFV for subjects on the 28-day schedule and Visits 2, 5, 8, 11, 14, 17/FTTV, and SFV for subjects on a 21-day schedule. The samples will be analyzed by a central laboratory:</p> <ul style="list-style-type: none"> <li>• <b>Hematology</b> (red blood cells [RBC], white blood cells, [WBC], platelets, hemoglobin, hematocrit, platelets, differential count, reticulocytes);</li> <li>• <b>Serum chemistry</b> (total bilirubin, creatinine, urea, total protein, lactate dehydrogenase [LDH], creatine kinase [CK], blood urea nitrogen [BUN], alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP]);</li> </ul> <p>The following will be obtained at all visits for all subjects:</p> <ul style="list-style-type: none"> <li>• <b>Urinalysis</b> (protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick; sediment analysis);</li> <li>• <b>Urine Pregnancy</b> test will be performed at all visits for females (if applicable).</li> <li>• <b>Testing for Hemolysis will include (see also flowchart in <a href="#">Section 1.4</a>):</b> <ul style="list-style-type: none"> <li>○ <b>Pre Infusion:</b> Serum haptoglobin, plasma free hemoglobin, Direct Coombs test, urine hemosiderin.</li> <li>○ <b>Post Infusion:</b> If, during an infusion the subject presents with evidence of hemolysis (i.e. sudden pallor or fatigue, red or brown urine, are present), then post infusion labs will be drawn before the subject leaves the site. This will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs</li> </ul> </li> </ul> |
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|  | <p>test, and urine hemosiderin. In addition, if the subject reports any of the following post infusion symptoms at home: abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, tachycardia; and on clinical assessment shows signs of enlargement of the spleen and liver and a heart murmur, a post infusion sample will be taken, which will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test and urine hemosiderin.</p> <ul style="list-style-type: none"> <li>○ <b>Positive Direct Coombs Test Results:</b> If any Direct Coombs test result is positive, the lab will notify the site within 2 business days. The site will then phone the subject to identify any signs or symptoms. The site will schedule the subject to return to the site or schedule a Home Health Nurse visit within 3 days of becoming aware of the positive test and will repeat the following tests: Direct Coombs test, RBC count, hematocrit, hemoglobin, serum haptoglobin, bilirubin (total, direct and indirect), LDH, and urine hemosiderin tests.</li> <li>○ <b>Hemoglobinuria:</b> If at any time the subject develops hemoglobinuria, the following tests will be repeated within 3 business days of the site becoming aware: serum haptoglobin, plasma free hemoglobin, urine hemosiderin, and LDH for differential diagnosis.</li> <li>○ <b>Drop in Hemoglobin:</b> If at any time the subject's Hemoglobin has dropped by &gt;2.0 g/dL from the baseline level, the subject will be asked to return to the site or schedule a Home Health Nurse visit within 5 business days of the site becoming aware of the drop. At this time a full panel of testing will be completed including: haptoglobin, plasma free hemoglobin, Direct Coombs test, LDH, reticulocyte count, urine hemosiderin, urine dipstick, urine microscopic analysis and repeat hemoglobin.</li> <li>○ At baseline only, an additional blood draw will be made between day 7 and day 14 to test for hemolysis.</li> </ul> <p><b>Laboratory Analysis for Pharmacokinetics; Total IgG, IgG Subclasses, and Specific IgG Antibodies (Visit 5 or 6 per Schedule of Events; see <a href="#">Section 1.1</a>)</b></p> <p>The following tests will be analyzed by a central laboratory:</p> <ul style="list-style-type: none"> <li>• Total IgG, and IgG subclasses (IgG1, IgG2, IgG3, and IgG4)</li> <li>• Specific antibodies against <i>Streptococcus pneumoniae</i></li> </ul> <p><b>Laboratory Analysis for Viral Testing (At Screening, Baseline and SFV per Schedule of Events; see <a href="#">Section 1.1</a>)</b></p> |
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|                                        | <p>The following tests will be analyzed by a central laboratory:</p> <ul style="list-style-type: none"> <li>NAT for HBV, HCV and HIV (at Screening only) and then NAT and serology testing for HAV, HBV, HCV, HIV-1, HIV-2, and PVB19</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>IMP Dosage &amp; Administration</b> | <p><b>IMP Dosage and Administration</b></p> <p>IMP is a 10% liquid formulation of human immunoglobulin in 50 mL vials. IMP will be administered every 21 or 28 days (<math>\pm</math> 2 days) in accordance with the subject's regimen at Screening for a period of 12 months. Subjects on a 21-day regimen will receive approximately 17 infusions, and subjects on a 28-day regimen will receive a total of approximately 13 infusions.</p> <p>To maintain a trough level of <math>\geq</math> 5 mg/mL, the PI will sign-off on the calculated IMP dose (mg/kg/infusion) based on the subject's current body weight, this will be the subject's dosing weight. If the subject's body weight increases or decreases by <math>\geq</math> 5%, the dose will be recalculated and will establish a new dosing weight. This dose will be consistent with previous IGIV or SCIG treatment. [REDACTED]</p> <p>[REDACTED] in the study must be on a 21-day cycle.</p> <p>Prior to each infusion, ensure the subject is properly hydrated, per site's standard of care.</p> <p><b>Infusion rate for Infusion 1</b></p> <p>The infusion, calculated using the dosing weight, is to be administered in a stepwise fashion as follows: For the first 30 minutes, IMP will be infused at 0.01 mL/kg/min. In the PI's opinion, if the rate is well tolerated, the rate of administration will be increased to 0.02 mL/kg/min for the next 30 minutes. If the increase is well tolerated, the rate will be increased to 0.04 mL/kg/min for the next 30 minutes. Finally, if this rate is well tolerated, the remainder of the infusion may be administered at a maximum rate of between 0.06 mL/kg/min - 0.08 mL/kg/min, as long as this rate does not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is sought.</p> <p><b>Infusion Rate for Interim and Final Infusions</b></p> <p>The rate for the interim and final infusions will follow the same approach described for Infusion 1, but the increases will be implemented every 15 minutes rather than every 30 minutes. For interim and final infusions, the maximum infusion rate should not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is granted.</p> |

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| <b>Efficacy Endpoints</b> | <p><b>Primary</b></p> <p>Rate of clinically documented serious bacterial infections (SBIs) defined as:</p> <ul style="list-style-type: none"> <li>• Bacterial pneumonia</li> <li>• Bacteremia and septicemia</li> <li>• Osteomyelitis / septic arthritis</li> <li>• Bacterial meningitis</li> <li>• Visceral abscess</li> </ul> <p><b>Secondary</b></p> <ul style="list-style-type: none"> <li>• Total serum IgG trough levels</li> <li>• Specific antibody levels</li> <li>• Number of infection episodes (serious and non-serious)</li> <li>• Episodes of fever &gt; 38.5°C [101.3°F]</li> <li>• The number of days out of work/school/daycare or unable to perform normal daily activities due to infections</li> <li>• Number of days of hospitalization due to infections</li> <li>• Use of antibiotics for infection and short-term prophylaxis prior to and following surgical and dental procedures</li> <li>• Total serum IgG trough levels and specific antibody levels</li> <li>• For months 5 through 12, the difference between the total serum IgG trough level and the baseline trough level (following the previous IGIV or SCIG treatment)</li> </ul> |
| <b>Safety Endpoints</b>   | <ul style="list-style-type: none"> <li>• Rate, severity and relatedness of any AEs per infusion and by subject</li> <li>• Rate of suspected <u>serious</u> adverse reactions or adverse reactions by subject</li> <li>• Rate of suspected adverse events or adverse events by subject</li> <li>• Frequency of temporally-related AEs</li> <li>• Assessment of local tolerability</li> <li>• Vital sign changes</li> <li>• Changes in physical examination results as compared to baseline assessment</li> <li>• Changes in routine laboratory parameters (serum chemistry, hematology, urinalysis) as compared to baseline assessments</li> <li>• Evidence of hemolysis</li> <li>• Changes in viral safety markers (HAV, PVB19, HBV, HCV, HIV-1, and HIV-2) as compared to baseline assessments</li> </ul>                                                                                                                                                                                                                                                                                                                                                             |

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| <b>Pharmacokinetic Endpoints</b> | <b>Group 1b and Group 2b</b> <ul style="list-style-type: none"> <li>• Total IgG levels</li> <li>• IgG subclasses (IgG1, IgG2, IgG3, and IgG4) (for subjects &gt;12 years of age)</li> <li>• Specific antibodies against <i>Streptococcus pneumoniae</i> (for subjects &gt;12 years of age)</li> <li>• AUC time curve (both AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>)</li> <li>• C<sub>max</sub></li> <li>• The volume of distribution at steady-state (V<sub>ss</sub>)</li> <li>• Mean residence time (MRT)</li> <li>• Total body clearance (Cl)</li> <li>• Terminal half-life (t<sub>1/2</sub>) (and half-life for equilibration phase as appropriate)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Statistics</b>                | <b>Sample size (power)</b><br><p>To estimate the power of this study, it is assumed that the number of SBIs experienced (per subject) during one year has a (true) mean below unity (1). To demonstrate efficacy, it is required that the observed mean across subjects should have an upper 99% one-sided confidence limit below a level of 1 infection per subject per year. Using a square root transformation to achieve approximate normality (see Primary Endpoint), the true mean of the response would be approximately <math>\sqrt{x}</math>, and the variance would be 0.25 (standard result if the untransformed data follow a Poisson distribution), hence the SD is 0.5. The regulatory upper threshold on the square root scale is <math>\sqrt{1} = 1</math>.</p> <p>Standard one-sample power calculations for comparison of an observed mean with a theoretical alternative hypothesis (assuming normality) indicate that for a study with [REDACTED] the probability of the upper one-sided 99% confidence limit (after back-transformation) being below 1 remains above 82.6% provided that the true mean of the population lies below 0.55 (0.742 with square root transformation).</p> <p>In practice, intra-subject variability in the probability of observing an SBI at a specific infusion may lead to the observed variance of the square root of the count of SBIs exhibiting greater dispersion than predicted from the Poisson distribution. The variance will then exceed 0.25 (as assumed in the power calculation). The calculations described above therefore give an upper limit to the maximum true mean SBI count necessary to provide adequate power. For practical purposes, the study should probably be considered appropriately powered if the true incidence of serious acute bacterial infections lies below 0.45 per subject per year.</p> |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p><b>General statistical approach</b></p> <p>Analyses will be presented for the adult group and the pediatric groups separately. A pooled analysis may also be presented.</p> <p>All subjects who are exposed to at least one dose of the IP will be included in the safety analysis set. The overall outcome of the study will be assessed using a population consisting of all subjects enrolled. Additionally, a per-protocol analysis set will be defined and analysed, including only subjects who provide data for at least 6 infusions and have do not have any major protocol deviations or violations that may impact data.</p> <p>No data will be imputed.</p> <p><b>Efficacy</b></p> <p><u>Primary endpoint</u></p> <p>For the primary endpoint, a 99% one-sided (upper) confidence limit for the annual incidence rate of SBIs will be derived, and the fact that the true infection rate is below 1 per subject per year will be considered confirmed if this upper limit is less than 1.</p> <p>To calculate the confidence limit for the rate, the number of reported SBIs will be modelled using a negative binomial regression model with the number of months 'at risk' included in the model as an independent variable and the confidence limit in question will be based on the intercept of that model. The 'at risk' variable will be defined as the time between enrollment and departure from the study, expressed in calendar months. The predicted number of SBIs (and its upper 99% one-sided confidence limit) for 12 months at risk will then be derived. The null hypothesis for this analysis is that the true SBI rate is <math>\geq 1</math> per subject per year, and the alternative hypothesis is that this rate is <math>&lt;1</math> per subject per year. Rejection of the null hypothesis will therefore achieve the study objective of showing that the true rate is below 1 per subject per year.</p> <p>The proposed method of analysis allows for any intra-subject correlation in the incidence of SBIs. Such correlations would simply give rise to larger variability in the individual subject SBI rates than would be expected if there was no intra-subject variation, and the statistical test is based on this observed inflated variance rather than on any theoretically expected value.</p> <p><u>Secondary endpoints</u></p> <p>Secondary endpoints will be presented using the appropriate descriptive statistics</p> <p><b>Safety</b></p> <p>The rate, severity, and relatedness of any AEs and suspected serious adverse reactions/AEs per infusion and subject will be tabulated by seriousness, severity and body system.</p> |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>The observed proportion will be reported for infusions with one or more temporally (within 1, 24, 48, and 72 hours) associated AE (including any AEs not considered product related). Infusion-related AEs will also be tabulated by the prevailing infusion rate. The proportion of infusions with a temporally associated AE will be analyzed with the objective of demonstrating that the percentage of infusions with one or more temporally related AE is less than [REDACTED]. This will be achieved by calculating the percentage of affected infusions for each subject, and then calculating a mean of these percentages, with a 95% (one-sided) confidence interval. The upper limit of this confidence interval should be below [REDACTED] in order to demonstrate that the true proportion lies below [REDACTED]. Additionally, the number and proportion of subjects who experience one or more suspected serious adverse reactions or adverse reactions and the number and proportion of subjects who experience one or more suspected AEs or AEs, as well as the sum total of such reactions and events will be reported.</p> <p><b>Pharmacokinetics (PK)</b></p> <p>For all subjects in the PK study, blood samples will be collected for the assessment of serum concentrations of total IgG. For subjects &gt;12 years of age, the PK study will also assess sub-classes of IgG and specific antibodies. The serum concentrations will be determined as defined in a laboratory assay plan. PK parameters will be estimated by a two-compartmental model using the piecewise robust linear regression approach suggested by Lee et al (1-3) employing the program Demitasse2000 or a non-compartmental approach to determine area under the curve (AUC) using the linear trapezoidal rule. Appropriate summary statistics will be determined. For all evaluable subjects, prior to each infusion, trough (predose at each infusion) serum total IgG concentrations will also be determined. PK data will be pre-dose baseline corrected.</p> |
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**1.1 Schedule of Events**

|                                               | Screening | Baseline,<br>Visit 1                        | Visits 2, 8,<br>11, (14) | Visits 3, 4, 7,<br>9, 10, 12, (15,<br>16) | Visit 5        |                |  | Visit 6        |                | 13 or<br>17/FTTV | SFV |
|-----------------------------------------------|-----------|---------------------------------------------|--------------------------|-------------------------------------------|----------------|----------------|--|----------------|----------------|------------------|-----|
|                                               |           |                                             |                          |                                           | 21<br>Day      | 28<br>Day      |  | 21<br>Day      | 28<br>Day      |                  |     |
| Informed Consent                              | X         |                                             |                          |                                           |                |                |  |                |                |                  |     |
| Demographics                                  | X         |                                             |                          |                                           |                |                |  |                |                |                  |     |
| Medical History <sup>a</sup>                  | X         |                                             |                          |                                           |                |                |  |                |                |                  |     |
| Review of Entry<br>Criteria                   | X         | X                                           |                          |                                           |                |                |  |                |                |                  |     |
| Vital Signs                                   | X         | X <sup>b</sup>                              | X <sup>b</sup>           | X <sup>b</sup>                            | X <sup>b</sup> | X <sup>b</sup> |  | X <sup>b</sup> | X <sup>b</sup> | X <sup>b</sup>   | X   |
| Physical Examination                          | X         | X                                           | X                        | X                                         | X              | X              |  | X              | X              | X                |     |
| Chest X-Ray <sup>c</sup>                      | X         |                                             |                          |                                           |                |                |  |                |                |                  |     |
| Pregnancy Test                                | X         | X                                           | X                        | X                                         | X              | X              |  | X              | X              | X                | X   |
| Safety Laboratory<br>Assessments <sup>d</sup> | X         | X                                           | X <sup>d</sup>           |                                           | X <sup>d</sup> | X <sup>d</sup> |  |                |                | X <sup>d</sup>   | X   |
| Hemolysis testing <sup>a</sup>                |           | X (plus one 7-<br>14 days post<br>baseline) | X                        | X                                         | X              | X              |  | X              | X              | X                |     |
| Viral Testing <sup>e</sup>                    | X         | X                                           |                          |                                           |                |                |  |                |                |                  | X   |
| IgG Trough with a<br>back up sample           | X         | X                                           | X                        | X                                         | X              | X              |  | X              | X              | X                | X   |
| IgG Subclasses <sup>f</sup>                   |           |                                             |                          |                                           |                | X              |  | X              |                |                  |     |
| Specific Antibodies <sup>f</sup>              |           |                                             |                          |                                           |                | X              |  | X              |                |                  |     |
| Retention Samples <sup>g</sup>                | X         | X                                           |                          |                                           |                |                |  |                |                |                  | X   |
| Infusion                                      |           | X                                           | X                        | X                                         | X              | X              |  | X              | X              | X                |     |

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|                                 | Screening              | Baseline,<br>Visit 1 | Visits 2, 8,<br>11, (14) | Visits 3, 4, 7,<br>9, 10, 12, (15,<br>16) | Visit 5   |           | Visit 6   |           | 13 or<br>17/FTTV | SFV |
|---------------------------------|------------------------|----------------------|--------------------------|-------------------------------------------|-----------|-----------|-----------|-----------|------------------|-----|
|                                 |                        |                      |                          |                                           | 21<br>Day | 28<br>Day | 21<br>Day | 28<br>Day |                  |     |
| Subject Diary                   |                        | X                    | X                        | X                                         | X         | X         | X         | X         | X                | X   |
| Full PK Profile <sup>h</sup>    |                        |                      |                          |                                           |           | X         | X         |           |                  |     |
| AE Telephone Calls <sup>i</sup> |                        | X                    | X                        | X                                         | X         | X         | X         | X         | X                |     |
| AEs and Concomitant Medications | X<br>(prior meds only) | X                    | X                        | X                                         | X         | X         | X         | X         | X                | X   |

- a: Subjects will provide their complete medical history to include past surgeries dating back two years including the form of birth control in females of childbearing potential. Any available documentation of immunoglobulin treatment (IVIG, SCIG or a combination of the two) for the past 3 months will be captured, including the current treatment regimen with dose and infusion rates. Documentation will need to be provided to demonstrate 3 months of a stable mg/kg/infusion dose. Prior medications will be captured for the 4 weeks prior to Screening. Serious Bacterial Infections will be documented for the past ten years
- b: Vital signs will be collected at all visits; however, additional vital signs (during and post-infusion) will be collected at visits with infusions in accordance with **Sections 7.3.9, 7.4.7, and 7.5.7.**
- c: Chest X-Ray to be obtained if not available in the previous 6 months.
- d: Safety laboratory assessments will consist of hematology, serum chemistry, and urinalysis, as described in **Sections 7.2.9, 7.3.5, 7.4.4, 7.5.4, and 7.6.2.** Testing for hemolysis will be performed at every visit, including once in the 7-14 day period after the baseline infusion, (urine hemosiderin, serum haptoglobin, plasma free hemoglobin, and Coombs test) with additional testing for suspected hemolysis in the event of hemoglobinuria, a positive Coombs test, or a drop in levels of hemoglobin; this testing will be conducted in accordance with **Sections 7.3.5, 7.4.4, 7.5.4, and 7.6.2** and the flowchart in **Section 1.4.**
- e: Virology testing will include serology and nucleic acid testing (NAT) assay types as follows: HBV, HCV, HIV-1, and HIV-2 NAT only at Screening; HAV, HBV, HCV, HIV-1, HIV-2, and PVB19 NAT and serology at baseline; and HAV, HBV, HCV, HIV-1, HIV-2, PVB19 NAT and serology at SFV (For each subject, the actual SFV testing will only be conducted for those tests that were negative at baseline).
- f: Only for subjects greater than 12 years of age.
- g: Samples of pre- and post-treatment sera will be retained from each subject for possible future testing of additional infectious agents.
- h: Additional PK samples will be obtained for Groups 1b and 2b in accordance with **Section 7.7.**
- i: Follow up phone calls or texts 24 and 72 hours after the infusion.

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*Confidential***1.2 Schedule of Infusions for 21-Day Regimen**

| Week        | Screening | Baseline    | 1  | 2  | 3                | 4  | 5  | 6           | 7  |
|-------------|-----------|-------------|----|----|------------------|----|----|-------------|----|
| 21-Day Reg. |           | Infusion 1  |    |    | Infusion 2       |    |    | Infusion 3  |    |
| Week        | 8         | 9           | 10 | 11 | 12               | 13 | 14 | 15          | 16 |
| 21-Day Reg. |           | Infusion 4  |    |    | Infusion 5       |    |    | Infusion 6  |    |
| Week        | 17        | 18          | 19 | 20 | 21               | 22 | 23 | 24          | 25 |
| 21-Day Reg. |           | Infusion 7  |    |    | Infusion 8       |    |    | Infusion 9  |    |
| Week        | 26        | 27          | 28 | 29 | 30               | 31 | 32 | 33          | 34 |
| 21-Day Reg. |           | Infusion 10 |    |    | Infusion 11      |    |    | Infusion 12 |    |
| Week        | 35        | 36          | 37 | 38 | 39               | 40 | 41 | 42          | 43 |
| 21-Day Reg. |           | Infusion 13 |    |    | Infusion 14      |    |    | Infusion 15 |    |
| Week        | 44        | 45          | 46 | 47 | 48               | 49 | 50 | 51          | 52 |
| 21-Day Reg. |           | Infusion 16 |    |    | Infusion 17/FTTV |    |    | SFV         |    |

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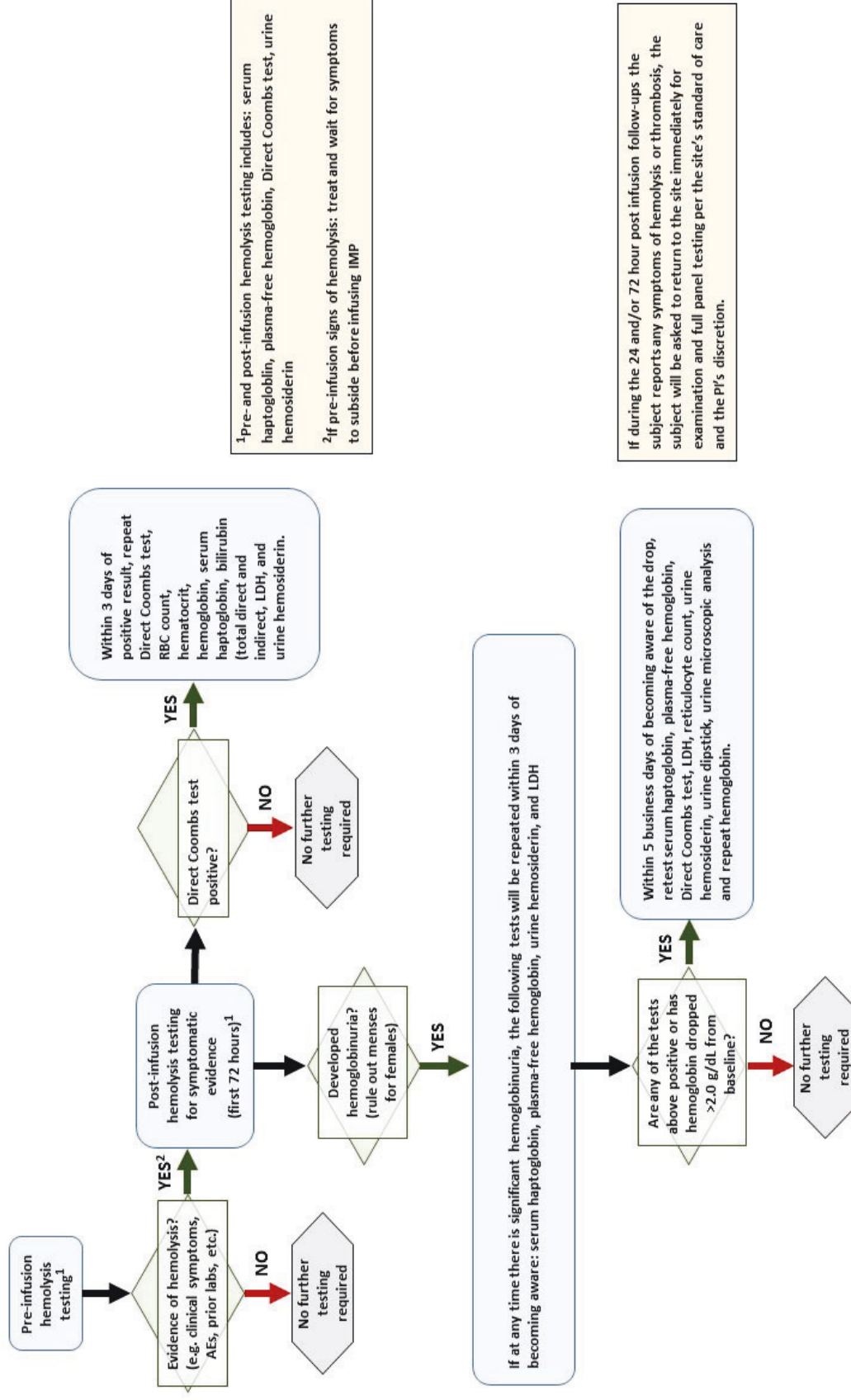
*Confidential***1.3 Schedule of Infusions for 28-Day Regimen**

| Week        | Screening   | Baseline    | 1          | 2          | 3                | 4           | 5          | 6          | 7          |
|-------------|-------------|-------------|------------|------------|------------------|-------------|------------|------------|------------|
| 28-Day Reg. |             | Infusion 1  |            |            |                  | Infusion 2  |            |            |            |
| Week        | 8           | 9           | 10         | 11         | 12               | 13          | 14         | 15         | 16         |
| 28-Day Reg. | Infusion 3  |             |            |            | Infusion 4       |             |            |            | Infusion 5 |
| Week        | 17          | 18          | 19         | 20         | 21               | 22          | 23         | 24         | 25         |
| 28-Day Reg. |             |             |            | Infusion 6 |                  |             |            | Infusion 7 |            |
| Week        | 26          | 27          | 28         | 29         | 30               | 31          | 32         | 33         | 34         |
| 28-Day Reg. |             |             | Infusion 8 |            |                  |             | Infusion 9 |            |            |
| Week        | 35          | 36          | 37         | 38         | 39               | 40          | 41         | 42         | 43         |
| 28-Day Reg. |             | Infusion 10 |            |            |                  | Infusion 11 |            |            |            |
| Week        | 44          | 45          | 46         | 47         | 48               | 49          | 50         | 51         | 52         |
| 28-Day Reg. | Infusion 12 |             |            |            | Infusion 13/FTTV |             |            |            | SFV        |

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## 1.4 Hemolysis Testing Flowchart



Protocol TBI-001-IGIV

## 2. ABBREVIATIONS

| Abbreviation     | Explanation                                                                  |
|------------------|------------------------------------------------------------------------------|
| ADA-SCID         | Adenosine deaminase deficiency resulting in severe combined immunodeficiency |
| ADR              | Adverse drug reaction                                                        |
| AE               | Adverse event                                                                |
| ALT              | Alanine transaminase                                                         |
| aPP              | Augmented per protocol                                                       |
| AST              | Aspartate transaminase                                                       |
| AUC              | Area under the curve                                                         |
| BUN              | Blood urea nitrogen                                                          |
| C                | Celsius                                                                      |
| CBC              | Complete blood count                                                         |
| CDC              | Centers for Disease Control                                                  |
| CRF              | Case report form                                                             |
| CK               | Creatine kinase                                                              |
| CL               | Total body clearance                                                         |
| C <sub>max</sub> | Maximum serum concentration                                                  |
| CMP              | Comprehensive metabolic panel                                                |
| CRF              | Case report form                                                             |
| CRO              | Clinical Research Organization                                               |
| CSF              | Cerebrospinal fluid                                                          |
| CT               | Computed tomography                                                          |
| CVID             | Common variable immune deficiency                                            |
| CXR              | Chest x-ray                                                                  |
| DAT              | Direct anti-globulin test                                                    |
| DVT              | Deep vein thrombosis                                                         |
| eGFR             | Estimated Glomerular Filtration Rate                                         |
| FDA              | Food and Drug Administration                                                 |
| FTTV             | Final Treatment and Termination Visit                                        |
| GCP              | Good Clinical Practice                                                       |
| HAV              | Hepatitis A virus                                                            |
| HBV              | Hepatitis B virus                                                            |
| HCV              | Hepatitis C virus                                                            |
| HIPAA            | Health Insurance Portability and Accountability Act                          |
| HIV-1            | Human immunodeficiency virus type 1                                          |
| HIV-2            | Human immunodeficiency virus type 2                                          |
| HBsAB            | Hepatitis B surface antibody                                                 |
| HIGM             | Hyper-IgM syndrome                                                           |
| HSCT             | hematopoietic stem cell transplantation                                      |

| Abbreviation     | Explanation                                                  |
|------------------|--------------------------------------------------------------|
| ICH              | International Conference on Harmonisation                    |
| IgA              | Immunoglobulin A                                             |
| IgG              | Immunoglobulin G                                             |
| IgM              | Immunoglobulin M                                             |
| IMP              | Investigational medicinal product                            |
| IND              | Investigational New Drug                                     |
| IRB              | Institutional Review Board                                   |
| IV               | Intravenous                                                  |
| IGIV             | Immunoglobulin intravenous <sup>1</sup>                      |
| kg               | Kilogram                                                     |
| L                | Liter                                                        |
| LDH              | Lactic dehydrogenase                                         |
| MCH              | Mean corpuscular hemoglobin                                  |
| MCHC             | Mean corpuscular hemoglobin concentration                    |
| MCV              | Mean corpuscular volume                                      |
| MedDRA           | Medical Dictionary for Regulatory Activities                 |
| mg               | Milligram                                                    |
| mL               | Milliliter                                                   |
| mm Hg            | Millimeter of mercury                                        |
| MRI              | Magnetic resonance imaging                                   |
| MRT              | Mean residence time                                          |
| NAT              | Nucleic acid testing                                         |
| PaO <sub>2</sub> | Partial pressure of O <sub>2</sub> in arterial blood         |
| pH               | Hydrogen ion concentration                                   |
| PHI              | Protected health information                                 |
| PI               | Principal Investigator                                       |
| PIDD             | Primary immune deficiency diseases                           |
| PIPEDA           | Personal Information Protection and Electronic Documents Act |
| PK               | Pharmacokinetic                                              |
| PP               | Per protocol                                                 |
| PRN              | When necessary                                               |
| PVB19            | Human parvovirus B19                                         |
| QA               | Quality assurance                                            |
| QC               | Quality control                                              |
| RBC              | Red blood cell                                               |
| RDW              | Red (cell) distribution width                                |
| REB              | Research Ethics Board                                        |

<sup>1</sup> In this protocol, the abbreviation IGIV is used for immunoglobulin intravenous. Elsewhere, the abbreviation IGIV is commonly used and the two abbreviations IGIV and IVIG are equivalent and interchangeable.

| Abbreviation | Explanation                                   |
|--------------|-----------------------------------------------|
| SAE          | Serious adverse event                         |
| SBI          | Serious bacterial infection                   |
| SCID         | Severe combined immunodeficiency              |
| SCIG         | Immunoglobulin subcutaneous                   |
| SD           | Standard deviation                            |
| SFV          | Safety Follow-up Visit                        |
| SUSAR        | Suspected unexpected serious adverse reaction |
| $t_{1/2}$    | Half-life                                     |
| TEE          | Thromboembolic event                          |
| $T_{max}$    | Time to reach the maximum serum concentration |
| TRALI        | Transfusion-related acute lung injury         |
| ULN          | Upper limit of normal                         |
| VD           | Volume of distribution                        |
| $V_{ss}$     | Volume of distribution at steady-state        |
| WBC          | White blood cell                              |
| WHO          | World Health Organization                     |
| XLA          | X-linked agammaglobulinemia                   |

### 3. INTRODUCTION

#### 3.1 Background

Primary immunodeficiencies are inherited disorders of the immune system. One common result of the disordered antibody production defect of PIDD is an inadequate immune response to microorganisms leading to increased susceptibility to infections. In addition, some patients with immunodeficiency inappropriately recognize and respond to self-antigens and tumor cells resulting in autoimmunity or malignant disease. In contrast to primary immunodeficiencies, secondary immune deficiencies are caused by exogenous factors such as chemotherapy or lymphotropic viral infection.

There is a wide variety of primary immune deficiencies. The World Health Organization (WHO) recognizes over 150 primary immune deficiency diseases (PIDD) including selective IgG deficiency, X-linked agammaglobulinemia (XLA or Bruton's Disease), common variable immune deficiency (CVID) that has an incidence of 1 in 75,000, selective IgA deficiency, and severe combined immune deficiency (boy-in-the-bubble disease). Some disorders such as selective IgA deficiency are quite common, occurring as often as in 1 in 500 to 1/1000 individuals. Others may be as rare as one individual affected per million (4).

More than 200 genetically-defined inborn errors of immunity responsible for PIDD have been described. The number of recognized disorders continues to increase, which has made maintaining current disease classification and patient management guidelines challenging (5). Globally, there are an estimated six million people with PIDD, the majority undiagnosed. In the United States, the estimated prevalence of PIDD is one in 1,200 persons, with an estimated prevalence of approximately one in 2000 in children. There are reports that the actual prevalence of PIDD may be significantly underestimated and that the true prevalence of these disorders is unknown (6,7).

The diagnosis of PIDD is often delayed until the patient has experienced repeated infections. In the USA, the time between onset of symptoms and treatment of PIDD can be over 12 years and up to one half of persons with PIDD are not diagnosed until they are 30 years of age or older (8). Untreated PIDD is characterized by frequent, potentially life-threatening infections and debilitating illnesses. Due to the availability of efficacious treatment for PIDD, the early recognition and diagnosis of PIDD leads to improved patient prognosis and quality of life.

##### 3.1.1 Benefit/Risk Statement

Disordered or absent antibody production and increased occurrence of severe, persistent, and recurrent infections is the most common defect causing morbidity and premature mortality among PIDD patients. Because of advances in the understanding and treatment of PIDD, subjects who, in the past, would not have survived childhood are now able to live nearly normal lives. The cornerstone of treatment for most PIDD patients is the life-long administration of immunoglobulin. Immunoglobulin replacement therapy, providing passive immunity, is the standard treatment for patients with PIDD resulting in significant defects in antibody production (9). Immunoglobulin replacement therapy maintains adequate serum IgG levels thereby markedly decreasing the frequency and

severity of bacterial infections resulting in a significantly improved quality of life for these patients. In subjects with antibody production disorders, prophylactic treatment with intravenous immunoglobulin (IGIV) or subcutaneous immunoglobulin (SCIG) has been shown to increase the time free from serious bacterial infection, decrease the overall incidence of infections and reduce the number of hospitalizations required for treatment of infection (9).

Most patients receive IGIV infusions at intervals of 2, 3, or 4 weeks or SCIG infusions biweekly, weekly or more frequently. Studies have shown reductions in hospitalization and infection rates in subjects receiving IgG therapy with the rate of infection inversely correlated with the IgG trough level and therefore the immunoglobulin dose. One study, published almost 30 years ago demonstrated that patients with an IgG trough level of >500mg/dL had significantly fewer pulmonary infections and consequently an IgG trough of >500mg/dL has come to be accepted as the minimum trough level (10).

As with any medication, there are risks associated with the administration of IGIV. Adverse effects associated with the use of IGIV range from mild acute reactions including infusion site pain, swelling, and/or erythema; headache; chest pain; back pain; abdominal pain; myalgia; arthralgia; fever; chills; flushing; nausea and vomiting; hypotension; hypertension; tachycardia; and rash to rare, serious reactions including anaphylaxis, renal failure, aseptic meningitis, hemolytic anemia, thromboembolic events, and transfusion-related acute lung injury (TRALI) (11).

Thrombotic events associated with the use of IGIV have been reported, and FDA warns that patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity (12). Recent reports of increased thromboembolic events (TEEs) after administration of a number of lots of IGIV were found to be related to contaminating activated factor XI (FXIa) (13). The risk of renal failure due to IgG treatment increases in older patients, those with preexisting renal disease, diabetes mellitus, vascular disease, and dysproteinemias such as multiple myeloma or cryoglobulinemia, as well as with the use of IGIV products with sucrose as a stabilizing agent (11). Although the cause of aseptic meningitis is unknown, it is more likely to occur in patients with a history of migraine (14).

Apolipoprotein H (ApoH), also known as  $\beta_2$ -glycoprotein I, is present in PlasmaCap IVIG preparations at a concentration of  $0.49 \pm 0.12$  mg/mL. The maximum allowable level of ApoH in PlasmaCap IG is less than 1.0 mg/mL. Apo H is a multifunctional lipoprotein present in human plasma at a concentration of between 50 and 500  $\mu$ g/mL (15). A concern regarding the potential procoagulant activity of ApoH was raised by F. Lackner et al in 2014 (16). The authors observed a correlation between exogenous ApoH concentration and thrombin generation; however, no correlation was observed between thrombin generation and the residual ApoH concentration in commercial IVIG products. It has not been definitely shown that the procoagulant activity correlated with exogenous ApoH was due to the activity of ApoH or due to copurified proteins present in the ApoH preparation from Fitzgerald International that was used in this study. The thrombin generation activity (TGA) measured in PlasmaCap IG is less than 1 mU/mL, and

does not correlate with the lot to lot variability in trace ApoH concentrations. The potential risk of procoagulant activity due to trace ApoH is considered to be very low.

Because IGIV is a blood product, there is also a risk of transmission of blood-borne infections. Although there are no reports of transmission of human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infection from IGIV products, there have been documented cases of hepatitis C virus transmission (17). In the 1980s, hepatitis C virus (HCV) transmission was reported in Europe for several IGIV products manufactured at pilot scale, prior to the development of robust viral inactivation methods that are now used in IGIV manufacturing processes. In 1994, HCV was transmitted by widely used IGIV product in several countries, which was attributed to first generation HCV screening assay used on plasma donations that resulted in false negative results on some infected plasma donations used to manufacture the product (18). The implementation of measures to select healthy plasma donors, screening all donations for relevant viruses, using manufacturing plasma pools that have been shown to be free of serologic or nucleic acid markers of viral infection, and the incorporation of dedicated virus inactivation and removal processes has essentially eliminated viral transmission from IGIV. There have been no documented cases of transmissions of HIV, HBV, or HCV through U.S.-licensed plasma-derived products in the past two decades (19).

There is also the extremely small risk of the transmission of the variant form of Creutzfeldt-Jakob disease (vCJD) in plasma-derived products. To date, no U.S.-licensed plasma-derived products have been manufactured from a donor known to have developed vCJD and no cases of vCJD have been reported from use of a U.S.-licensed plasma derivative (20).

### 3.2 Rationale

Prior to the introduction of immunoglobulin therapy, subjects suffering from hypogammaglobulinemia and agammaglobulinemia experienced approximately four or more acute serious bacterial infections each year (21). However, maintenance of an adequate trough IgG significantly decreases the frequency of serious and mild infections dramatically improving the patient's quality of life.

Since the 1980's, prophylaxis with IGIV has been the standard therapy for patients suffering from hypogammaglobulinemia and agammaglobulinemia due to PIDD in the US and much of Europe. Recently, SCIG has become accepted as a well-tolerated and effective treatment. The availability of treatment regimens with both IGIV and SCIG has allowed flexibility in treatments for PIDD patients, who differ widely in their clinical backgrounds and lifestyles (22).

[REDACTED]

[REDACTED] In recent years, there have been a number of reports that PIDD patients benefit from increased doses of IGIV with corresponding increased trough IgG levels. In a meta-analysis conducted by Orange et al of 676 PIDD patients in 17 studies, the incidence of pneumonia decreased by 27% with each 100 mg/dL increase in trough IgG levels. Also,

the incidence of pneumonia was five-times higher when trough IgG levels were maintained at 500 mg/dL than when trough levels were maintained at 1000 mg/dL (23).

Although patients receiving increased doses of IgG have better outcomes, it appears that each individual exhibits his or her own biologic trough below which infections occur and requires adjustment of the dosing regimen to achieve and maintain that level (24). Instead of establishing an arbitrary trough IgG level based on the normal population, the optimal dose and frequency of IGIV administration should be determined individually for each patient by the treating physician based on the biological trough level at which the patient remains free from serious acute infection (25). The IGIV dosing regimen should be based upon the response of the patient and regular monitoring of circulating IgG levels to ensure that the dosing is correct.

## **4. STUDY PURPOSE AND OBJECTIVES**

### **4.1 Study Purpose**

The purpose of this study is to investigate the efficacy, safety, tolerability, and pharmacokinetic profile of the investigational medicinal product (IMP) and to determine, on the basis of historical control data, how it compares with other 10% IGIV products currently licensed in North America for the treatment of subjects with primary immune deficiency diseases (PIDD).

### **4.2 Efficacy Objectives**

#### **Primary Efficacy Objective**

The primary efficacy objective of the study is to demonstrate the efficacy of the IMP by determining the mean annual acute serious bacterial infection (SBI) rate (as defined in [Appendix 20.1](#)) and demonstrating that it is statistically significantly lower than one infection per subject per year.

#### **Secondary Efficacy Objectives**

The secondary efficacy objectives of the study are to assess:

- Average serum total IgG trough concentrations prior to each infusion;
- Number of infection episodes (serious and non-serious)
- Number of days out of work/school/daycare or;
- Number of days unable to perform normal daily activities due to infections;
- Ability of the IMP to maintain stable, therapeutic IgG levels;
- Episodes of fever;
- Number of days subjects are hospitalized due to infections;
- Use of antibiotics to treat infection and for short-term prophylaxis prior to and following surgical and dental procedures.

### **4.3 Safety Objectives**

The safety objectives of this study are:

- To examine the safety and tolerability of IMP by monitoring Adverse Events (AEs) from the start of the first infusion of IMP through the Safety Follow-up Visit (SFV);
- To examine temporally associated AEs, (within 72 hours after infusion of the IMP), regardless of their relationship to IMP;
- To monitor viral safety;
- To monitor for hemolysis and thromboembolic events.

- To observe the number and proportion of subjects who experience one or more suspected serious adverse reactions or adverse reactions, as well as the sum total of such reactions.
- To observe the number and proportion of subjects who experience one or more suspected adverse events or adverse events, as well as the sum total of such events.

#### 4.4 Pharmacokinetic Sub-Study Objective

The pharmacokinetic objectives of this study are:

- To determine the pharmacokinetic profiles based on a plasma concentration-time curve; half life ( $t_{1/2}$ ) for each of the phases of this curve; area under the curve (AUC) including both  $AUC_{0-t}$  and  $AUC_{0-inf}$ ; volume of distribution at steady state ( $V_{ss}$ ), mean residence time (MRT), clearance (CL), elimination rate constants and maximum plasma concentration ( $C_{max}$ ) for total IgG, IgG subclasses and specific antibodies following administration of IMP;
- To determine the serum concentrations of total IgG, IgG subclasses (IgG1, IgG2, IgG3, and IgG4), and specific antibodies against *Streptococcus pneumoniae*.

## 5. INVESTIGATIONAL PLAN

### 5.1 Study Design

This is a prospective, open-label, multicenter, phase 3 study to assess the efficacy, safety, tolerability, and pharmacokinetics of IMP in adults, children, and adolescents with PIDD. Approximately [REDACTED] will be enrolled, of which [REDACTED] will be between 2 and <17 years of age. No pediatric subjects under age 17 will be enrolled until [REDACTED] adults have received a minimum of three infusions of IMP (including the 72-hour observation period post-infusion) prior to Screening. At least [REDACTED] subjects in the study must be on a 21-day cycle.

**Group 1** will enroll [REDACTED] 17 to 70 years of age to obtain [REDACTED]

Within Group 1, a PK subset (**Group 1b**) will enroll [REDACTED] 17 to 70 years of age to obtain [REDACTED]

Group 1 subjects who are not in Group 1b will be designated as **Group 1a** (Non-PK).

**Group 2** will enroll approximately [REDACTED] Group 2 will enroll up to [REDACTED] 2 to <6 years of age, at least [REDACTED] 6 to <12 years of age, and up to [REDACTED] 12 to <17 years of age (at time of Screening).

Within Group 2, a PK subset (**Group 2b**) will enroll approximately [REDACTED] to obtain [REDACTED] Group 2b will enroll up to [REDACTED] 2 to <6 years of age, at least [REDACTED] 6 to <12 years of age, and up to [REDACTED] 12 to <17 years of age (at time of Screening).

Group 2 subjects who are not in Group 2b will be designated as **Group 2a** (Non-PK).

Prior to Screening, all subjects on IGIV therapy must have received regular treatment at 21- or 28-day intervals for at least 3 consecutive months (12 weeks) [REDACTED] [REDACTED] For subjects on investigational SCIG therapy, they must have received a stable equivalent dose of commercial IVIG or SCIG for at least 4 consecutive weeks in one of the following combinations:

- a. commercial SCIG [REDACTED] (without having a >25% change in dose) at any dosing schedule for at least 28 days prior to Screening;
- b. investigational SCIG [REDACTED] (without having a >25% change in dose) at any dosing schedule for at least 8 consecutive weeks prior to Screening, and commercial SCIG for at least 28 days prior to Screening; or
- c. investigational SCIG [REDACTED] (without having a >25% change in dose) at any dosing schedule for at least 8 consecutive weeks prior to Screening, and commercial IVIG for at least 28 days prior to Screening as long it is given at the same calculated dose as the investigational SCIG.

Subjects on SCIG must have received and tolerated IGIV treatment prior to SCIG treatment, and supporting documentation, including dose, and frequency must be available for review. Subjects receiving SCIG prior to entering the study should be treated

with the same monthly dose that they had been receiving subcutaneously [REDACTED] without a  $\geq 25\%$  change in dose). Additionally, subjects must have at least one documented trough IgG level of  $\geq 500$  mg/dL in the prior 6 months to study entry.

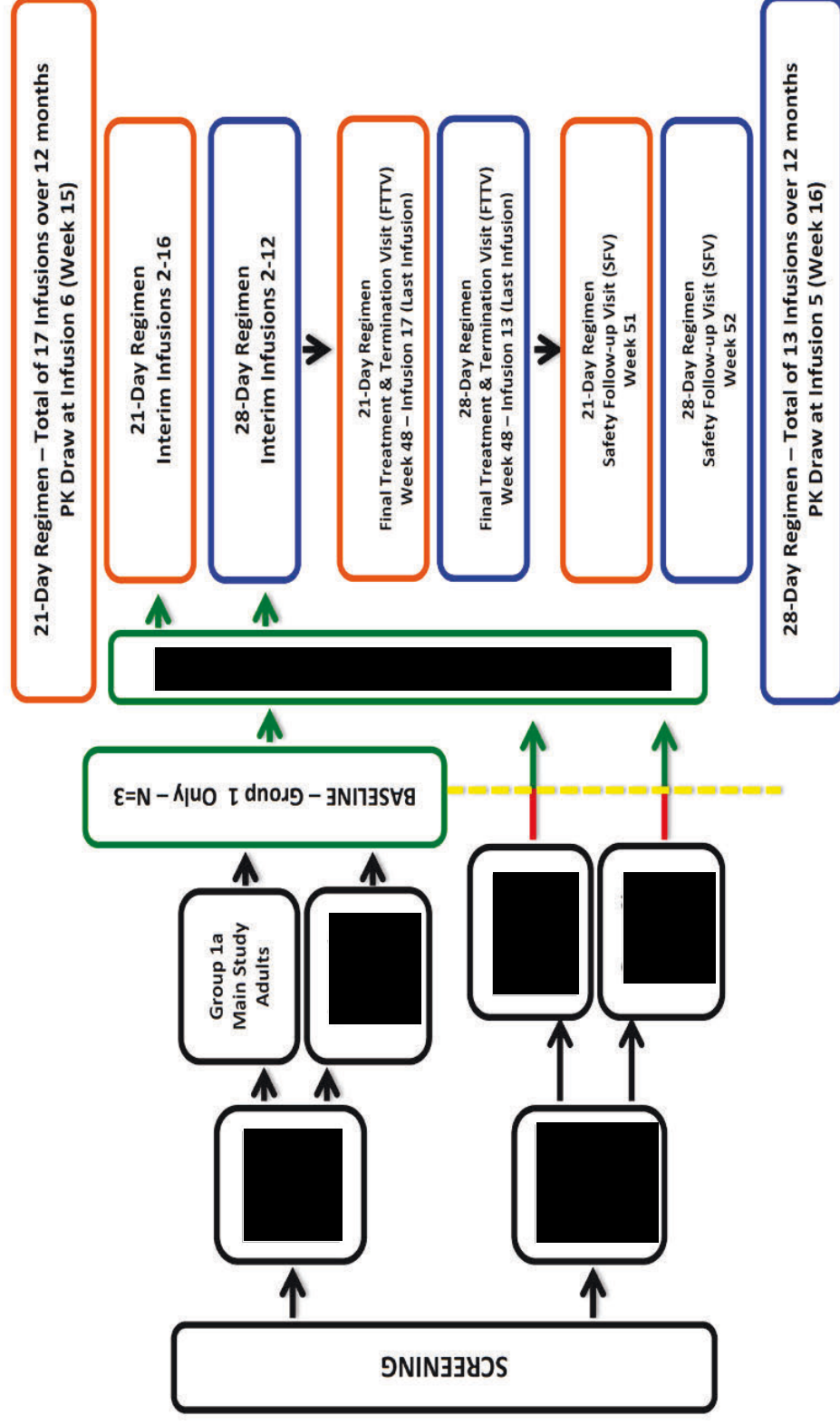
At the Baseline Visit (Visit 1), subjects will begin IMP therapy, resuming the same regimen as their pre-enrollment IGIV therapy. The rate will be determined and adjusted as needed (based on tolerability) in accordance with [Section 8.6](#). The treatment period will last 12 months. During the treatment period, standard safety blood draws will be taken, and IgG trough levels will be measured prior to infusions.

At Screening, Baseline, and the Safety Follow-up Visit (SFV), blood samples will be taken to evaluate for evidence of a monitored viral infection. Subjects who consent to participate in the PK study will undergo a series of blood draws to assess their PK profile at Visit 5 (28-day regimen subjects) or Visit 6 (21-day regimen subjects).

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## 5.2 Study Design Diagram



Protocol TBI-001-IGIV

### 5.3 Study Duration and Centers

This study will be conducted at approximately [REDACTED] in the US and Canada specializing in treating patients with primary immunodeficiencies. Central and Local ethics committees (Investigational Review Boards [IRBs] or Research Ethics Boards [REBs]) will be utilized depending on the site's preference and standard operating procedures (SOPs). Depending on the IRB/REB review procedures and frequency at the various centers, as well as the time needed to collect all pre-study regulatory documents, it is anticipated to take between one and four months for all centers to be initiated. Following site initiations, the overall recruitment period will vary for the two populations (adults and children), and is dependent on whether the subject is enrolled in the PK groups.

It is estimated that Group 1 will take approximately 3 months to complete enrollment, and Group 2 will take approximately 14 months.

Prior to receiving the first dose of IMP, each subject will be screened for a period dependent on their infusion schedule: subjects receiving SCIG will be screened approximately 7, 14, 21, or 28 days before the Baseline Visit (per their standard regimen), subjects on a 21-day IGIV regimen will be screened approximately 21 days before the Baseline Visit, and subjects on a 28-day IGIV regimen will be screened approximately 28 days before the Baseline Visit. Subjects will receive treatment for 12 months. Subjects on a 21-day regimen will receive 17 infusions, and subjects on a 28-day regimen will receive 13 infusions. AEs will be monitored for the entire period (21 days [ $\pm 2$  days] through 28 days [ $\pm 2$  days]) following the last infusion. All subjects return for the SFV, which will occur either 21 or 28 days after the last infusion of IMP, respective to each subject's treatment regimen.

Up to three additional months will be required to closeout the study.

|                                                      | Group 1a and 1b | Group 2a and 2b |
|------------------------------------------------------|-----------------|-----------------|
| Study Set up IRB/REB approvals:                      | Up to 4 months  | Up to 4 months  |
| Recruitment period:                                  | 3 months        | 14 months       |
| Efficacy period:<br>(includes 1 month for screening) | 13 months       | 13 months       |
| Follow-up Safety Period:                             | ~one month      | ~one month      |
| Data Cleaning and Lock:                              | ~ 3 months      | ~ 3 months      |
| Total Duration:                                      | 24 months       | 35 months       |

**The initial clinical study report with adult data only will be submitted for marketing applications in the USA and Canada.**

**A final study report including the pediatric data will be issued to expand the label to include children in the USA and Canada.**

## 6. SUBJECT POPULATION

The study will enroll subjects with a confirmed clinical diagnosis of a PIDD that requires treatment with IGIV.

They must satisfy the inclusion and exclusion criteria listed below. There will be two groups, depending on the subjects' ages.

### 6.1 Inclusion Criteria

1. Subject has a confirmed clinical diagnosis of a PIDD, which requires treatment with IGIV. Documented hypogammaglobulinemia in the setting of PIDD is required in one of the following PIDDs:
  - Agammaglobulinemia
  - Common Variable Immune Deficiency (CVID)
  - Hypogammaglobulinemia, with documented IgG levels <500 mg/dL and demonstration of specific deficiency of antibody production when available.
  - Hyper-IgM Syndrome (HIGM), with documented IgG levels <500 mg/dL
  - Severe combined immunodeficiency (SCID) status post hematopoietic stem cell transplantation (HSCT) with normal T cell function and deficient antibody production with documented IgG levels <500 mg/dL
  - Adenosine deaminase deficiency resulting in severe combined immunodeficiency (ADA-SCID) receiving Adagen with normal T cell function and deficient antibody production with documented IgG levels <500 mg/dL
2. Subject/guardian has provided written informed consent (and assent, as applicable).
3. Subject is between the ages of 2 and 70 years.
4. Subject has received IGIV therapy at 21- or 28-day ( $\pm 4$  days) intervals for at least three consecutive months (12 weeks) [REDACTED]  
[REDACTED]  
[REDACTED] or;
5. Subject has received commercial SCIG [REDACTED] (without having a  $\geq 25\%$  change in dose) on any dosing schedule for at least 4 consecutive weeks prior to Screening. Subjects on SCIG must have received and tolerated IGIV treatment prior to SCIG treatment.
6. Subject has a documented trough of  $\geq 500$  mg/dL in the 6 months prior to and including Screening.
7. Females of childbearing potential must be willing to use an effective form of birth control (eg, oral contraceptives) for the duration of the study, per IRB/REB guidelines.
8. Subject agrees to comply with the requirements of the protocol.

## 6.2 Exclusion Criteria

1. Subject has had a documented bacterial or viral infection within seven days prior to the Baseline Visit or is receiving antibiotic treatment (Note: Subjects who have been asymptomatic for seven days but have not completed treatment or use a topical antibacterial, that is minimally absorbed systemically, PRN are not excluded).
2. Subject has secondary immunodeficiency.
3. Subject has been diagnosed with specific antibody deficiency or IgG subclass deficiency.
4. Subject has history of thrombotic events, such as deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism, etc within the year prior to Screening.
5. Subject has had an immune globulin associated arterial or venous thrombotic/thromboembolic event (TEE) within 7 days of an IgG infusion or a TEE that is not associated with an immune globulin within one year of Screening.
6. Subject has received any IMP under investigation within the past 30 days ( $\pm$  2 days) at the time of the Baseline Visit.
7. Subject has received blood products (except for IGIV, SCIG, or albumin) within 6 months of Screening.
8. Subject's lab results show evidence of infection with a positive NAT test of HIV-1 and HIV-2, HBV, or HCV
9. Subject has anemia ( $\leq$ 8.5 g/dL).
10. Subject has levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $>$ 3.0 times the upper limit of normal (ULN).
11. Subject has severe neutropenia ( $\leq$ 1000 neutrophils per  $\text{mm}^3$ ).
12. Subject has creatinine concentration  $>$ 1.5 times the ULN and eGFR as calculated by the CMP as  $<$ 60mL/min/1.73  $\text{m}^2$ .
13. Subject is receiving other immunosuppressive or immunomodulatory drugs or chemotherapy.
14. Subject is taking or has taken within the four weeks prior to Screening prednisone at  $\geq$ 0.15 mg/kg/day for more than 10 days.
15. Subject has ever had a severe anaphylactic reaction to a blood or IgG product in the opinion of the PI.
16. Subject has lymphoid malignancy, leukemia, or any other history of malignancy within the past five years, except squamous cell or basal cell carcinoma of the skin (not melanoma).
17. Subject has hypoalbuminemia, protein-losing enteropathy, or proteinuria greater than 300 mg/24 hours except for subjects with documented orthostatic proteinuria.
18. Subject has immunoglobulin A (IgA) deficiency with known antibodies to IgA.
19. Female who is pregnant, breastfeeding, or planning a pregnancy during the course of the study (women who become pregnant during the study will be withdrawn from the study).

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20. Any condition that is likely to interfere with evaluation of IMP or satisfactory conduct of the trial in the PI's opinion.
21. Subjects who may not be compliant or have a history of non-compliance in the opinion of the PI.

## **7. STUDY CONDUCT**

### **7.1 Pre-screening**

In order to identify subjects who meet the eligibility criteria, sites will review their patient records according to their own center's procedures for pre-screening, ensuring that they comply with all applicable requirements of the Health Insurance Portability and Accountability Act (HIPAA) in the USA or the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada.

### **7.2 Screening Visit**

For subjects receiving IGIV prior to enrollment, the Screening Visit (Visit 0) will be conducted at 21 days ( $\pm 2$  days) before the Baseline Visit for subjects on a 21-day regimen or at 28 days ( $\pm 2$  days) before the Baseline Visit for subjects on a 28-day regimen. For subjects receiving SCIG prior to enrollment, the Screening Visit (Visit 0) will be conducted at 7, 14, 21 or 28 days, based on their standard regimen, ( $\pm 2$  days) before the Baseline Visit. For SCIG 7-day subjects, they can be given an additional dose of their prior SCIG if all the Screening lab results are not back in time for the Baseline visit.

If the subject is between the ages of 2 and <17 years, **at least** [REDACTED] (including the 72-hour observation period post-infusion) prior to Screening.

#### **7.2.1 Informed Consent (Screening Visit)**

Eligible subjects and guardians (in the case of subjects less than 18 years of age) will first participate in informed consent and assent (if appropriate) procedures prior to any study procedures being performed. After informed consents and assents have been obtained, subjects will undergo a Screening visit to confirm their eligibility.

#### **7.2.2 Demographic Information (Screening Visit)**

Demographic information will be collected including the subject's date of birth, race, ethnicity, and sex, and for pediatric subjects we will also collect height for the eGFR calculation.

#### **7.2.3 Medical History (Screening Visit)**

A complete medical and surgical history, going back two years, will be obtained including the form of birth control in females of childbearing potential. Evaluation of medical history will specifically include the year of diagnosis of PIDD, the date (for subjects who have been treated for more than one year, the year of treatment initiation will be sufficient) of initiation of treatment with IGIV and SCIG (as appropriate), and all documented proven SBIs recorded within the past 10 years prior to Screening. In the event that a concomitant medication is ongoing at the time of Screening, the associated indication must be included in the Medical History even if greater than two years.

## **7.2.4 Current and Prior Medications (Screening Visit)**

Current and prior medications taken within the past four weeks prior to Screening will be collected including non-prescription, prescription, and herbal medications, as well as transfusion medications. The subject will be asked if they routinely receive medications prior to IG infusions, and the respective routes, doses, and indications will be collected.

### **7.2.4.1 Previous IGIV/SCIG treatment**

Current and prior IGIV or SCIG treatment (or a combination of the two) received within the past three months prior to Screening will be collected, including doses, regimens, steady state trough levels, and well-tolerated infusion rates.

## **7.2.5 Review of Entry Criteria (Screening Visit)**

The medical history, prior medications, physical exam, review of chest x-rays within the past six months prior to Screening, and other collected tests/data and safety parameters will be reviewed to ascertain if the subject meets all inclusion criteria and does not meet any of the exclusion criteria. The PI or physician sub-investigator will determine if the subject is eligible to participate and will follow the protocol throughout the subject's participation in the trial.

Subjects who do not meet the eligibility criteria at Screening due to an active infection may repeat the Screening after the infection has resolved.

## **7.2.6 Physical Examination (Screening Visit)**

The examination will include height and weight, examination of body systems and organs including: head, eyes, ears, nose, and throat (HEENT); respiratory; musculoskeletal; cardiac; abdomen; lymph nodes; skin; and neurologic. The weight at Screening is to be used as the dosing weight at the Baseline Visit unless there has been a  $\geq 5\%$  change in weight.

## **7.2.7 Chest X-ray (Screening Visit)**

A screening chest x-ray will be performed if a normal, or "not clinically significant" one, is not available from the last 6 months.

## **7.2.8 Vital Signs (Screening Visit)**

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

## **7.2.9 Laboratory Assessments (Screening Visit)**

Subjects are allowed to receive their last commercial IGIV dose at the Screening visit as long as screening laboratory samples are taken prior to the infusion. Specimens for laboratory analysis will be obtained to ascertain whether a subject meets the eligibility criteria and to assess for possible AEs. The following assessments will be performed, and retention serum samples will be obtained and stored for IgG and virology testing (note that for any visit, any post-visit redraw can be done by a Home Health Nurse):

**Hematology** – Complete blood count (CBC) including red blood cell count (RBC), reticulocytes, white blood cell count (WBC) and differential, hemoglobin, hematocrit, RBC

indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red cell distribution width [RDW]), and platelet count

**Serum chemistry** – Total bilirubin, creatinine, urea, total protein, LDH, CK, BUN, ALT, AST, and ALP.

**Urinalysis** – Protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick with a reflex microscopic examination if any of the dipstick parameters are abnormal and clinically significant.

**Pregnancy Test** – Urine pregnancy test will be performed on all female subjects of childbearing potential

**IgG trough** – Serum total IgG level. Back-up sample collected.

**Viral Testing (NAT)** – HBV, HCV, HIV-1, and HIV-2. (Additionally, retention of pre-treatment serum samples will be collected from each subject for possible future testing of additional infectious agents.)

### 7.3 Baseline Visit

The Baseline Visit (Visit 1) will be conducted at 7, 14, 21, or 28 days, based on their standard regimen, ( $\pm 2$  days) after Screening for subjects previously receiving SCIG, 21 days ( $\pm 2$  days) after Screening for subjects on a 21-day regimen of IGIV and 28 days ( $\pm 2$  days) after Screening for subjects on a 28-day regimen of IGIV.

#### 7.3.1 Medical History and Medication Review (Baseline Visit)

A review of medical history and concurrent medications will be performed to assess for any changes since Screening.

#### 7.3.2 Review of Entry Criteria (Baseline Visit)

The entry criteria will be reviewed again to ensure ongoing subject eligibility.

#### 7.3.3 Physical Examination (Baseline Visit)

A physical examination will be conducted, during which the subject's weight will be measured and examination of body systems and organs as defined in the CRF. If the subject has gained or lost  $\geq 5\%$  body weight since the last visit, the dose of IMP will be adjusted accordingly to maintain the same dose expressed in mg/kg/infusion. If there is a change in weight  $\geq 5\%$  then that weight becomes the subject's new dosing weight.

The examination will include weight, examination of body systems and organs including: HEENT, respiratory, musculoskeletal, cardiac, abdomen, lymph nodes, skin, and neurologic.

#### 7.3.4 Clinical Assessments (Baseline Visit)

- During the physical (**Section 7.3.3**), infusion, or while the subject is in the clinic, specific attention will be paid for signs and symptoms of hemolysis and thrombosis.

- **Follow up calls/texts:** If during the 24- and/or 72-hour post infusion phone calls/text message follow-ups the subject reports any symptoms of hemolysis or thrombosis, the subject will be asked to return to the site immediately for examination and full panel of testing per the site's standard of care and the PI's discretion.
- **Note:** The subjects will be asked about any AEs during the 24- and 72-hour post infusion phone/text message follow-ups.

**The following are some of the common symptoms of Hemolysis and Thrombosis:**

- **Hemolysis:** Abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, enlargement of the spleen and liver, tachycardia, and heart murmur.
- **Thrombosis:** Tenderness and pain along line of femoral or popliteal veins, entire limb swelling, pitting edema, lower leg pain. Systemic signs of thrombosis include dyspnea, cough, hemoptysis, diaphoresis or sudden chest pain that worsens with deep inspiration, sweating, anxiety and fatigue.

### 7.3.5 Laboratory Assessments (Baseline Visit)

All laboratory samples will be drawn prior to administration of IMP.

Blood samples will be collected for the following and will be used for the baseline comparison of all other sequential laboratory draws:

- Hematology including CBC (RBC, reticulocytes, WBC and differential, hemoglobin, hematocrit, RBC indices [MCV, MCH, MCHC, RDW], and platelet count)
- Serum chemistry including total bilirubin, creatinine, urea, total protein, LDH, CK, BUN, ALT, AST, and ALP.
- **Testing for Hemolysis will include (see also flowchart in [Section 1.4](#)):**
  - **Pre Infusion:** Serum haptoglobin, plasma free hemoglobin, Direct Coombs test, urine hemosiderin.
  - **Post Infusion:** If, during an infusion the subject presents with evidence of hemolysis (i.e. sudden pallor or fatigue, red or brown urine, are present), then post infusion labs will be drawn before the subject leaves the site. This will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test, and urine hemosiderin. In addition, if the subject reports any of the following post infusion symptoms at home: abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, tachycardia; and on clinical assessment shows signs of enlargement of the spleen and liver and a heart murmur, a post infusion sample will be taken, which will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test and urine hemosiderin.
  - **Positive Direct Coombs Test Results:** If any Direct Coombs test result is positive, the lab will notify the site within 2 business days. The site will then phone the subject to identify any signs or symptoms. The site will schedule the subject to return to the site or schedule a visit with a Home Health Nurse within 3 days of becoming aware of the positive test and will repeat the

following tests: Direct Coombs test, RBC count, hematocrit, hemoglobin, serum haptoglobin, bilirubin (total, direct and indirect), LDH, and urine hemosiderin tests.

- **Hemoglobinuria:** If at any time the subject develops hemoglobinuria, the following tests will be repeated within 3 business days of the site becoming aware: serum haptoglobin, plasma free hemoglobin, urine hemosiderin, and LDH for differential diagnosis.
- **Drop in Hemoglobin:** If at any time the subject's Hemoglobin has dropped by >2.0 g/dL from the baseline level, the subject will be asked to return to the site or schedule a visit with a Home Health Nurse within 5 business days of the site becoming aware of the drop. At this time a full panel of testing will be completed including: haptoglobin, plasma free hemoglobin, Direct Coombs test, LDH, reticulocyte count, urine hemosiderin, urine dipstick, urine microscopic analysis and repeat hemoglobin.
- An additional blood draw will be performed between day 7 and day 14 after infusion to test for evidence of hemolysis.
- Pregnancy test (if applicable)
- IgG trough and retention sample
- Viral Testing (NAT and Serology) – HAV, HBV, HCV, PVB19, HIV-1, and HIV-2
- Serum retention samples for possible future testing of additional infectious agents
- Urine protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick with a reflex microscopic examination if any of the dipstick parameters are abnormal and clinically significant.

### 7.3.6 Subject Diary Distribution and Completion Instructions (Baseline Visit)

The subject will be issued a subject diary.

The subject will be instructed on how to document data in real time. The subject will be instructed to record any changes in medication and/or changes in their medical status in the diary. Subjects will be instructed to record signs and symptoms rather than diagnoses. Specifically, the subject will be asked to record all antibiotics prescribed and taken for infection. All hospitalizations or visits to the emergency room or any other doctor visits will be recorded by the subject in the diary, with the dates of the visit/admission, and the reason for visit/admission. At any time a subject requires an anti-pyretic for fever the subject must record their temperature in their subject diary. The subject will record any missed days of work, school, or daycare (as appropriate). If the subject is unable to perform normal daily activities due to infection(s), the subject will record how long they were unable to perform normal daily activities in their diary.

The subject will be instructed to bring his or her diary to each study visit.

Delegated site personnel will discuss the diary with the subject and compare diary entries to the notes the site has made from the phone call/text message contacts that had been made up to 72 hours after administration of IMP.

### 7.3.7 Pre-infusion Vital Signs (Baseline Visit)

Vital signs will be collected  $\leq 30$  minutes prior to the first infusion including blood pressure, body temperature, respiratory rate, and heart rate.

### 7.3.8 Infusion (Baseline Visit)

[REDACTED] The dose will be adjusted by weight if the weight has changed  $\geq 5\%$  from the Screening Visit. If the weight changes by  $\geq 5\%$  then that weight becomes the new dosing weight. Ensure the subject is properly hydrated per the site's standard of care prior to start of infusion.

The infusion, calculated using the dosing weight, is to be administered in a conservative, stepwise fashion as follows:

- For the first 30 minutes, IMP will be infused at 0.01 mL/kg/min.
- If, in the PI's opinion, the rate is well tolerated, the rate of administration will be increased to 0.02 mL/kg/min for the next 30 minutes.
- If the increase is well tolerated, the rate will be increased to 0.04 mL/kg/min for the next 30 minutes.
- If 0.04 mL/kg/min is well tolerated, the remainder of the infusion may be administered at a maximum rate of between 0.06 mL/kg/min to 0.08 mL/kg/min at the PI's discretion.
- The maximum infusion rate should not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is sought.

### 7.3.9 Infusion Vital Signs (Baseline Visit)

Vital signs (blood pressure, body temperature, respiratory rate, and heart rate) will be recorded while the subject is at rest at the following time points:

- 10 minutes ( $\pm 5$  minutes) after the start of infusion;
- 10 minutes ( $\pm 5$  minutes) after each rate change, including after the final rate change even if the infusion has stopped prior to the 10 minute mark;
- 30 minutes ( $\pm 5$  minutes) after the final rate change, including after the final rate change even if the infusion has stopped after the 10 minute mark but prior to the 30 minute mark;
- and then hourly ( $\pm 10$  minutes) after that if the infusion is still ongoing;

#### 7.3.9.1 Post Infusion Vital Signs (Baseline Visit)

Once the infusion has stopped, the post infusion vital signs (blood pressure, body temperature, respiratory rate, and heart rate) will be recorded while the subject is at rest at the following time points:

- 30 minutes post-infusion ( $\pm 5$  minutes); and
- 60 minutes post-infusion ( $\pm 15$  minutes).

### 7.3.10 Infusion-related Adverse Events (Baseline Visit)

Subjects will be carefully monitored for adverse events during the infusion and for up to 72 hours post infusion. Subjects will be observed directly for one hour after each infusion, and all AEs will be documented. In addition, study staff will call/text message the subject 24 hours ( $\pm 6$  hours) and 72 hours ( $\pm 12$  hours) after the infusion to discuss the status of AEs and to ensure that the subject diary is being kept current.

Infusion related adverse events are defined as AEs that occur during infusions and/or up to 72 hours after infusions. The subject will be encouraged to record these in the subject diary after they leave the site as referenced in [Section 7.3.6](#).

For further details on handling infusion-related AEs see [Section 10.2](#).

## 7.4 Visits 2-16 or Visits 2-12 (Interim Infusion Visits)

Subjects on a 21-day regimen will receive infusions from Week 3 (Infusion 2) every 21 days (3 weeks) to Week 48 (Infusion 17). Infusion 17 is at Visit 17 (FTTV), after which the SFV occurs in 21 days. Infusions may be scheduled within  $\pm 2$  days of the 21-day cycle infusion time points throughout the trial.

Subjects on a 28-day regimen will receive infusions from Week 4 (Infusion 2) every 28 days (4 weeks), to Week 48 (Infusion 13). Infusion 13 is at Visit 13 (FTTV), after which the SFV occurs in 28 days. Infusions may be scheduled within  $\pm 2$  days of the 21-day cycle infusion time points throughout the trial.

See also [Sections 1.2](#) and [1.3](#) (Schedules of Infusions).

### 7.4.1 Diary Review (Interim Infusion Visits)

Subjects will bring their subject diaries to each visit for discussion and review with the PI or designee (ie, physician, physician's assistant or nurse practitioner) to ensure completeness and accuracy of entries made by the subject.

Comparisons with data entered up to the 72-hour post infusion period by the study center from phone calls/text messages will also be reviewed to discuss and resolve discrepancies. Any discrepancies found in the subject diary should be corrected, initialed and dated by the subject at each visit.

The PI or designee will review concomitant medications, AEs, and other information recorded in the subject diary prior to administering IMP. In addition, laboratory data from prior visits will have been reviewed prior to administration of IMP at Visit 2.

A new diary will be issued with instructions to complete the diary and return with the diary at the next visit.

### 7.4.2 Physical Exam (Interim Infusion Visits)

A physical examination will be conducted, during which the subject's weight will be measured and examination of body systems and organs as defined in the CRF.

The examination will include weight, examination of body systems and organs including: HEENT, respiratory, musculoskeletal, cardiac, abdomen, lymph nodes, skin, and neurologic.

If the subject has gained or lost  $\geq 5\%$  body weight since the last visit, the dose of IMP will be adjusted to maintain a constant dose in mg/kg/infusion during the study.

#### 7.4.3 Clinical Assessments (Interim Infusion Visits)

- During the physical (**Section 7.4.2**), infusion, or while the subject is in the clinic, specific attention will be paid for signs and symptoms of hemolysis and thrombosis.
- **Follow up calls/texts:** If during the 24- and/or 72-hour post infusion phone calls/text message follow-ups the subject reports any symptoms of hemolysis or thrombosis, the subject will be asked to return to the site immediately for examination and full panel of testing per the site's standard of care and the PI's discretion.
- Note: The subjects will be asked about any AE's during the 24- and 72-hour post infusion phone/text message follow-ups.

**The following are some of the common symptoms of Hemolysis and Thrombosis:**

- **Hemolysis:** Abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, enlargement of the spleen and liver, tachycardia, and heart murmur.
- **Thrombosis:** Tenderness and pain along line of femoral or popliteal veins, entire limb swelling, pitting edema, lower leg pain. Systemic signs of thrombosis include dyspnea, cough, hemoptysis, diaphoresis or sudden chest pain that worsens with deep inspiration, sweating, anxiety and fatigue.

#### 7.4.4 Laboratory Assessments (Interim Infusion Visits)

All laboratory samples will be drawn prior to administration of IMP.

Blood samples will be collected at Visits 2, 5, 8, 11, (and Visit 14 for subjects on the 21-day schedule) for the following:

- Hematology including CBC (RBC, reticulocytes, WBC and differential, hemoglobin, hematocrit, RBC indices [MCV, MCH, MCHC, RDW], and platelet count)
- Serum chemistry including total bilirubin, creatinine, urea, total protein, LDH, CK, BUN, ALT, AST, and ALP.

The following will be collected at every visit:

- **Testing for Hemolysis will include (see also flowchart in Section 1.4):**
  - **Pre Infusion:** Serum haptoglobin, plasma free hemoglobin, Direct Coombs test, urine hemosiderin.
  - **Post Infusion:** If, during an infusion the subject presents with evidence of hemolysis (i.e. sudden pallor or fatigue, red or brown urine, are present), then post infusion labs will be drawn before the subject leaves the site. This will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test, and

urine hemosiderin. In addition, if the subject reports any of the following post infusion symptoms at home: abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, tachycardia; and on clinical assessment shows signs of enlargement of the spleen and liver and a heart murmur, a post infusion sample will be taken, which will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test and urine hemosiderin.

- **Positive Direct Coombs Test Results:** If any Direct Coombs test result is positive, the lab will notify the site within 2 business days. The site will then phone the subject to identify any signs or symptoms. The site will schedule the subject to return to the site or schedule a visit with a Home Health Nurse within 3 days of becoming aware of the positive test and will repeat the following tests: Direct Coombs test, RBC count, hematocrit, hemoglobin, serum haptoglobin, bilirubin (total, direct and indirect), LDH, and urine hemosiderin tests.
- **Hemoglobinuria:** If at any time the subject develops hemoglobinuria, the following tests will be repeated within 3 business days of the site becoming aware: serum haptoglobin, plasma free hemoglobin, urine hemosiderin, and LDH for differential diagnosis.
- **Drop in Hemoglobin:** If at any time the subject's Hemoglobin has dropped by >2.0 g/dL from the baseline level, the subject will be asked to return to the site or schedule a visit with a Home Health Nurse within 5 business days of the site becoming aware of the drop. At this time a full panel of testing will be completed including: haptoglobin, plasma free hemoglobin, Direct Coombs test, LDH, reticulocyte count, urine hemosiderin, urine dipstick, urine microscopic analysis and repeat hemoglobin.
- Pregnancy test (if applicable)
- IgG trough and retention sample
- Urine protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick with a reflex microscopic examination if any of the dipstick parameters are abnormal and clinically significant.

Samples for IgG subclasses (IgG1, IgG2, IgG3, and IgG4) and specific antibodies (*Streptococcus pneumoniae*) **will be drawn at Infusion 5** for subjects on a 28-day regimen and **Infusion 6** for subjects on a 21-day regimen. For pediatric PK subjects ages 12 and under, only total IgG will be measured.

#### 7.4.5 Pre-infusion Vital signs (Interim Infusion Visits)

Vital signs will be collected ≤30 minutes prior to the first infusion including blood pressure, body temperature, respiratory rate, and heart rate.

#### 7.4.6 Infusions (Interim Infusion Visits)

The second infusion will occur at Week 3 for subjects on a 21-day Regimen and Week 4 for subjects on a 28-day Regimen.

The mg/kg/infusion dose will be adjusted by weight if the weight has changed  $\geq 5\%$  from the prior dosing weight. If the weight changes  $\geq 5\%$ , that weight then becomes the new dosing weight used in the calculation of the mg/kg/infusion dose.

The IMP dose in mg/kg/infusion should remain the same throughout the study unless the Investigator deems it necessary to change the dosage regimen. [REDACTED]

Ensure the subject is properly hydrated per the site's standard of care prior to start of infusion.

At least 5 subjects enrolled must be on the 21-day cycle.

The infusion, calculated using the dosing weight, is to be administered in a stepwise fashion as follows:

- For the first 15 minutes, IMP will be infused at 0.01 mL/kg/min.
- If, in the PI's opinion, the rate is well tolerated, the rate of administration will be increased to 0.02 mL/kg/min for the next 15 minutes.
- If the increase is well tolerated, the rate will be increased to 0.04 mL/kg/min for the next 15 minutes.
- If 0.04 mL/kg/min is well tolerated, the remainder of the infusion may be administered at a maximum rate of between 0.06 mL/kg/min to 0.08 mL/kg/min at the PI's discretion.
- The maximum infusion rate should not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is sought.

If an infusion-related AE occurs, the infusion rate should be adjusted or halted in accordance with [Section 10.2](#).

#### **7.4.7 Infusion Vital Signs (Interim Infusion Visits)**

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded at the following time points:

- 10 minutes ( $\pm 5$  minutes) after the start of infusion;
- 10 minutes ( $\pm 5$  minutes) after each rate change, including after the final rate change even if the infusion has stopped prior to the 10 minute mark;
- 30 minutes ( $\pm 5$  minutes) after the final rate change, including after the final rate change even if the infusion has stopped after the 10 minute mark but prior to the 30 minute mark;
- and then hourly ( $\pm 10$  minutes) after that if the infusion is still ongoing;

#### 7.4.7.1 Post Infusion Vital Signs (Interim Infusion Visits)

Once the infusion has stopped, vital signs (blood pressure, body temperature, respiratory rate, and heart rate) will be recorded while the subject is at rest at the following time points:

- 30 minutes post-infusion ( $\pm 5$  minutes); and
- 60 minutes post-infusion ( $\pm 15$  minutes and at least 5 minutes prior to any PK sampling, as applicable. See section 7.7)

#### 7.4.8 Infusion-related Adverse Events (Interim Infusion Visits)

Subjects will be carefully monitored for adverse events during the infusion and for up to 72 hours post infusion. Subjects will be observed directly for one hour after each infusion, and all AEs will be documented. In addition, study staff will call/text message the subject 24 hours ( $\pm 6$  hours) and 72 hours ( $\pm 12$  hours) after the infusion to discuss the status of AEs and to ensure that the subject diary is being kept current.

Infusion related adverse events are defined as AEs that occur during infusions and/or up to 72 hours after infusions. The subject will be encouraged to record these in the subject diary after they leave the site as referenced in [Section 7.3.6](#).

For further details on handling infusion-related AEs see [Section 10.2](#).

### 7.5 Visit 17 or Visit 13 (Final Treatment and Termination Visit – FTTV)

The Final Treatment and Termination Visit (FTTV) will take place at Visit 17  $\pm 2$  days for subjects on a 21-day regimen or at Visit 13  $\pm 2$  days for subjects on a 28-Day Regimen.

#### 7.5.1 Diary Review (FTTV)

The PI or designee will review the subject diary with the subject to ensure completeness and accuracy of entries in accordance with the same diary procedures described at Visit 2 ([Section 7.4.1](#)).

#### 7.5.2 Physical Exam (FTTV)

A physical examination will be conducted, during which the subject's weight will be measured and examination of body systems and organs as defined in the CRF.

The examination will include weight, examination of body systems and organs including: HEENT, respiratory, musculoskeletal, cardiac, abdomen, lymph nodes, skin, and neurologic.

The dose will be adjusted by weight if the weight has changed  $>5\%$  from the Baseline Visit. The IMP dose in mg/kg/infusion should remain the same throughout the study.

#### 7.5.3 Clinical Assessments (FTTV)

- During the physical ([Section 7.5.2](#)), infusion, or while the subject is in the clinic, specific attention will be paid for signs and symptoms of hemolysis and thrombosis.
- **Follow up calls/texts:** If during the 24- and/or 72-hour post infusion phone calls/text message follow-ups the subject reports any symptoms of hemolysis or

thrombosis, the subject will be asked to return to the site immediately for examination and full panel of testing per the site's standard of care and the PI's discretion.

- Note: The subjects will be asked about any AE's during the 24- and 72-hour post infusion phone/text message follow-ups.

**The following are some of the common symptoms of Hemolysis and Thrombosis:**

- **Hemolysis:** Abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, enlargement of the spleen and liver, tachycardia, and heart murmur.
- **Thrombosis:** Tenderness and pain along line of femoral or popliteal veins, entire limb swelling, pitting edema, lower leg pain. Systemic signs of thrombosis include dyspnea, cough, hemoptysis, diaphoresis or sudden chest pain that worsens with deep inspiration, sweating, anxiety and fatigue.

#### 7.5.4 Laboratory Assessments (FTTV)

All laboratory samples will be drawn prior to administration of IMP.

Blood samples will be collected for the following:

- Hematology including CBC (RBC, reticulocytes, WBC and differential, hemoglobin, hematocrit, RBC indices [MCV, MCH, MCHC, RDW], and platelet count)
- Serum chemistry including total bilirubin, creatinine, urea, total protein, LDH, CK, BUN, ALT, AST, ALP.
- **Testing for Hemolysis will include (see also flowchart in [Section 1.4](#)):**
  - **Pre Infusion:** Serum haptoglobin, plasma free hemoglobin, Direct Coombs test, urine hemosiderin.
  - **Post Infusion:** If, during an infusion the subject presents with evidence of hemolysis (i.e. sudden pallor or fatigue, red or brown urine, are present), then post infusion labs will be drawn before the subject leaves the site. This will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test, and urine hemosiderin.
  - **Positive Direct Coombs Test Results:** If any Direct Coombs test result is positive, the lab will notify the site within 2 business days. The site will then phone the subject to identify any signs or symptoms. The site will schedule the subject to return to the site or schedule a visit with a Home Health Nurse within 3 days of becoming aware of the positive test and will repeat the following tests: Direct Coombs test, RBC count, hematocrit, hemoglobin, serum haptoglobin, bilirubin (total, direct and indirect), LDH, and urine hemosiderin tests. In addition, if the subject reports any of the following post infusion symptoms at home: abnormal paleness, jaundice, fever, weakness, dizziness, confusion, intolerance to physical activity, tachycardia; and on clinical assessment shows signs of enlargement of the spleen and liver and a heart murmur, a post infusion sample will be taken, which will include: serum haptoglobin, plasma free hemoglobin, Direct Coombs test and urine hemosiderin.

- **Hemoglobinuria:** If at any time the subject develops hemoglobinuria, the following tests will be repeated within 3 business days of the site becoming aware: serum haptoglobin, plasma free hemoglobin, urine hemosiderin, and LDH for differential diagnosis.
- **Drop in Hemoglobin:** If at any time the subject's Hemoglobin has dropped by  $>2.0$  g/dL from the baseline level, the subject will be asked to return to the site or schedule a visit with a Home Health Nurse within 5 business days of the site becoming aware of the drop. At this time a full panel of testing will be completed including: haptoglobin, plasma free hemoglobin, Direct Coombs test, LDH, reticulocyte count, urine hemosiderin, urine dipstick, urine microscopic analysis and repeat hemoglobin.
- Pregnancy test (if applicable)
- IgG trough and retention sample
- Urine protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick with a reflex microscopic examination if any of the dipstick parameters are abnormal and clinically significant.

#### 7.5.5 Pre-Infusion Vital signs (FTTV)

Vital signs will be collected  $\leq 30$  minutes prior to all infusions to include body temperature, blood pressure, respiratory rate, and heart rate.

#### 7.5.6 Final Infusion (FTTV)

The dose will be adjusted by weight if the weight has changed  $\geq 5\%$  from the established dosing weight. Ensure the subject is properly hydrated per the site's standard of care prior to start of infusion.

The infusion, calculated using the dosing weight, is to be administered in stepwise fashion as follows:

- For the first 15 minutes, IMP will be infused at 0.01 mL/kg/min.
- If, in the PI's opinion, the rate is well tolerated the rate of administration will be increased to 0.02 mL/kg/min for the next 15 minutes.
- If the increase is well tolerated, the rate will be increased to 0.04 mL/kg/min for the next 15 minutes.
- If 0.04 mL/kg/min is well tolerated, the remainder of the infusion may be administered at a maximum rate of between 0.06 mL/kg/min to 0.08 mL/kg/min at the PI's discretion.
- The maximum infusion rate should not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is sought.

If an infusion-related AE occurs, the infusion rate should be adjusted or halted in accordance with [Section 10.2](#).

#### 7.5.7 Infusion Vital Signs (FTTV)

Vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be recorded at the following time points:

- 10 minutes ( $\pm 5$  minutes) after the start of infusion
- 10 minutes ( $\pm 5$  minutes) after each rate change, including after the final rate change even if the infusion has stopped prior to the 10 minute mark;
- 30 minutes ( $\pm 5$  minutes) after the final rate change, including after the final rate change even if the infusion has stopped after the 10 minute mark but prior to the 30 minute mark;
- and then hourly ( $\pm 10$  minutes) after that if the infusion is still ongoing;

#### **7.5.7.1 Post Infusion Vital Signs (FTTV)**

Once the infusion has stopped, vital signs (blood pressure, body temperature, respiratory rate, and heart rate) will be recorded while the subject is at rest at the following time points:

- 30 minutes post-infusion ( $\pm 5$  minutes); and
- 60 minutes post-infusion ( $\pm 15$  minutes).

#### **7.5.8 Infusion-related Adverse Events (FTTV)**

Subjects will be carefully monitored for adverse events during the infusion and for up to 72 hours post infusion. Subjects will be observed directly for one hour after each infusion, and all AEs will be documented. In addition, study staff will call the subject 24 hours ( $\pm 6$  hours) and 72 hours ( $\pm 12$  hours) after the infusion to discuss the status of AEs and to ensure that the subject diary is being kept current.

Infusion related adverse events are defined as AEs that occur during infusions and/or up to 72 hours after infusions. The subject will be encouraged to record these in the subject diary after they leave the site as referenced in [Section 7.3.6](#).

For further details on handling infusion-related AEs see [Section 10.2](#).

#### **7.5.9 Early Termination Subjects (FTTV)**

If the subject terminates treatment prior to their final infusion with the IMP (Visit 17 for the 21-day regimen or Visit 13 for the 28-day regimen), all procedures for the FTTV should be added to the procedures for the scheduled visit.

If the subject is terminating early from the study and cannot return for the Safety Follow-up Visit (SFV), the procedures for the SFV should also be completed.

### **7.6 Visit 18 or Visit 14 (Safety Follow-up Visit – SFV)**

The Safety Follow-up Visit (SFV) will take place at Visit 18  $\pm 2$  days for subjects on a 21-day regimen or Visit 14  $\pm 2$  days for subjects on a 28-day regimen.

All study related activities should be conducted prior to administration of a commercial immunoglobulin product (not the IMP).

#### **7.6.1 Vital Signs (SFV)**

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

### 7.6.2 Laboratory Assessments (SFV)

Blood samples will be collected for the following prior to the administration of the next commercial immunoglobulin product infusion:

- Hematology including CBC (RBC, reticulocytes, WBC and differential, hemoglobin, hematocrit, RBC indices [MCV, MCH, MCHC, RDW], and platelet count)
- Serum chemistry including total bilirubin, creatinine, urea, total protein, LDH, CK, BUN, ALT, AST, and ALP.
- Pregnancy test (if applicable)
- IgG trough and retention sample
- Viral Testing (NAT and Serology) – HAV, HBV, HCV, PVB19, HIV-1, and HIV-2 (with the exception of any tests that are positive at baseline)
- Serum retention samples for possible future testing of additional infectious agents.
- Urine protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick with a reflex microscopic examination if any of the dipstick parameters are abnormal and clinically significant.

### 7.6.3 Diary Collection (SFV)

The PI/Designee will collect and review the subject diary with the subject to ensure completeness and accuracy of entries in accordance with the same diary procedures described at Visit 2 ([Section 7.4.1](#)).

## 7.7 Pharmacokinetic Sub Study Procedures (Groups 1b and 2b)

For those subjects who consented to enroll into the PK sub-study, samples will be taken at Infusion 6, for the 21-day regimen subjects or Infusion 5 for the 28-day regimen subjects. Samples will be obtained from at least [REDACTED] in Group 1b and at least 12 subjects in Group 2b. Note that vitals should be taken at least 5 minutes prior to any PK sampling.

Additional samples for PK pre-dose baseline analysis will be obtained between  $\geq 15$  and  $\leq 30$  minutes prior to the infusion for Group 1b and Group 2b and then as follows:

#### **Group 1b:**

- 15 minutes ( $\pm 5$  minutes) after the end of the infusion
- 1 hour ( $\pm 10$  minutes) after the end of the infusion
- 4 hours ( $\pm 15$  minutes) after the end of the infusion
- 24 hours ( $\pm 1$  hour) after the end of the infusion
- 7 days ( $\pm 1$  day) after the end of the infusion
- 14 days ( $\pm 1$  day) after the end of the infusion
- 21 days ( $\pm 2$  days) after the end of the infusion (only for subjects on a 21-day cycle)
- 28 days ( $\pm 2$  days) after the end of the infusion (only for subjects on a 28-day cycle)

**Group 2b:**

- 15 minutes ( $\pm$  5 minutes) after the end of the infusion
- 4 hours ( $\pm$  15 minutes) after the end of the infusion
- 24 hours ( $\pm$  1 hour) after the end of the infusion
- 7 days ( $\pm$  1 day) after the end of the infusion
- 14 days ( $\pm$  1 day) after the end of the infusion
- 21 days ( $\pm$  2 days) after the end of the infusion (only for subjects on a 21-day cycle)
- 28 days ( $\pm$  2 days) after the end of the infusion (only for subjects on a 28-day cycle)

**7.8 Screen Failures**

Subjects who do not meet the entry criteria at Screening or anytime through baseline will be ineligible for treatment on Visit 1 and be assigned a screen failure. Only demographic information will be collected on the CRF with the reason for ineligibility confirmed by the Study Monitor.

Subjects who do not meet the eligibility criteria at baseline due to an active infection may repeat the Screening after the infection has resolved.

**7.9 Subject Replacement**

Subjects withdrawn from the study may be replaced as needed at the discretion of the sponsor to ensure the desired number of evaluable subjects in each group of the study is achieved for both Non-PK and PK groups.

**7.10 Subject Identification**

Subjects require approval for Screening centrally by the CRO, to ensure that no group is over enrolled or under enrolled and to ensure [REDACTED] are enrolled on the 21 day regimen. Subjects will be identified by the site number and a 3-digit code. All subjects who are considered for Screening will receive a Subject Identification Number according to the following format: XX-YYY (site number-and a sequential number) to be defined in a Study Manual supplied to the site. Personal identifying information may only be obtained by the PI or their designee to complete the requirements of the protocol and must be kept by the PI in strictest confidence and may not be released unless required by law. See [Section 13.4](#) for additional information regarding confidentiality.

**7.11 Treatment Compliance**

All subjects will be infused under the supervision of the PI or designee and in accordance with the the respective treatment cycle. These data will be recorded in the CRF. Only subjects who have been enrolled into the trial will receive IMP. Under no circumstance

must any subject receive IMP without a written informed consent on file. For more information on IMP dispensing and accountability, please see [Section 8](#).

## 7.12 Protocol Deviations

All efforts will be made to avoid deviations from the study protocol. When protocol deviations do occur, the PI or designee should promptly inform the Study Monitor as soon as they are discovered. The implications of each deviation must be reviewed and the outcome/action/resolution documented (vital signs collected outside their respective timeframes and similar, minor deviations can be reviewed during interim monitoring visits and do not need to be promptly reported to the Study Monitor). It is expected most deviations will occur due to misunderstanding of the protocol at the site which the Monitor will find at a monitoring visit. These will be entered into the database and depending on if they are minor or major may have to be reported to the IRB. The impact of all deviations for the subject and/or trial for each deviation will be documented. This documentation must be kept in the sponsor files and Investigator files. In case of any major protocol deviations or violations, the Principal PI (PI) and sponsor will decide on the further participation of the affected subject, after having discussed all relevant aspects.

This process will continue throughout the entire study duration, which starts after site initiation and ends at study close out, and will be submitted to the IRB/REB according to the requirements of each of these institutions.

## **8. INVESTIGATIONAL MEDICINAL PRODUCT**

### **8.1 IMP Packaging and Formulation**

IMP is a sterile, 10% liquid preparation of highly purified normal human immunoglobulin derived from pools of US sourced human plasma for iv administration.

The IMP is provided in a 50 mL volume single-use, type-1 glass bottles seated with a stopper and a metallic seal with plastic flip-top cap.

Further details will be included in a separate IMP Manual.

### **8.2 IMP Dosage**

IMP is a 10% liquid formulation of human IgG in 50 mL vials. IMP will be administered every 21 days ( $\pm 2$  days) or 28 days ( $\pm 2$  days) in accordance with the subject's regimen at Screening for a period of 12 months. Subjects on a 21-day regimen will receive approximately 17 infusions, and subjects on a 28-day regimen will receive approximately 13 infusions.

[REDACTED]

To maintain a trough level of  $\geq 5$  mg/mL, the PI or qualified sub-investigator will sign-off on the calculated mg/kg/infusion IMP dose, based on the subject's current body weight at the Screening Visit. If the subject's body weight increases or decreases by  $\geq 5\%$ , the dose will be recalculated and will establish a new dosing weight. The new weight will then become the dosing weight.

Doses can be rounded up or down according to the following criteria:

When the calculated dose in ml is less than the contents of a whole vial, the remainder of the product in the vial is administered to the subject to avoid waste of the product (ie, the dosage amount is "rounded up" up to 1g (10mL) or 3% of the calculated dose, whichever is smaller).

When the calculated dose in ml would require a small amount of product from an additional vial (up to 1 g (10mL) or 3% of the calculated dose, whichever is smaller) the dose would be "rounded down". For example, if a 5.1 g dose (51mLs) were calculated, it would be rounded down to 5.0 g. Thus, only one 50 mL vial of IMP (containing 5.0 g of product) would be used, and a second 50 mL vial would not be opened.

### **8.3 IMP Labeling**

IMP vial labels will include information to comply with all applicable FDA and Health Canada regulations.

Full instructions on drug accountability procedures will be provided in an IMP Manual. This will also include how to account for any lost infusion volume due to IMP remaining in the iv line following each infusion.

## 8.4 IMP Storage Conditions

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

## 8.5 IMP Preparation

IMP should be inspected for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Allow the IMP to warm up to room temperature for 1-4 hours prior to administration and once this has occurred, unused IMP should not be returned to the refrigerator for future use.

Further details will be included in a separate IMP Manual.

Solutions should be visually inspected before use. If the solution is cloudy or has particulates it must not be used. Vials must not be shaken.

Only in the case where a site has a research pharmacist or a qualified designee can IMP be pooled and aseptically transferred into an empty sterile iv bag according to their standard operating procedures. The dose will be communicated to the pharmacist or a qualified designee who can then prepare the appropriate bottles of IMP that will be drawn into a syringe and aseptically transferred into an appropriately sized sterile iv bag or spiked into an appropriately sized sterile iv bag and labeled. The volume transferred will take into account the rounding up or rounding down volume (See [Section 8.2](#)) plus a standard amount to prime a pump, (if applicable). In this case the IMP will be stored in the research pharmacy.

In the event that a pharmacy will not be used, IMP may be stored in an alternate location (eg, an IMP refrigerator monitored by site staff, etc.), as long as such location meets the requirements of [Section 8.4](#).

Empty and partially used IMP vials must be maintained for drug accountability. These supplies should be clearly marked by subject (eg, empty and partially empty IMP vials from a single infusion should be placed in a plastic bag that bears the subject number and initials) and must not be discarded until authorization has been provided by the Study Monitor, noting the approximate volume not infused.

For any single infusion to a subject, the same lot must be used (ie, vials from different lots cannot be used together for the same infusion).

Further details will be included in a separate IMP Manual.

## 8.6 IMP Administration

IMP may only be administered under the direct supervision of the PI or a qualified sub-PI.

Pre-medication will be allowed for subjects who experience typical IgG systemic side effects during or after two infusions of the IMP.

IMP should be administered through a dedicated iv line. The iv line should be primed and flushed with IMP or saline solution, and no other medications should be injected into the iv line being used for IMP administration. Saline and IMP volumes must be clearly documented in the CRF.

### **Infusion Rates for the First, Second and Interim Infusions**

The first infusion, calculated using the dosing weight, is to be administered in a conservative, stepwise fashion as follows:

- For the first 30 minutes, IMP will be infused at 0.01mL/kg/min.
- If, in the PI's opinion, the rate is well tolerated, the rate of administration will be increased to 0.02 mL/kg/min for the next 30 minutes.
- If the increase is well tolerated, the rate will be increased to 0.04 mL/kg/min for the next 30 minutes.
- If 0.04 mL/kg/min is well tolerated, the remainder of the infusion may be administered at a maximum rate of between 0.06 mL/kg/min to 0.08 mL/kg/min at the PI's discretion.
- The maximum infusion rate should not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is sought.

The second infusion at Visit 2 and subsequent Interim Infusions, calculated using the dosing weight, are administered in a stepwise fashion as follows:

- For the first 15 minutes, IMP will be infused at 0.01 mL/kg/min.
- If, in the PI's opinion, the rate is well tolerated, the rate of administration will be increased to 0.02 mL/kg/min for the next 15 minutes.
- If the increase is well tolerated, the rate will be increased to 0.04 mL/kg/min for the next 15 minutes.
- If 0.04 mL/kg/min is well tolerated, the remainder of the infusion may be administered at a maximum rate of between 0.06 mL/kg/min to 0.08 mL/kg/min at the PI's discretion.
- The maximum infusion rate should not exceed 8.0 mL/min for adults and 5.6 mL/min for children, unless a medical waiver is sought.

If an infusion-related AE occurs, the infusion rate should be adjusted or halted in accordance with [Section 10.2](#).

## **8.7 IMP Shipment**

A central drug repository will be used for the study. The sponsor will ship IMP to the drug repository at 2-8°C, where it will be stored and shipped to sites as needed throughout the course of the study. During shipments, the temperature of the IMP storage/shipping

environment will be continuously monitored to ensure that temperature conditions are maintained at 2-8°C and documented.

Further details will be included in a separate IMP Manual.

The PI or designee will be responsible for verifying the accuracy of IMP shipments received, accurate drug accountability records, and following all instructions provided by the sponsor, CRO, and drug repository. At the end of the trial or upon request of the sponsor, all unused, partially used, or empty vials will either be returned the sponsor, CRO, or drug repository as instructed, or it may be destroyed onsite upon authorization by the Study Monitor and in accordance with any applicable institutional procedures.

## **8.8 Drug Accountability**

The PI or designee will complete and provide the pertinent inventory records upon receipt of all IMP shipments, as instructed. The PI or designee is responsible for maintaining accurate and complete inventory records of IMP. The PI or designee must ensure that IMP is stored in a secure location at the site in accordance with the required storage conditions, 2-8°C. Inventory records for the IMP include but are not limited to the following:

- Study sponsor;
- Site number;
- Protocol number;
- IMP name and description;
- Name of PI;
- IMP lot number and expiration date;
- Number of vials received, including sizes;
- Number of vials dispensed, including date and study subject receiving each dispensation.

The drug accountability logs and records will be reviewed by the Study Monitor and may be reviewed by regulatory agencies. All correspondence with the sponsor regarding stability and product release should be kept with the study specific documents at the site and/or the pharmacy as applicable.

## **9. CONCOMITANT MEDICATIONS AND DISALLOWED MEDICATIONS**

### **9.1 Concomitant Medications**

The use of pre-medication for pain relief and/or an antihistamine prior to infusion is only permitted in subjects who experience typical IgG systemic side effects during or after two infusions of the IMP. For pediatric subjects, pre-medication will be allowed for all infusions if this was the standard of care for prior IGIV infusions in order to minimize the discomfort to the subject and prevent aseptic meningitis.

The administration of concomitant medications is permitted during the trial period as is standard of care for subjects with PIDD. Any medications (ie, prescription and over the counter medications) taken by the subject during the course of the trial, as well as the reason for use will be recorded in the CRF, including the last commercial dose of IGIV the subject was receiving. Topical agents, inhaled corticosteroids, and dermatologics are permitted, and intermittent use of prednisone (or equivalent corticosteroid) of  $\leq 0.15$  mg/kg/day is allowed for up to 10 days.

### **9.2 Disallowed Medications**

The subject may not receive any of the following medications at any time during the study:

- Other IG therapy after the Screening Visit
- Any blood products other than IGIV
- Steroids (oral and parenteral, daily  $\geq 0.15$  mg of prednisone equivalent/kg/day, for more than 30 days).
- Any immunosuppressive or immunomodulatory drugs or chemotherapy

## **10. EVALUATION OF SAFETY PARAMETERS**

### **10.1 Definitions**

#### **10.1.1 Adverse Event**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding considered clinically significant), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

#### **10.1.2 Adverse Drug Reaction**

All noxious and unintended responses to an IMP related to any dose should be considered adverse drug reactions (ADRs). The phrase “responses to an IMP” means that a causal relationship between an IMP and AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

#### **10.1.3 Serious Adverse Event**

A serious adverse event (SAE) is defined as an AE that results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- 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.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### **10.1.4 Suspected Adverse Event/Adverse Reaction**

Suspected adverse events/adverse reactions are defined as:

- treatment-emergent adverse events that are considered at least possibly related to administration of the test product according to either the investigator or sponsor (or both)
- all adverse events that began during or within 72 hours of an infusion,
- and all adverse events for which the investigator’s causality assessment was either missing or indeterminate.

### 10.1.5 Adverse Event Severity

The PI or sub-investigator will assess the severity of AEs according to the criteria below:

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

### 10.1.6 Adverse Event Relationship to IMP

The following 4-point scale will be used by the PI or sub-investigator to rate the relationship of adverse events to the IMP:

- **Definitely related:** A clinical event (including laboratory test abnormality if considered clinically significant) occurring in a plausible time relationship to drug administration that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitively associated pharmacologically, using a satisfactory rechallenge procedure, if necessary.
- **Probably related:** A clinical event (including laboratory test abnormality if considered clinically significant) with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly related:** A clinical event (including laboratory test abnormality if considered clinically significant) with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related:** An event for which sufficient information exists to conclude that the etiology of the event is unrelated to the IMP.

The PI or sub-investigator will assign causality at their respective sites during the study. The sponsor's Medical Monitor responsible for the study will review the assigned causality for all AEs and SAEs prior to database lock. This assignment will be included in the study database and final study report.

### 10.1.7 Infusion-Related Adverse Event

AEs that occurred during or within 72 hours following an infusion of test product, regardless of other factors that may affect a possible causal association with product administration, will be defined as infusion-related AEs (ie, an AE temporally associated with an infusion of IMP).

IgG infusion-related AEs could include, but are not limited to: headache, fatigue, chills, dyspnea, pallor, backache, other body ache, leg cramps, light-headedness, fever, urticaria, flushing, elevation of blood pressure, nausea, vomiting, anaphylactic reactions, hypersensitivity reactions, oliguria, and anuria. On rare occasion, immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the subject has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis, isolated cases of reversible hemolytic anemia/hemolysis, and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin. Increase in serum creatinine level and/or acute renal failure have been observed. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis occur.

## 10.2 Management of Infusion-Related Adverse Events

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

- 1) Document the infusion rate when the AE occurred.
- 2) Reduce the current infusion rate to one-half the rate of the infusion at which the AE was observed; or
- 3) Reduce the rate of the infusion more than one-half the rate at which the AE was observed, as necessary to allow symptoms to subside; or
- 4) Reduce the rate of the infusion progressively by reducing to more than one-half the rate at which the AE was observed and then stop the infusion, if necessary to allow symptoms to subside; or
- 5) Stop the infusion to allow symptoms to subside.

The study staff will evaluate the subject's AE and then, at the discretion of the PI or sub-investigator:

- Will increase or resume the infusion at a rate tolerated by the subject once the symptoms have subsided; or
- Will stop the infusion and not resume it.

If a subject has an infusion-related AE at the same infusion rate twice, then subsequent infusion escalations, if any, should be halted prior to reaching the rate associated with the AE before the AE occurs depending on the severity of the AE. No subsequent infusions will be increased above the maximum rate tolerated by that subject.

If an infusion-related TEE occurs during the infusion, the study staff will stop the infusion to allow symptoms to subside.

The study staff will evaluate the subject's TEE symptoms and then, if TEE is excluded, at the discretion of the PI or sub-investigator, the study staff will resume the infusion at a rate tolerated by the subject once the symptoms have subsided.

### 10.3 Assessment and Documentation of Adverse Events

The condition of the subject will be monitored throughout the study. At each visit, AEs will be elicited using a standard, non-leading question such as “*How have you been since the last visit / during the previous study period?*” AEs will also be elicited using Subject Diaries, which the PI or designee will review in detail with the subject at each visit, ensuring accuracy and completeness of entries recorded by the subject. The study staff will compare their study progress notes of the telephone calls/text messages made by the site per protocol, in the first 72 hours compared to those recorded on the Subject Diary. Any missing information will be completed by the subject who will date and initial the addition in the Diary.

Any AE or ADR occurring during the study will be noted in detail on the appropriate pages of the CRF. If the subject reports several signs or symptoms, that represent a single syndrome or diagnosis, the latter should be recorded in the CRF. The investigator will grade the severity of all AEs or ADRs (mild, moderate or severe), the seriousness (non-serious or serious) and relatedness, as defined in [Section 10.1](#).

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

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

### 10.4 Reporting Serious Adverse Events

Adverse events and SAEs occurring after the signing of the ICF through the SFV (or FTTV for early withdrawals) will be assessed and recorded on the CRF.

All SAEs must be followed until the event resolves, the event or sequelae stabilizes, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (eg, the subject or Investigator is unable to provide additional information, the subject is lost to follow-up, etc.). If the database lock occurs prior to event resolution, the SAE will be reported as ongoing.

All SAEs regardless of their relationship to the IMP will be reported within 24 hours of the investigator becoming aware of the event to the CRO in accordance with the Safety Management Plan.

The CRO and Medical Monitor will review all safety information/documentation and liaise with the site as needed in support of SAE reconciliation. Follow-up information should be actively sought by the Investigator and reported to the CRO as it becomes available in accordance with the Safety Management Plan.

The sponsor is responsible for reporting the SAE to the regulatory authorities.

## 10.5 Pregnancy

Per inclusion criteria #7 every effort must be made to avoid a pregnancy during the trial, as stipulated by the site IRB/REB. The techniques to avoid pregnancy discussed at Screening should preferably not be changed during the course of the trial. A pregnancy test will be performed at all visits.

If a subject becomes pregnant during the trial, she must be withdrawn. Pregnancies occurring during the study after exposure to the IMP must be reported. The pregnancy notification form must be sent to the Safety Monitor. Follow-up information on the outcome of both mother and fetus must also be reported and the subject will have all tests performed per the SFV and terminated.

## 10.6 Reporting Adverse Events to the IRB/REB

All AEs and SAEs will be reported to the IRB/REB according to the guidelines of the IRB/REB. However, as a general guideline, ethics committees need to know about any AEs that are unknown or of a greater severity than what is reported in the IB. Updated Investigator Brochures and Annual Reports will be submitted to the IRB/REB as provided by the sponsor with current safety information. Any new safety data (or other finding) that might affect an IRB/REB's judgments regarding their risks versus benefits analysis should always be reported to the IRB/REB. The sponsor and the Study Monitor will assist the investigator in determining which events require reporting and in what timeframes.

## 10.7 Trial Discontinuation Criteria

The sponsor and/or PI may elect to terminate the trial early as defined by the clinical trial agreement. The trial may be terminated at any or all sites by the sponsor and individual subjects withdrawn by the PI for any of the following reasons:

- The safety data demonstrate or strongly suggest that the trial treatment (or participation in the trial) is unsafe.
- Two or more thrombotic, thromboembolic, or hemolysis events occur (see [Section 10.7.1](#)).
- The subject withdraws consent for any reason.
- The protocol or conduct of the trial is flawed such that the safety or rights of the trial subjects may be adversely affected.
- The IRB/REB has withdrawn approval for the trial and has denied reconsideration.
- The investigational treatment is found to be ineffective.
- Relocation of the PI or reallocation of PI's responsibilities, or disqualification of the PI by order of the regulatory authority.
- Non-adherence to the protocol or unavailability/lack of supervision by the PI and/or inadequate resource to conduct the study.

- Clinical hold imposed by the regulatory authorities.

Any decision to voluntarily suspend or terminate a clinical trial will be carefully reviewed and fully justified. The sponsor will notify the regulatory authorities and the IRBs/REBs of any suspension or termination, along with justification for restarting or terminating the study as applicable.

#### **10.7.1 Thrombosis and Hemolytic Events Stopping Criteria**

If two or more thrombotic or thromboembolic vascular events occur during the trial after the administration of IMP to the subjects, enrollment and continued treatment of enrolled subjects will be suspended until a medical review has been completed and the impact on future treatment determined.

In the event a subject has a confirmed diagnosis of hemolysis (see Section 1.4 and Sections 7.3.5, 7.4.3, and 7.5.3), the lot of IMP infused will be changed. If hemolysis persists with the new lot of IMP, then the subject will be discontinued from the study. If two or more subjects have a confirmed diagnosis of hemolysis with a specific lot of IMP, use of that lot of IMP will be discontinued from use in the study and replaced with a new lot of IMP.

## 11. STUDY ENDPOINTS

### 11.1 Efficacy Endpoints

The criteria for primary evaluation are the rates of clinically documented SBIs defined as:

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

When a subject is suspected of having an SBI, the subject should be evaluated for the infection according to the methods defined in the FDA Guidance Document, 2008 and outlined in [Section 20.1](#).

All incidences of SBIs will be recorded in the CRF, together with the associated confirmatory diagnostic tests.

The criteria for secondary evaluation are:

- Total serum IgG trough levels
- Specific antibody levels
- Number of infection episodes (serious and non-serious)
- Episodes of fever  $>38.5^{\circ}\text{C}$
- The number of days out of work/school/daycare
- The number of days subject is unable to perform normal daily activities due to infections
- Number of days of hospitalization due to infections
- Use of antibiotics for infection and short-term prophylaxis prior to or after surgical and dental procedures

In order to obtain these data for secondary evaluation, subjects will be asked to record data in their diaries and maintain them. It will be issued at the Baseline Visit. Diaries will collect all the information above as well as any concomitant medications taken during the periods between visits.

IgG trough levels will be assessed at all scheduled visits.

### 11.2 Safety Endpoints

The criteria for safety evaluation are:

- Rate, severity, and relatedness of any AEs per infusion and by subject;
- Frequency of temporally related AEs. The percentage of infusions with one or more adverse events will be calculated. This calculation will be made for all

adverse events, and also separately for any of the following types of infusion-related AEs:

- *Headache, fatigue, chills, dyspnea, pallor, backache, other body ache, leg cramps, light-headedness, fever, urticaria, flushing, hypotension, elevation of blood pressure, nausea, vomiting, anaphylactic reactions, hypersensitivity reactions, oliguria and anuria, and other (non-urticarial) rash.*

All AEs will be classified as being “infusion-related” (ie, temporally related to an infusion) or not according to the following criteria (both must be true) – (a) it must be one of the above listed event types, (b) it must have occurred within 72 hours from the start of infusion.

- The number and proportion of subjects who experience one or more suspected serious adverse reactions or adverse reactions, the number and proportion of subjects who experience one or more suspected adverse events or adverse events, as well as the sum total of such reactions and events
- Reactions at infusion site (assessment of local tolerability);
- Significant vital sign changes. Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature will be recorded at Screening; before, during, and after each infusion; and FTTV. For each infusion, vital signs will be measured at rest at the time points listed in [Section 7.3.9](#).
- Changes in physical examination results as compared to the baseline assessment;
- Changes in routine laboratory parameters (Serum chemistry, hematology, urinalysis, hemolysis) as compared to baseline assessments. The following laboratory assessments will be collected at the Baseline Visit, Interim Infusion Visits, FTTV, and SFV:
  - **Hematology** – CBC [RBC, reticulocytes, WBC and differential, hemoglobin, hematocrit, RBC indices (MCV, MCH, MCHC, RDW), and platelet count].
  - **Serum chemistry** – Total bilirubin, creatinine, urea, total protein, LDH, CK, BUN, ALT, AST, and ALP
  - **Urinalysis** – Protein, glucose, blood, bilirubin, urobilinogen, pH, and ketones by dipstick
  - **Hemolysis** – Tests performed at each visit will be urine hemosiderin, serum haptoglobin, plasma free hemoglobin, and Coombs test (direct anti-globulin).
- Concomitant medications;
- Changes in viral safety markers for NAT and serology testing of HAV, HBV, HCV, HIV-1, HIV-2, and PVB19, compared to baseline assessments as follows:
  - Screening – HBV, HCV, HIV-1, HIV-2;
  - Baseline – HAV, HBV, HCV, HIV-1, HIV-2, and PVB19;
  - SFV – HAV, HBV, HCV, HIV-1, HIV-2, and PVB19 (Tests will include only those for which the subject had negative results at baseline).

### 11.3 Pharmacokinetics Endpoints

The endpoints for PK evaluation of the following entities: Total IgG levels (for all subjects), IgG subclasses (IgG1, IgG2, IgG3, and IgG4 for subjects >12 years of age), specific antibodies against *Streptococcus pneumoniae* (for subjects >12 years of age) include:

- AUC (both AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>)
- C<sub>max</sub>
- V<sub>ss</sub>
- Mean residence time (MRT)
- Total body clearance (Cl)
- Terminal half-life (t<sub>1/2</sub>) (and half-life for equilibration phase as appropriate)

## 12. STATISTICS

There will be two analyses in order to provide two study reports as described below.

The first report will consider subjects in Group 1 (adults) only. The second report will be an addendum describing the results from Group 2 (pediatric), with the pediatric groups analyzed separately as well as pooled. This second report may also include an analysis of the primary endpoint covering both the adult and pediatric groups pooled, provided that the results indicate homogeneity of the two groups.

The primary assessment of the results of the trial will be based on the all subjects enrolled analysis set. However, an analysis based on the augmented per-protocol analysis set, including all subjects with data for at least 6 infusions, will also be presented as a check on robustness.

### 12.1 Sample Size

The power of this study, to establish that the true infection rate is lower than 1 per subject per year, depends primarily on the unknown true infection rate. However, an estimate of the power can be made for a range of assumptions about the true infection rate, provided it is assumed that the distribution of the number of infections per year is approximately Poisson.

For the purposes of the power calculation, it is assumed that the analysis of these data may be based on a square root transformation, and a successful outcome will be claimed if the upper 99% 1-sided confidence limit for the mean of these transformed data is less than 1. It is a standard result in statistical theory that the square root transformation of a Poisson distribution yields a variable which is approximately normally distributed and has a standard deviation which is independent of the mean and approximately equal to 0.5.

The following table shows the power of a study with [REDACTED] to achieve an upper 99% confidence limit below 1, for various true values of the population mean infection rate, when infections are Poisson distributed. These results were obtained using STATA V10SE.

#### 12.1.1 Power Calculations

| True population infection rate per subject per year |                         | Chance of upper 99% one-sided confidence limit being below 1 |                   |
|-----------------------------------------------------|-------------------------|--------------------------------------------------------------|-------------------|
| Absolute                                            | Square-root transformed | N=40<br>(Group 1)                                            | N=20<br>(Group 2) |
| 0.40                                                | 0.632                   | 99.0%                                                        | 83.3%             |
| 0.45                                                | 0.671                   | 96.7%                                                        | 73.1%             |
| 0.50                                                | 0.707                   | 91.6%                                                        | 61.6%             |
| 0.55                                                | 0.742                   | 82.6%                                                        | 49.3%             |
| 0.60                                                | 0.775                   | 69.8%                                                        | 37.7%             |

The study therefore has adequate power provided that the true rate of acute bacterial infections in the study population is below 0.55 per subject per year (for adults), or below 0.4 per subject per year (children), and if the assumption of a Poisson distribution is appropriate.

It should be noted, however, that these are not conservative estimates of power. In practice, the data may show some over-dispersion relative to the Poisson distribution assumed in these calculations, partly due to different subjects having different susceptibilities (or exposures), ie, the presence of some intra-subject correlation, but also due to some subjects not having a full year of observation. The method of analysis proposed for the primary endpoint takes due account of any such over-dispersion. However, it is not allowed for in the power calculation described above. For practical purposes, the study should probably be considered adequately powered for a population in which treatment with the IMP reduces the true incidence of serious acute bacterial infections to below 0.45 per subject per year (adults) or 0.3 per subject per year (children).

## **12.2 Analysis Populations**

The 'all subjects enrolled' analysis set will include all subjects who meet the Screening criteria and are formally enrolled into the study. The safety analysis set will consist of all subjects in this analysis set who received study product.

A per-protocol (PP) analysis set will consist of all subjects who complete the whole 12-month study period and who do not have any major protocol deviations or violations that may impact the data. An augmented per-protocol (aPP) set, consisting of all subjects who remain in the study (and provide data) for at least six months, will also be defined in order to provide a robustness analysis for the primary efficacy outcome.

## **12.3 Statistical Analysis Plan (SAP)**

### **12.3.1 Descriptive Analyses**

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

Demographic data, and treatment-related data (eg, dose), will be summarized as described above.

### **12.3.2 Primary Efficacy Endpoint**

The primary efficacy endpoint in this clinical trial is the rate of acute serious bacterial infections (pneumonia, bacteremia and septicemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess) per subject during the 12-months study observation period.

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

For the primary analysis of the primary efficacy endpoint, a 99% one-sided (upper) confidence limit for the incidence rate of serious acute bacterial infections will be derived, and the objective of demonstrating that the true infection rate is below 1 per subject per year will be considered established if this upper limit is below 1.

To calculate the confidence limit for the rate, the number of reported SBIs will be modelled using a negative binomial regression model with the number of months 'at risk' included in the model as an independent variable and the confidence limit in question will be based on the intercept of that model. The 'at-risk' variable will be defined as the time between enrollment and departure from the study, expressed in calendar months. The predicted number of SBIs (and its upper 99% one-sided confidence limit) for 12 months at risk will then be derived. Because this method of analysis is based on individual subject data, any intra-subject correlation between events is automatically taken care of appropriately. The null hypothesis for this analysis is that the true serious acute bacterial infection rate is at least 1 per subject per year, and the alternative hypothesis is that this rate is below 1 per subject per year. Rejection of the null hypothesis is therefore equivalent to demonstration of the study objective to show that the true rate is less than 1 per subject per year.

As a secondary, supportive analysis, the annual infection rate observed for each subject will be transformed using a square root transformation (since the data are expected to be approximately Poisson), and the mean and variance calculated, weighting by the number of weeks data available for each subject. The upper 99% one-sided confidence limit for the population mean (on the transformed scale) will then be calculated using standard normal distribution theory, and the resulting limit will be squared (to back-transform it to the original scale) for comparison with the target value of 1 per subject per year.

As a further secondary analysis of the primary efficacy endpoint, a frequency table of the number of SBIs experienced by individual subjects will be presented.

All analyses of the primary endpoint will be presented for the all subjects enrolled analysis set, the PP analysis set and the aPP analysis set. As described in Section 12, the analysis using the "all subjects enrolled" analysis set will be regarded as the primary analysis, with the other analysis sets regarded as providing supportive analyses.

Additionally, subgroup analyses for the primary endpoint ("all subjects enrolled" analysis set only) will be provided for sex, race and geographic region (United States, Canada). Subgroup analyses based on age will be presented for Group 2 (pediatric subjects) as defined in [Section 5.1](#). For Group 1 (adults), two subgroups based on age will be defined and analysed, by splitting the population at the median age for this group.

### 12.3.3 Secondary Efficacy Endpoints

Secondary endpoints are:

- Total serum IgG trough levels

- Specific antibody levels
- Number of infection episodes (serious and non-serious)
- Episodes of fever  $>38.5^{\circ}\text{C}$
- The number of days out of work/school/day care or unable to perform normal daily activities due to infections
- Number of days of hospitalization due to infections
- Use of antibiotics for infection prophylaxis and treatment
- For months 5 through 12, the difference between the total serum IgG trough level and the baseline trough level (following the previous IGIV or SCIG treatment)

Qualitative secondary efficacy endpoints will be summarized using frequency tables with percentages. Quantitative secondary efficacy endpoints will be summarized using the standard set of statistics as defined in [Section 12.3.1](#). Secondary endpoints may be summarized for both the all subjects enrolled and PP/aPP populations, if the difference between these populations is large enough to justify separate presentations. The study population will be divided into low and high dose groups, by the administered dose (in mg/kg) at the median dose for the all subjects enrolled population. This division will be used as a classifying factor in the presentations.

#### 12.3.4 Safety Endpoints

Evaluation of safety includes the analysis of adverse events and the analysis of laboratory investigations. The severity and relatedness to the study drug of AEs will be observed on repeated administrations of the study drug.

The FDA recommends that for a novel IGIV formulation, a trial should demonstrate an AE rate of not more than 40 AEs associated with the study drug per 100 administrations (26). An AE should be established as related to the infusion of study drug by implicating temporal association.

For the purpose of this study, AEs are considered temporally associated with the study drug infusion if they occur in the period from the start of the infusion until 72 h after the end of the infusion. The overall AE rate considered temporally associated with the study drug infusion and the rate of at least possibly related AEs considered temporally associated with the study drug infusion will be considered. In addition, subsets of the temporally associated AEs will be identified, based on different definitions (ie, within 1 hour, 24 hours and 48 hours of the end of the infusion). One-sided 95% upper confidence boundaries for these percentages will be calculated by using the normal approximation.

The proportion of infusions with a temporally associated AE will be analyzed with the objective of demonstrating that the percentage of infusions with one or more infusion-related AEs is less than [REDACTED]. This will be achieved by calculating the percentage of affected infusions for each subject, and then calculating a (weighted) mean of these percentages, with a 95% (one-sided) confidence interval. A suitable transformation will be used if appropriate. The upper limit of this confidence interval should be below [REDACTED] in order to demonstrate that the true proportion lies below the [REDACTED] limit. Weighting will

be based on the number of IMP infusions for which data are available. This method of calculation of the confidence interval takes proper account of the observed intra-subject correlation because it is based on a single summary data point for each subject. An unweighted simple quotient of the overall number of infusion-related AEs divided by the total number of infusions will also be presented, together with an upper 95% one-sided confidence limit based on the binomial distribution.

All adverse events and suspected adverse reactions/AEs will be listed and summarized by body system and treatment group. Serious adverse events will be similarly summarized. The number and proportion of subjects who have one or more AEs, suspected adverse reactions/AEs, and who have one or more temporally related AEs, will be presented.

The following observations will be summarized for the safety population, using the standard set of summary statistics. These summaries will be classified by dose group (high or low), as defined for the secondary efficacy analyses.

- The number of infusions administered;
- The total number of AEs experienced (irrespective of causality);
- The total number of AEs temporally associated with infusions;
- The number and proportion of infusions with which one or more infusion-related AEs are associated;
- The number of infusion-related AEs per infusion;

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

#### **12.4 Handling of Missing Data**

All subjects who remain in the study for at least one month will provide a data value for the primary endpoint. Completely missing data are therefore expected to be rare. However, in the event that one or more subjects have missing data for the primary endpoint a multiple imputation technique, e.g. hot-decking (5 imputations), will be used, for which further details will be given in a separate Statistical Analysis Plan. No data imputation will be used for other endpoints, or for secondary analyses of the primary endpoint.

#### **12.5 Pharmacokinetic Analyses**

For all subjects in the pharmacokinetic study, blood samples will be collected for the assessment of serum concentrations of total IgG. For subjects > 12 years of age, additional assessments will be done for sub-classes of IgG, and specific antibodies. The serum concentrations will be determined as defined in a laboratory assay plan. Pharmacokinetic parameters (half-life, elimination rate constants and  $C_{max}$ ) will be estimated by a compartmental model using the piecewise robust linear regression approach suggested

by Lee et al employing the program Demitasse2000<sup>2</sup> or a non-compartmental approach to determine area under the curve ( $AUC_{0-t}$  and  $AUC_{0-inf}$ ) using the linear trapezoidal rule and related parameters such as volume of distribution, clearance and mean residence time (1-3).

$AUC_{0-inf}$  will be calculated from the  $AUC_{0-t}$  plus the additional triangle, where the hypotenuse is determined by linear extrapolation to baseline from the last three observed time points. Appropriate summary statistics such as means, medians, standard deviations and inter-quartile ranges will be determined. For all safety subjects, prior to each infusion, trough (predose at each infusion) serum total IgG concentrations will also be determined. Pharmacokinetic data will be pre-dose baseline corrected.

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<sup>2</sup> [REDACTED]

### **13. ETHICS**

#### **13.1 Investigational Review Board/Research Ethics Board**

For this IND study, the IRB must operate in compliance with FDA regulations 21 CFR 50 and 21 CFR 56, and in conformance with applicable ICH E6 Guidelines on GCP, Institutional Review Board (IRB) (27).

The PI or sponsor will obtain IRB/REB approval for the clinical protocol and corresponding informed consent/assent form(s), amendments to the clinical protocol and corresponding informed consent forms, advertisements to be used for study recruitment, and any other material presented to a subject.

The PI or sponsor will be responsible for obtaining annual IRB/REB renewal, as required, and submitting SAE reports, updated Investigator Brochures, and Annual Reports to the IRB/REB for the duration of the study in accordance with the IRB/REB's policies and procedures. Copies of the PI's reports and/or copies of IRB/REB renewal approvals and relevant correspondence must be provided to the sponsor.

#### **13.2 Ethical Conduct of the Trial**

The clinical study will be conducted in accordance with the current IRB/REB-approved clinical protocol, ICH E6 Guidelines on GCP (27), and any relevant policies, requirements, and regulations of the IRB/REB and regulatory authorizations.

Protocol deviation and violations will be reported to the IRB/REB as required.

The IRB/REB and the regulatory authorities will be notified promptly of discontinuation of the entire clinical study. Respective protocol modifications will be submitted prospectively to the IRB/REB and to the FDA and Health Canada for discontinuation or modification of parts of the clinical study. Investigators will be notified immediately of discontinuation of parts of the clinical study or if the study ends or the discontinuation of a subject is necessary, and must promptly inform study subjects accordingly.

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

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

### 13.3 Informed Consent and Assent

The PI must explain to each subject and/or guardian the nature of the study and the option of enrolling in the PK Group of the study as well as the purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort participation may entail. The investigational product(s) should be identified as “experimental” and that its side effects are not completely known. This information must be provided in language that the subject understands. Each subject must be informed that participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician. The subject should be given sufficient time to read the informed consent form and the opportunity to ask questions and consider the statement before signing and dating it, and should be given a copy of the signed document. No subject can enter the study before informed consent or assent with parental (guardian’s) consent has been obtained.

During the study, subjects will be given any new information that may affect their decision to continue participation.

The sponsor or its designee will supply a model informed consent form that complies with regulatory requirements and is considered appropriate for the study. Any changes to the sample consent form suggested by the PI must be agreed to by the sponsor or its designee before submission to the IRB/REB, and a copy of the approved version must be provided to the sponsor or the designated Medical Monitor after IRB/REB approval.

Subjects under the age of 18-years-old (per local IRB/REB requirements) will go through an informed consent process with their parent or guardian. The discussion should be had at a level of understanding related to the age and comprehension of the subject. The subject will give assent to participate, with the parent or authorized representative giving consent, using the approved informed assent form and the informed consent form respectively, according to local state laws.

### 13.4 Confidentiality

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

The PI will ensure that the subjects’ anonymity will be maintained. The privacy rules of HIPAA (US) and PIPEDA (Canada) will be followed to obtain authorization for most uses and disclosures of PHI. On CRFs or other documents submitted to the sponsor or its designee, subjects will not be identified by their names, but by an identification code, consisting of a number assigned for the study. Documents not for submission to the sponsor or its designee (eg, the site confidential subject enrollment log, signed informed consent forms, etc.) will be maintained by the PI in strict confidence.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss

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or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

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

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

## **14. QUALITY CONTROL AND QUALITY ASSURANCE**

### **14.1 Quality Control by the Monitoring Team**

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

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

The present study sponsored by Therapure Biopharma Inc. will be conducted in accordance with ICH GCP (27). The clinical team at the CRO will systematically control the essential documents generated during this trial. The trial will be monitored by the clinical team and will be subject to internal audits by QA. All clinical study monitoring visits and audits by QA will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to sites after all visits and any findings should be addressed by the PI. The follow-up letters should be filed with the study correspondence and other essential documentation.

### **14.2 Quality Assurance by an Audit Team**

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

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

### **14.3 Quality Assurance by Data Management**

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

## **15. DATA HANDLING AND RECORD KEEPING**

### **15.1 Direct Access to Source Data/Documents**

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

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

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

### **15.2 Data Collection and Management**

Data generated as per protocol will be entered onto the CRF in accordance with the ICH Topic E6 (R1) Guidelines for GCP (CPMP/ICH/135/95) (27). When the CRFs have been completed, a Study Monitor, with the assistance of the study site coordinator, will verify the source documentation records and review the data.

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

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

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

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

### **15.3 Record Keeping**

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

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

The sponsor requires that each PI retain records (all regulatory documents such as the protocol, study approval letters, all CRFs, drug dispensing and accountability logs, all

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original subject consent forms and all correspondence pertaining to the conduct of the study) for a period of no less than 25 years from the date of final regulatory approval or as per local regulations, whichever is longer. If the study is discontinued, or if no application/license is to be filed or if the application/license is not approved for such indication, records should be retained for two (2) years (25 years in Canada) after the investigation is discontinued or as per local regulations, whichever is longer.

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

**16. CHANGES IN THE CONDUCT OF THE STUDY**

The PI may deviate from the protocol without IRB/REB or sponsor approval, if it is necessary in order to safeguard the safety or rights of the subjects. Any protocol amendment must be submitted for information or consideration to the applicable regulatory agencies.

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

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

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

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

## **17. PUBLICATION POLICY**

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

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

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## **18. LIABILITIES AND INSURANCE**

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

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

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## 20. APPENDICES

### 20.1 Diagnostic Criteria for Serious Infection Types (FDA guidance, June 2008)

The primary endpoint of the study is the annual rate of validated acute serious bacterial infections per FDA guidance document, 2008 (26). The primary endpoint will be assessed based on the diagnostic criteria provided in the FDA Guidance for Industry document, Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (2008).

**Note:** Items in bold are considered essential diagnostic features.

#### Infection: Bacteremia/sepsis<sup>a</sup>

*Symptoms:* chills, rigors

*Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction

*Laboratory tests:* **positive blood culture<sup>b</sup>**, leukocytosis (white blood cell (WBC) count > 12,000/mm<sup>3</sup>), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis

#### Infection: Bacterial Meningitis

*Symptoms:* headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures

*Physical findings:* Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38°C oral or >39°C rectal

*Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay**, positive blood culture<sup>c</sup>, CSF leukocytosis with neutrophil predominance, decrease in CSF glucose

#### Infection: Osteomyelitis/Septic Arthritis

*Symptoms:* pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults.)

*Physical findings:* evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal

*Laboratory tests:* positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture

*Imaging studies:* **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (CT) scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra**

**Infection: Bacterial Pneumonia<sup>d</sup>**

*Symptoms:* productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias

*Physical findings:* rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or > 39°C rectal, or <36°C, hypothermia (temperature < 36°C oral or < 37°C rectal)

*Laboratory tests:* leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO<sub>2</sub> < 60 mmHg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum<sup>e</sup>, positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage (BAL) or protected brush sampling,

*Imaging studies:* **Pulmonary infiltrate with consolidation on chest X-Ray (CXR)** (new in comparison with baseline CXR)

**Infection: Visceral Abscess**

*Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present)

*Physical findings:* intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice

*Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen**, positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess

*Imaging studies:* **typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan**

<sup>a</sup> Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/ > 39°C rectal or <36°C oral or < 37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or PaCO<sub>2</sub> <32 mm Hg; WBC count >12,000/mm<sup>3</sup>, <4,000/mm<sup>3</sup>, or >10% immature (band) forms (28). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (29).

<sup>b</sup> Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGIV replacement therapy. For subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. (Multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

<sup>c</sup> A blood culture positive for growth of *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (FDA Guidance, Acute Bacterial Meningitis (30)).

<sup>d</sup> For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IGIV, the finding of a new pulmonary infiltrate with consolidation on CXR is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature  $>38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ). In children  $>2$  years, fever is more commonly defined as a rectal temperature  $>38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ). In pediatric patients, elevations of WBC counts  $>15,000/\text{mm}^3$  are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count  $<5000/\text{mm}^3$  may be observed, usually associated with severe infection (FDA Guidance Community Acquired Pneumonia (31)).

<sup>e</sup> We recommend a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and  $<10$  squamous epithelial cells and  $>25$  polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture (FDA Guidance Community Acquired Pneumonia (31)).

## 20.2 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (32)

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

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

**Preamble**

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

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or

regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

#### **Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

#### **Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

#### **Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

#### **Research Ethics Committees**

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

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

**Privacy and Confidentiality**

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

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the

- physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

### **Use of Placebo**

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

### **Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an

intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

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

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