Clinical Study Protocol

NCT Number: NCT03277313

Title: Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects With Primary Immunodeficiency Diseases

Study Number: 161503

Document Version and Date: Protocol Amendment #2, 25-MAR-2019

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

PROTOCOL: 161503

TITLE:	Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases
SHORT TITLE:	Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric PIDD Subjects
STUDY PHASE:	Phase 3
DRUG:	HYQVIA
IND NUMBER:	013840
EUDRACT NUMBER:	Not Applicable
SPONSOR:	Baxalta US Inc.*, 300 Shire Way, Lexington, MA 02421, USA AND Baxalta Innovations GmbH*, Industriestrasse 67, A-1221 Vienna, Austria *Baxalta is now part of Shire
PRINCIPAL/ COORDINATING INVESTIGATOR:	Not Applicable
PROTOCOL HISTORY:	**Amendment 2: 2019 MAR 25** Replaces: Amendment 1: 2017 JUL 20 All Versions: Amendment 2: 2019 MAR 25 Amendment 1: 2017 JUL 20 Original: 2016 JUL 22

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	**Date:**
[redacted] MD [redacted] Global Clinical Development Operations	

Investigator's Acknowledgement

I have read this protocol for Study 161503.

Title: Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], [redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report form.

Refer to SAE Protocol Sections and the study team roster for further information.

For definitions and information on the assessment of these events, refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	1. HYQVIA Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase 2. GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution, for intravenous (IV) and subcutaneous (SC) administration (For better readability the names HYQVIA and GAMMAGARD LIQUID will be used throughout the document.)
Name(s) of Active Ingredient(s)	Immune Globulin Infusion 10% (Human) (IGI 10%)
CLINICAL CONDITION(S)/INDICATION(S) • Primary Immunodeficiency Diseases (PIDD)	
PROTOCOL ID	161503
PROTOCOL TITLE	Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases
Short Title	Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric PIDD Subjects
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017
Primary Completion	2023
Study Completion	2023
Duration	Approximately six years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of the study is to acquire additional data on efficacy, safety, tolerability, immunogenicity, pharmacokinetic (PK) and other parameters of HYQVIA in pediatric (age ≥ 2 to <16 years) subjects with PIDD.	
Primary Objective Efficacy of HYQVIA treatment in pediatric subjects with PIDD who have received prior IV or SC immunoglobulin therapy before enrollment into the study.	

Secondary Objective(s) Further efficacy and safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, and PK parameters.	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy, Safety, Immunogenicity, Pharmacokinetics
Control Type	No control
Study Indication Type	Treatment
Intervention Model	Single-group
Blinding/Masking	Open-label
Study Design	This is a Phase 3, open-label, prospective, non-controlled, multicenter study to evaluate the efficacy, safety, tolerability, immunogenicity, PK, and other parameters of SC treatment using HYQVIA in approximately 40 pediatric subjects with PIDD who have received IV or SC immunoglobulin therapy before enrollment into this study. Subjects will have regular testing for binding anti-recombinant human hyaluronidase PH20 (rHuPH20) antibodies approximately every three months throughout the study. **Epoch 1:** Pediatric subjects with PIDD who are on non-HYQVIA IV or SC treatment with immunoglobulin (IV-pre-treated, SC pre-treated) will be enrolled and treated with HYQVIA subcutaneously with a dose or interval ramp-up period of up to six weeks. Epoch 1 infusions will be administered at the study site. **Epoch 2:** ***1. Treatment*** The ramp-up (Epoch 1) is followed by Epoch 2 with HYQVIA treatment at the following intervals: • For IV-pre-treated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule. • For SC-pre-treated subjects: every three or four weeks, at the discretion of investigator and subject. After one year in Epoch 2, the anti-rHuPH20 binding antibody assay results during that year will be used to decide the next steps in the study: • Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study completion visit at the next possible occasion following the 12-months visit. • Subjects with anti-rHuPH20 antibody titer ≥ 160 during the study and/or at the last measurement will continue in Epoch 2 for an

	additional two years of HYQVIA treatment and observation, and complete the study completion visits at the next possible occasion following the 36-months visit. The first two or three infusions during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions (with the exception of the per-protocol planned study site visits approximately every three months) be performed at home (or equivalent site) by the subject / caregiver, if in the opinion of the investigator such treatment is safe and appropriate. In that case, the investigator/designee must have trained the subject or caregiver and must be satisfied that the subject or caregiver is capable of self-administration of SC infusions at home before the subject or caregiver will be permitted to conduct the SC infusion at home. The termination/completion visit will be conducted at the study site. ***2. Pharmacokinetic Assessment*** At the six-month infusion visit (site visit), a PK assessment should be performed. If the PK assessment cannot be done at the six-month visit for any reason, it may alternatively be performed at the infusion before or after the six-month visit. For subjects who do not undergo the PK assessments at Month 6, an additional infusion visit at the site may be required. Serum samples will be collected at the following time points: • Pre-infusion (i.e., trough level of previous infusion, within one hour of infusion start time) (Day 0 of PK); • Only for subjects 12 years of age and older: Day 2 (± one day, from infusion start time of Day 0); • Day 4 (± two days from infusion start time of Day 0); • Day 10 (± two days); • Day 21 (± three days, = trough level blood draw before next infusion) (end of PK assessment for three-week treatment interval) and, • Day 28 (± three days, = trough level blood draw before next infusion). (end of PK assessment for four-week treatment interval). **Epoch 3**: Epoch 3 is approximately one year safety follow-up, if needed: subjects whose anti-rHuPH20 antibody titer was ≥ 160 during Epoch 1 or Epoch 2 and who experience either a study drug-related Serious Adverse Event (SAE) or a related severe Adverse Event (AE) will be followed accordingly. Subjects in Epoch 3 continue regular anti-rHuPH20 antibody testing (approximately every three months), for approximately one year. Subjects in Epoch 3 will be treated with GAMMAGARD LIQUID intravenously (IV) or subcutaneously (SC), at the discretion of the

	investigator and the subject. Infusions in Study Epoch 3 will be administered at home or at the study site. In the event that a subject in Epoch 1 or during the first year in Epoch 2 experiences a related SAE or related severe AE **without** anti-rHuPH20 antibody titer ≥ 160, the subject can (at the discretion of the investigator and subject): 1) be terminated from the study; or, 2) change directly to Epoch 3; or, 3) continue in Epoch 1 or 2 with appropriate medical intervention such as decreasing the HYQVIA infusion rate and/or premedication. The study termination/completion visit will be conducted at the study site.
Planned Duration of Subject Participation	Study Epoch 1 (Ramp-up): Up to six weeks Study Epoch 2 (Final dosing): Up to three years Study Epoch 3 (Safety Follow-up): Up to one year The maximum subject participation period is approximately four years.

Primary Outcome Measure

The rate of acute serious bacterial infections defined as the mean number of acute serious bacterial infections per subject per year. Acute serious bacterial infections will include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, diagnosed according to the Diagnostic Criteria for Acute Serious Bacterial Infections (see Section 12.9).

Secondary Outcome Measure(s)

Efficacy

1. Number of all infections per patient-year
2. Trough levels of IgG and IgG subclasses for Study Epoch 2
3. Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and Hepatitis B Virus [HBV]) for Study Epoch 2

Pharmacokinetics

1. For the PK assessment in Epoch 2 the following PK parameters will be determined: area under the curve (AUC), clearance (CL), maximum concentration (C_{max}), minimum concentration (C_{min}), time to maximum concentration (T_{max}), and terminal half-life

Safety

1. Number and rate per infusion (excluding infections) of SAEs, related and not related
2. Number and rate per infusion (excluding infections) of all AEs, related and not related
3. Number and rate per infusion (excluding infections) of local AEs, related and not related
4. Number and rate per infusion (excluding infections) of systemic AEs, related and not related
5. Number and rate per infusion (excluding infections) of all temporally associated AEs (begin during or within 72 hours of completion of infusion)
6. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
7. Rates of all AEs (excluding infections) defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of infusions
8. Number/proportion of subjects who develop positive titer (≥ 160) of binding or neutralizing antibodies

to rHuPH20

Mode of Product Administration

1. Infusions (Study Epoch 2)
    a. Number of infusions per month
    b. Number of infusion sites (needle sticks) per infusion/month
    c. Duration of infusion
    d. Maximum infusion rate / site
    e. Infusion volume / site
    f. Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE
2. Number of weeks to reach final dose interval (three weeks or four weeks) (Epoch 1)
3. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
4. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months

Health-related Quality of Life (HRQoL)

Assessment of Health-related Quality of Life (HRQoL) Questionnaire:

1. Pediatric Quality of Life Inventory (Peds-QL)
2. EuroQol five dimensions questionnaire (EQ-5D)

Treatment Preference and Satisfaction

1. Assessment of Life Quality Index (LQI)
2. Assessment of Treatment Satisfaction and Medication Questionnaire (TSQM-9)
3. Assessment of Treatment Preference Questionnaire

Health Resource Utilization

1. Days not able to go to school or work, or to perform normal daily activities due to infection or other illnesses per patient-year
2. Days on antibiotics per patient-year
3. Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized per patient-year
4. Number of acute physician visits (office and emergency room) due to infection or other illnesses per patient-year

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**1. HYQVIA** Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase Subjects will be treated with HYQVIA in Study Epoch 1 and Study Epoch 2. **Dosage Form**: Injection **Mode of Administration:** SC **Dosage Frequency**: Study Epoch 1 (Ramp-up): One treatment interval of one week, then one treatment interval of two weeks, then one treatment interval of three weeks (for subjects who are planned to be treated every four weeks) Study Epoch 2 (Final dosing): HYQVIA dose once every three or four weeks: • For IV-pre-treated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule. • For SC-pre-treated subjects: every three or four weeks, at the discretion of investigator and subject.

Epoch 1			**Epoch 2**
First Infusion at Baseline: One week dose	Second infusion at Week 1: Two-week dose	If applicable: Third infusion at Week 3: Three-week dose	Final dose: at interval of 3 or 4 weeks

Dose: HYQVIA weekly dose will be equivalent to 100% (± 5%) of pre-study treatment.

Infusion Rate:

Study Epoch 1 (Ramp-up):

- For subjects with a body weight (BW) of < 40 kg: 5 mL/h/site (at start) to 80 mL/h/site (maximum, if tolerated)
- For subjects with a BW of ≥ 40 kg: 10 mL/h/site (at start) to 240 mL/h/site (maximum, if tolerated)

Study Epoch 2 (Final dosing):

- For subjects with a BW of < 40 kg: 10 mL/h/site (at start) to 160 ml/h/site (maximum, if tolerated)
- For subjects with a BW of ≥ 40 kg: 10 mL/h/site (at start) to 300 mL/h/site (maximum, if tolerated)

If infusions have been tolerated after the subject has received two HYQVIA infusions at the dose for the final infusion interval (three or four week dose), then investigators may choose an infusion rate schedule at their own discretion.

	Infusion Volume: Administer up to 600 mL per infusion site for subjects with a BW ≥ 40 kg, and up to 300 mL per site for subjects with a BW < 40 kg. A second site can be used at the discretion of the physician and subject based on tolerability and total volume. If a second site is used, administer half the total volume of rHuPH20 of HYQVIA in each site. **2. <u>GAMMAGARD LIQUID</u>** Subjects may be treated with GAMMAGARD LIQUID in **Study Epoch 3** (Safety Follow-up). Treatment will follow the suggestions of the GAMMAGARD LIQUID product information and the site´s standard of care. **Dosage form**: Injection **Mode of Administration:** IV or SC **Dosage frequency for IV administration**: Once every three or four weeks, at the investigator´s and subject´s discretion. **Dosage frequency for SC administration:** Once every week The infusion rate and infusion volume per site will follow the suggestions of the GAMMAGARD LIQUID product information. **Dose:** For IV administration, the weekly dose will be equivalent to 100% (± 5%) of the dose in the previous study epoch. For SC administration, the weekly dose will be equivalent to 137% (± 5%) of the weekly dose equivalent in the previous study epoch.
SUBJECT SELECTION	
Targeted Accrual	Sample size: Approximately 40 pediatric subjects already on IgG treatment pre-study will be enrolled in the United States (U.S.). At least six subjects in each of the three age groups of 2 to < 6 years, 6 to < 12 years, and 12 to < 16 years will be enrolled. Study sites: Approximately 20
Number of Groups/ Arms/ Cohorts	1

Inclusion Criteria

Subjects who meet ALL of the following criteria are eligible for this study:

1. Subject must have a documented diagnosis of a form of primary immunodeficiency (PI) involving a defect in antibody formation and requiring gamma globulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Scientific Committee 2015 (Picard et al., 2015) prior to enrollment. The diagnosis must be confirmed by the sponsor´s Medical Director prior to first treatment with investigational product (IP) in the study.
2. Subject is at least two and below 16 years of age at the time of screening.
3. Subject has been receiving a consistent dose of IgG, administered in compliance with the respective

product information for a period of at least three months prior to screening. The average minimum pre-study dose over that interval was equivalent to 300 mg/kg BW/four weeks and a maximum dose equivalent to 1000 mg/kg BW/four weeks.
4. Subject has a serum trough level of IgG > 5 g/L at screening.
5. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
6. Subject/legally authorized representative is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. Subject has a known history of or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
    a. Persistent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) for the testing laboratory
    b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] ≤ 500/mm3)
3. Subject has anemia that would preclude phlebotomy for laboratory studies, according to standard practice at the site.
4. Subject has an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or Immune Serum Globulin (ISG) infusions.
5. Subject has severe immunoglobulin A (IgA) deficiency (less than 7.0 mg/dL) with known anti-IgA antibodies and a history of hypersensitivity.
6. Subject has a known allergy to hyaluronidase.
7. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening.
8. Subject has a bleeding disorder or a platelet count less than 20,000/µL, or who, in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of SC therapy.
9. Subject has severe dermatitis that would preclude adequate sites for safe product administration in the opinion of the investigator.
10. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
11. Subject is a family member or employee of the investigator.
12. If female, subject is pregnant or lactating at the time of enrollment.

STATISTICAL ANALYSIS

Sample Size Calculation

The planned sample size for this study is 40 subjects. The primary objective of this study is to evaluate the efficacy of HYQVIA in terms of the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year. A sample size of 35 provides 83% power to reject the null hypothesis of an acute serious bacterial infection rate greater or equal 1.0, by means of a 1-sided test and a significance level of 0.01, versus the alternative hypothesis of less than 1.0, assuming a true rate of 0.5/year. Based on previous clinical experience, a dropout rate of 12% is assumed. Allowing for 12% dropouts, approximately 40 subjects will be enrolled in the study. Subjects who prematurely discontinued the study will not be replaced. The sample size (40), power (at least 80%) and hypothesis testing (significance level of 0.01, 1-sided) are consistent with the FDA's guidance ("Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency")

Planned Statistical Analysis

Analysis details will be provided in the study Statistical Analysis Plan (SAP).

For the primary and secondary outcome measures, statistical hypothesis testing will be performed only if specified. For all outcome measures, descriptive analysis will be performed:

The primary outcome measure is the rate of acute serious bacterial infection, defined as the mean number of acute serious bacterial infections per subject per year. The primary analysis of the primary outcome measure will be based on a Poisson model, accounting for the length of the observation periods per subject. The Full Analysis Set will be used. The null hypothesis of an acute serious bacterial infection rate greater or equal 1.0 will be tested against the alternative hypothesis of less than 1.0 at the 0.01 significance level (1-sided). The mean number of acute serious bacterial infections per subject per year and the corresponding 99% upper confidence limit will be provided. The null hypothesis will be rejected in favor of the alternative hypothesis if the resulting p-value is less than 0.01; equivalently, if the upper bound of the 99% confidence limit is less than 1. Efficacy of HYQVIA will be claimed if the null hypothesis is rejected.

Secondary outcome measures will be analyzed using descriptive statistics, unless otherwise specified in Section 13.

A single, formal interim analysis is planned and will be performed when all subjects have completed 12 months (one year observation period) in Epoch 2, for planned submission to regulatory authorities in support of HYQVIA label expansion to pediatric population. The final analysis of all study data will be performed after clinical database lock.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
AE	Adverse event
Ag	Antigen
AR	Adverse reaction
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
B19V	Parvovirus B19
BUN	Blood urea nitrogen
BW	Body weight
C1q	Complement 1q
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CRF	Case report form
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Clinical Trial Agreement
CVID	Common variable immunodeficiency
CXR	Chest x-ray
EC	Ethics committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediamine tetracetic acid
EQ-5D	EuroQol five dimensions questionnaire
EU	European Union

Abbreviation	Definition
FAS	Full analysis set
Fc	Crystallizable region of antibody
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h, hr	Hour(s)
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGI	Immune Globulin Infusion
IGIV	Immune globulin intravenous (human)
IGSC	Immune globulin subcutaneous (human)
IP	Investigational Product
ISG	Immune serum globulin
ISMC	Internal safety monitoring committee
IUIS	International Union of Immunological Societies
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MMN	Multi-focal motor neuropathy
MRI	Magnetic resonance imaging
NMC	Non-medical complaint
$PaCO_2$	Partial pressure (tension) of carbon dioxide
PCR	Polymerase chain reaction

Abbreviation	Definition
Peds-QL	Pediatric Quality of Life Inventory
PI	Primary humoral immunodeficiency
PIDD	Primary immunodeficiency disease
PKAS	Pharmacokinetic analysis set
PPS	Per-protocol analysis set
RBC	Red Blood Cell (count)
rHuPH20	Recombinant human hyaluronidase PH20 (active ingredient in the U.S. marketed product HYLENEX)
SAP	Statistical analysis plan
SD	Standard deviation
SAE	Serious adverse event
SAER	Serious adverse event report
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin G
SIC	Subject identification code
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
U.S.	United States
VASBI	Validated acute serious bacterial infection
WBC	White blood cell (count)
WNL	Within normal limits

6. BACKGROUND INFORMATION

Purified human immunoglobulin G (IgG) preparations were first used in 1952 for the treatment of patients with primary immunodeficiency diseases (PIDD), a class of disorders that result in increased susceptibility to infection, including both recurrent pyogenic infections secondary to defects of humoral immunity and opportunistic infections resulting from defects in cell-mediated immunity (Rosen et al., 1995). Individuals with these disorders require replacement therapy with immunoglobulin products to prevent or reduce the severity of infections. In addition to PIDD syndromes, immunoglobulin preparations have been indicated for secondary immunodeficiencies, such as B-cell chronic lymphocytic leukemia (CLL), acquired immunodeficiency syndrome (AIDS), and immunodeficiency after bone marrow transplantation (Abdel-Mageed et al., 1999, Griffiths and Chapel, 1997, Rechtman, 1997, Wolin and Gale, 1997). Immunoglobulins are also effective in the management of autoimmune disorders, such as idiopathic thrombocytopenic purpura (George and Raskob, 1998, Imbach et al., 1995, McMillan, 2000), Kawasaki syndrome (Barron et al., 1990, Rosenfeld et al., 1995), and multi-focal motor neuropathy (MMN) (Hahn et al., 2013).

6.1 Description of Investigational Product

6.1.1 HYQVIA

The Immune Globulin Infusion [IGI] 10% (Human) provides the therapeutic effect of HYQVIA. The recombinant human hyaluronidase PH20 (rHuPH20) component of HYQVIA increases dispersion and absorption of the IGI 10% (Human). The IGI 10% (Human) of HYQVIA supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The IGI 10% (Human) also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in the IGI 10% (Human) of HYQVIA have not been fully elucidated.

Hyaluronan is a polysaccharide found in the extracellular matrix of the connective tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a very fast turnover with a half-life of approximately 0.5 days. The rHuPH20 component of HYQVIA increases permeability of the subcutaneous (SC) tissue by temporarily depolymerizing hyaluronan. In the doses administered, the rHuPH20 component of HYQVIA acts locally. The effects of the hyaluronidase are reversible and permeability of the SC tissue is restored within 24 to 48 hours.

HYQVIA is an immune globulin with rHuPH20 indicated for the treatment of PIDD in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

For more detailed information refer to the Prescribing Information. The above information is derived from the Prescribing Information for the United States (U.S.). Local prescribing information should be consulted if the study is conducted in other areas.

6.1.2 GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration [IGI 10%]

GAMMAGARD LIQUID is a ready-for-use sterile, liquid preparation of highly purified and concentrated IgG antibodies. The distribution of the IgG subclasses is similar to that of normal plasma. The crystallizable region of antibody (Fc) and Fab functions are maintained in GAMMAGARD LIQUID. Pre-kallikrein activator activity is not detectable. GAMMAGARD LIQUID contains 100 milligram/mL protein. At least 98% of the protein is immune globulin, the average immunoglobulin A (IgA) concentration is 37 μg/mL, and immunoglobulin M is present in trace amounts. GAMMAGARD LIQUID contains a broad spectrum of IgG antibodies against bacterial and viral agents. Glycine (0.25M) serves as a stabilizing and buffering agent, and there are no added sugars, sodium or preservatives. The pH is 4.6 to 5.1. The osmolality is 240 to 300 mOsmol/kg, which is similar to physiological osmolality (285 to 295 mOsmol/kg).

GAMMAGARD LIQUID is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older. This includes, but is not limited to, CVID, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

GAMMAGARD LIQUID is also indicated as a maintenance therapy to improve muscle strength and disability in adult patients with MMN.

Pediatric Use

GAMMAGARD LIQUID administered intravenously was evaluated in 15 pediatric subjects with PI (seven were 2 to < 12 years old and eight were 12 to < 16 years old) in a multicenter clinical study. GAMMAGARD LIQUID administered subcutaneously was evaluated in 18 pediatric subjects with PI (14 were 2 to < 12 years old and four were 12 to < 16 years old) in another multicenter clinical study.

The safety and efficacy profiles were similar to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and efficacy of GAMMAGARD LIQUID in pediatric patients below the age of two years have not been established.

A detailed description of GAMMAGARD LIQUID is provided in the Prescribing Information for IGI (Human), 10% Solution, for intravenous (IV) and SC administration in the U.S.

Local prescribing information should be consulted if the study is conducted in other areas.

6.1.3 Immunoglobulin Treatment

Defective antibody production with or without decreased levels of serum immunoglobulins, is the most common abnormality in the majority of PIDD. It leads to increased susceptibility to viral and bacterial infections, especially of the sinopulmonary and gastrointestinal tracts. Decreased immunoglobulin levels are found not only in the group made up predominantly of antibody defects (e.g., X-linked or autosomal recessive agammaglobulinemia, selective IgG subclass deficiency, CVID, or X-linked hyperimmunoglobulin M syndrome), but also in the group of combined immunodeficiencies (e.g., severe combined immunodeficiency, Wiskott-Aldrich Syndrome) that have defects in both T- and B-cells (Picard et al., 2015).

Immunoglobulin treatment to prevent infections is also performed in Secondary Immunodeficiencies, such as CLL or multiple myeloma (MM). CLL is the most frequent form of leukemia in Western countries. It is characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen (Rozman and Montserrat, 1995). MM is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, and hypercalcemia but also recurrent infections (Kyle and Rajkumar, 2004).

Individuals with PIDD require lifelong replacement therapy with immunoglobulin products to prevent or reduce severity of infections. Initially, immunoglobulin replacement therapy was given by the intramuscular route; however, since the early 1980s in the U.S., the overwhelming majority of patients have been treated by the IV route. In the past several years SC administration has gained popularity. Currently, the majority of immunoglobulin products in the U.S. are licensed for IV administration; though, in December 2005, the first SC preparation was licensed by ZLB-Behring (Gardulf et al., 2006, Ochs et al., 2006).

SC administration of immunoglobulin preparations for PIDD patients has been accepted in many countries worldwide and is the predominant mode in the Scandinavian countries, particularly in Sweden. The first attempts, in the late 1970s, used intramuscular preparations administered at slow infusion rates, but in later years, rapid infusion rates have been used more successfully (Berger et al., 1980, Gardulf et al., 1993, Gustafson et al., 2008, Roord et al., 1982, Welch and Stiehm, 1983).

All of the gammaglobulin preparations licensed for SC use are formulated at 10% to 20%. Commonly they are formulated at 16% and are similar to Cohn Fraction II; therefore, they cannot be infused intravenously. The higher concentration, relative to IV preparations that are formulated at 5% to 12%, allows for a smaller infusion volume. This method of immunoglobulin replacement therapy is considered to be effective, safe and also highly appreciated by patients, as it has a low risk of systemic adverse reactions (ARs). When given weekly or every other week, subcutaneous immunoglobulin G (SCIG) leads to higher trough serum IgG concentrations than monthly IV infusions (at the same monthly dose) (Gardulf et al., 1995, Gardulf et al., 1991). After adequate training by healthcare professionals, SC infusions of immunoglobulin can easily be performed by many patients at home, thus, increasing patient comfort and independence and reducing cost (Gardulf and Hammarström, 1996).

Immunoglobulin administered intravenously is immediately available in the blood, and slowly equilibrates to the extra-vascular compartment over three to five days (Schiff and Rudd, 1986). Subcutaneously administered immunoglobulin is slowly absorbed from the SC space into the blood and at the same time equilibrates with the extra-vascular compartment. Consequently, there is no high spike in the IgG concentration as is seen following IV infusion. A study in 1972 by Smith, et al., used pharmacokinetic (PK) modeling and determined that the bioavailability of SC and intramuscular was 100% when compared to IV (Smith et al., 1972). More recent studies mandated by the Food and Drug Administration (FDA) showed that the bioavailability (measured as the area under the curve (AUC) of immune globulin concentration over time) of SC immunoglobulin is lower than that of IV immunoglobulin (Ochs et al., 2006, Supersaxo et al., 1990, ZLB Behring, 2006). Accordingly, it is recommended that the dose of SC immunoglobulin be adjusted to 137% of the IV dose to provide a comparable IgG exposure (Ochs et al., 2006, Wasserman et al., 2011). Despite the technical difficulties of comparing AUC for two different routes and frequencies of administration, studies of intradermally administered immunoglobulin in rats[i]

[i] Halozyme Report Number R1005-0551.

suggest that there is decreased bioavailability through the SC route.
This may be due to the mode of absorption of large protein molecules, which cannot readily diffuse through the capillary walls and must be absorbed via the lymphatics (Supersaxo et al., 1990).

The primary practical disadvantage of SC administration of immunoglobulin is that only small volumes can be infused at each site, necessitating the use of multiple sites on a weekly or biweekly (every-other-week) basis. Generally, using a 16% solution, approximately 20 mL can be infused per site; an adult patient receiving 400 mg/kg body weight (BW) would require at least three sites per week or 12 sites per month. Even though weekly or biweekly administration has the benefit of maintaining better IgG trough levels than monthly IV infusions, the requirement for multiple needle insertions may deter many patients.

6.1.4 Immunoglobulin and Hyaluronidase Treatment

The SC space is formed by a collagen and elastin network filled with a gel-like substance, hyaluronan, or hyaluronic acid. It is largely responsible for the resistance to fluid flow through this tissue. Hyaluronidase derived from sheep or cows has been used for the last 60 years to temporarily depolymerize the hyaluronan and facilitate SC infusions of fluids for re-hydration (Olsson and Löjgren, 1949). rHuPH20 is a 61 kd protein genetically engineered from the sequence of the naturally occurring human protein. It temporarily depolymerizes hyaluronan, decreasing the resistance to fluid flow and thus facilitating infusions into the SC space. The high molecular weight hyaluronan has a rapid turnover and is restored within 24 to 48 hours (h), leaving no observable histopathologic changes[ii]. Weekly infusions into cynomolgus monkeys in doses up to 2 mg/kg (> 1,000 fold higher than the HYQVIA dose in humans) did not lead to ARs during a follow-up of 39 weeks[iii]. Infusion of rHuPH20 improved the absorption and bioavailability of intradermally injected IgG in rabbits, pegylated interferon and infliximab in rats, and increased the rate of infusion and comfort of infusions of lactated Ringer's solution in the arms of adult human volunteers three- to four-fold (Thomas et al., 2007). Studies investigating the effects of rHuPH20 on SC infusions of large quantities of IgG in dogs and rabbits have been difficult to interpret due to the rapid absorption of IgG alone in this model. However, at higher doses of rHuPH20, bioavailability seemed to increase. The human SC compartment is much tighter than that of these animal species, and thus, human studies were required. rHuPH20 can facilitate absorption of small molecules such as insulin and

[ii] Halozyme Report R08014.
[iii] Halozyme Report R09050.

morphine in humans; in Phase 1 trials rHuPH20 improved the bioavailability of proteins such as infliximab[iv] and enabled drug dispersion and absorption at the administration site of rituximab and trastuzumab (Shpilberg and Jackisch, 2013). In a Phase 1/2 clinical study of HYQVIA (Study 160602) the average bioavailability of the IgG in seven subjects was 92%, suggesting a significant improvement compared to SC administration in the absence of rHuPH20.

The immunogenicity of rHuPH20 has been monitored in a number of clinical trials[v] (Bass et al., 2018, Riedl et al., 2016, Rosengren et al., 2015). No positive skin reactions were observed when rHuPH20 was administered to 100 healthy volunteers in a skin allergy clinical trial (Yocum et al., 2007). In Study 160603, a total of 13 subjects had at least one plasma sample that tested positive for rHuPH20-binding antibodies (positivity defined as a sample with a titer of ≥ 160) following HYQVIA treatment. The peak of the observed positive titers ranged from 160 up to 81,920 and declined during the long-term extension study despite continued exposure to rHuPH20. None of these samples contained neutralizing antibodies. No local or systemic reactions were attributed to the presence of anti-rHuPH20 antibodies. Based upon data available to date, including data from long-term exposure in Study 160902 (63 subjects received HYQVIA for a total number of 187.7 subject-years), the incidence of the formation of anti-rHuPH20 binding antibodies is 18%, no neutralizing antibodies have been observed, and no clinical signs or symptoms have been associated with positive anti-rHuPH20 binding antibody titers. In addition, there was no evidence of a lack of treatment effect when rHuPH20-binding antibodies were detected.

Antibodies reactive to rHuPH20 have also been identified in the normal population with a prevalence between 3 and 12% (Rosengren et al., 2015, Rosengren et al., 2018). No signal of associated infertility or autoimmune/inflammatory condition could be identified.

Non-clinical data for rHuPH20 or antibodies to rHuPH20 reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and developmental toxicity. Reversible effects on fertility have been reported in male and female guinea pigs immunized to produce antibodies to hyaluronidase. However, antibodies to hyaluronidase did not influence reproduction in mouse, rabbit, sheep, or cynomolgus monkey.

[iv] Halozyme Report R05109.
[v] Halozyme Report Number 10059.

6.2 Clinical Condition/Indication

Primary antibody deficiencies are characterized by decreased serum levels of immunoglobulin isotypes and increased susceptibility to infection by various microorganisms, including encapsulated bacteria. Treatment with immunoglobulins is indicated whenever there is a defect in antibody production, regardless of the actual level of IgG. Studies have clearly demonstrated that antibody replacement reduces the number and severity of patients' symptoms and infections as immunoglobulins are able to neutralize infectious agents, enhance phagocytosis, and modulate the immune response. Antibody replacement can be accomplished either intravenously or subcutaneously.

6.3 Findings from Nonclinical and Clinical Studies

6.3.1 Clinical Study 160602

Phase I/II Determination of the Dose of Recombinant Human Hyaluronidase Required Enabling up to 600 mg/kg Body Weight of Immune Globin Intravenous (Human) 10% to be Administered Subcutaneously in a Single Infusion Site in Subjects with Primary Immunodeficiency Disease

This study was a prospective, open-label, non-controlled, two-arm, multicenter study with the aim of determining the dose of rHuPH20 necessary to infuse a full four-week dose of Immune globulin intravenous (IGIV) 10% in a single SC site with good tolerability (Melamed et al., 2008). An infusion was defined as having been tolerated if it caused no more than mild local adverse drug reactions (e.g., minimal swelling, redness, or pain) that the investigator did not assess as unacceptable for other medical reasons. All infusions were administered at the study site.

A total of 11 adult subjects (four male, seven female) participated in the study. In Study Arm 1, four adult/adolescent subjects received only SC infusions of IGIV 10% to determine tolerability. After this initial assessment of tolerability, seven subjects (five female and two male) were enrolled in Study Arm 2 for determination of tolerability of SC infusions as described for Study Arm 1 and for comparison of PK parameters obtained after IV and SC administration of IGIV 10% in the initial phase of Study Arm 2.

The only severe and potentially life-threatening adverse event (AE) that occurred in the study was an anaphylactic reaction that was attributed to an antibiotic drug taken immediately prior to onset of the symptoms. This serious adverse event (SAE) occurred more than 24 hours after an infusion and was not considered related to use of the study drugs by the investigator. The subject continued in the study without further reactions.

All other AEs, which occurred in four subjects in Study Arm 1 and six of seven subjects in Study Arm 2, were non-serious local AEs, of which the majority were mild and none were severe. Local AEs included infusion site erythema, infusion site pain, infusion site edema, infusion site warmth, injection site pruritus, infusion site swelling, and symptoms categorized as infusion site reactions.

The primary safety endpoint was the proportion of SC infusions, which were not interrupted or stopped due to AEs. Two SC infusions, one in each study arm, had to be interrupted due to mild infusion site pain and mild chest pain, respectively. In one subject in Study Arm 2, the infusion rate had to be decreased due to a mild infusion site reaction.

In conclusion, this study of SC use of IGIV 10% facilitated by prior injection of rHuPH20 yielded initial favorable results in terms of tolerability of a full four-week dose of IGIV 10% administered by SC infusion in a single infusion site and in terms of bioavailability of IgG after SC administration.

6.3.2 Clinical Study 160603

Efficacy, Tolerability and Pharmacokinetic Comparison of Immune Globulin Intravenous (Human) 10% (GAMMAGARD LIQUID, KIOVIG) Administered Intravenously or Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases

Study 160603 was a prospective, open-label, non-controlled, multicenter, Phase III study (Wasserman et al., 2012). The purpose of the study was to develop a SC treatment option for subjects with PIDD that allows SC administration of GAMMAGARD LIQUID/KIOVIG at the same frequency as IV administration. The study consisted of two study parts:

- Study Epoch 1: IV treatment with GAMMAGARD LIQUID/KIOVIG
- Study Epoch 2: SC treatment with GAMMAGARD LIQUID/KIOVIG after administration of 75 U rHuPH20 /g IgG at three- or four-week treatment intervals

Study Arm 1 was comprised of subjects who previously participated in Study 160601 and wished to also participate in this follow-up study; these subjects only completed Study Epoch 2. Study Arm 2 comprised all other subjects; these subjects completed Study Epoch 1 and Study Epoch 2.

Eighty-nine subjects were enrolled in the study, of which 87 were treated via both IV and SC routes. Eighty-four subjects completed Study Epoch 1, and 68 subjects completed Study Epoch 2. Sixteen subjects withdrew or were discontinued from the study, including three subjects who withdrew during the ramp-up period at the beginning of HYQVIA treatment. Four adults withdrew due to local pain and swelling; in two of these subjects, the swelling extended from the abdominal site to the genitalia, causing transient discomfort. In one of the subjects, the swelling was accompanied by erythema. One other subject withdrew due to a perceived increase in infections.

Of the 1,359 SC infusions with rHuPH20 during the ramp-up[vi] period and Epoch 2, 90.1% were administered in the abdomen and 8.6% in the thighs. The median duration of individual infusions was similar or lower when GAMMAGARD LIQUID/KIOVIG was administered SC with rHuPH20 than for IV administration. The percentage of subjects who had no infusions that required a reduction in flow rate, interruption, or had to be stopped due to tolerability concerns or AEs was similar between SC infusions with rHuPH20 (84.0%) and IV administration (88.5%).

The rate of infusions temporally associated with systemic AEs was lower for SC administration with rHuPH20 compared to IV administration, whereas the rate of infusions temporally associated with local AEs was higher for SC administration with rHuPH20. The trend toward less frequent systemic AEs and more frequent local AEs during SC administration with rHuPH20 compared to IV treatment was also evident in the nature of AEs reported in the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms. Of the AEs in Epoch 1 that were considered by the investigator to be possibly or probably related to GAMMAGARD LIQUID/KIOVIG, the most common were headache, chills, nausea, fatigue, pyrexia, and vomiting. The most common AEs possibly or probably related to both GAMMAGARD LIQUID/KIOVIG and rHuPH20 in Epoch 2 (excluding the ramp-up) were infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritus, infusion site edema, and infusion site swelling. No severe headache was related to SC infusions with rHuPH20. AEs possibly or probably related to rHuPH20 but not GAMMAGARD LIQUID/KIOVIG in Epoch 2 (excluding the ramp-up) included infusion site pain and infusion site pruritus. The majority of AEs were mild; very few severe AEs occurred. All SAEs were assessed as unrelated to the study drugs.

[vi] The treatment intervals and doses used for the initial infusions were gradually increased during the first weeks of treatment (referred to as the ramp-up) in order to allow the subjects to adjust to increasing volumes administered SC.

A comparison of data from this study and Study 160601 demonstrated no appreciable differences in the median rates of AEs temporally associated with or related to either or both study drugs.

GAMMAGARD LIQUID/KIOVIG administered SC with rHuPH20 at 108% of the IV dose was effective in preventing bacterial infections in pediatric and adult subjects with PIDD. Analysis of the secondary endpoints demonstrated that GAMMAGARD LIQUID/KIOVIG given SC with rHuPH20 had higher bioavailability as determined by AUC per dose/kg than when infused SC without rHuPH20. Compared to IV infusion, SC administration with rHuPH20 was administered at the same dosing interval and resulted in similar IgG trough levels while eliciting fewer systemic ARs. Furthermore, SC infusion with rHuPH20 was the subjects' preferred mode of treatment with GAMMAGARD LIQUID/KIOVIG.

6.3.2.1 Pharmacokinetic Properties

With administration of HYQVIA, peak serum IgG levels are achieved in the recipient's circulation in three to five days after dosing.

Data from the clinical trial of HYQVIA show that serum IgG trough levels from prior treatments can be maintained by dosing regimens of 320 to 1,000 mg/kg BW/four weeks given at intervals of three or four weeks.

The PK of HYQVIA was evaluated in this Phase 3 efficacy and safety study in 60 patients with PIDD aged 12 years and older. The PK results are presented in Table 1 below as compared to data for IV administration of IGI 10% obtained in the same study.

Table 1
Pharmacokinetic Parameters of HYQVIA Compared to Intravenous Administration of IGI 10%

Parameter	HYQVIA Median (95% CI[e]) N=60	IGIV, 10% Median (95% CI[e]) N=68
C_{max}[a] [g/l]	15.5 (14.5; 17.1)	21.9 (20.7; 23.9)
C_{min}[b] [g/l]	10.4 (9.4 to 11.2)	10.1 (9.5 to 10.9)
AUC[c] per week [g*days/l]	90.52 (83.8 to 98.4)	93.9 (89.1 to 102.1)
T_{max}[d] [days]	5.0 (3.3 to 5.1)	0.1 (0.1 to 0.1)
Apparent clearance or clearance [ml/kg/day]	1.6 (1.4 to 1.79)	1.4 (1.2 to 1.4)
Terminal half-life [days]	45.3 (41.0 to 60.2)	35.7 (32.4 to 40.4)

[a] Concentration maximum.
[b] Concentration minimum.
[c] Area under the curve.
[d] Time to maximum concentration.
[e] Confidence interval.

6.3.3 Clinical Study 160902

Long-Term Tolerability and Safety of Immune Globulin Subcutaneous (IGSC) Solution Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases

The purpose of the study was to assess the long-term safety, tolerability, and practicability of the SC treatment with IGI, 10% facilitated with rHuPH20 in subjects with PIDD who completed Baxter Clinical Study Protocol 160603. The primary objective of this study was to evaluate the long-term tolerability and safety of IGI, 10% given SC after an SC administration of rHuPH20 in subjects with PIDD. The secondary objectives included, monitoring the long-term efficacy of IG, 10% given SC after an administration of rHuPH20 in subjects with PIDD, evaluating the effect of varying the dose frequency of IG, 10% rHuPH20 on IgG trough levels, and assessing the practicability of treating PIDD with IGI, 10% given SC after an administration of rHuPH20 when treatment occurs in a home treatment environment.

In Study 160902, subjects began on the same doses of IGI, 10% and rHuPH20 that were used for the last infusions in Study Epoch 2 of Study 160603. In order to pursue the secondary objective "effect of varying the dose frequency of IGI, 10%/rHuPH20 on IgG trough levels", subjects were requested to change their drug administration interval to a two-week drug interval (receiving a two-week dose) from a three- or four-week drug administration interval, provided both the subject and the investigator agreed that the change was appropriate. This new treatment interval started after three infusions on the three- or four-week interval and was maintained for a minimum of four months. It was intended to allow for evaluation of whether a more frequent administration of IGI, 10% leads to improved IgG trough levels. After the four-month trial period, subjects could revert to their previous dose interval or continue on the two-week interval, depending on the subject's preference.

On 2012 August 01, the FDA requested administration of rHuPH20 drug product in all ongoing HYQVIA clinical studies in the U.S. to be suspended and patients were switched to treatment with KIOVIG/GAMMAGARD LIQUID only (Protocol Amendment 5). Subjects were treated with conventional IGIV or Immune globulin subcutaneous (human) (IGSC) for 24 weeks, or, for those who had anti-rHuPH20 antibody titers ≥ 160 at the time rHuPH20 was discontinued, for 48 weeks.

6.3.3.1 Disposition of Subjects

Sixty-six subjects were screened for eligibility to participate in this study. Out of the 66 patients who rolled over from Study 160603 into 160902, 63 subjects were treated with IGSC, 10% with rHuPH20; three subjects received IGIV, 10%. Of the 63 subjects under IGSC, 10% with rHuPH20 treatment, 15 withdrew or were discontinued from the study; 48 switched to the Safety Follow-up when Protocol Amendment 5 went into effect. Of the 15 subjects discontinued from IGSC, 10% with rHuPH20, four withdrew, one subject died, one subject had bone marrow transplant, six subjects had their clinical site closed out by sponsor, and three had their site elected to exit study. Of the 48 subjects switched to the Safety Follow-up period, one subject withdrew after experiencing an AE. In total, 50 subjects completed the study: 47 subjects from the Safety Follow-up and three subjects who received IGI, 10% IV or SC without rHuPH20 throughout the study. The majority of enrolled subjects were in the age range category of 16 to < 65 years (47 out of 66), followed by 65 years and older (eight subjects) with seven subjects in the range of 12 to < 16 years and four subjects in the range of 2 to < 12 years. The median age was 43.0 years. Of the 66 subjects who met all inclusion/exclusion criteria, 50 subjects (75.8%) completed the study.

6.3.3.2 Extent of Exposure

IGSC, 10% with rHuPH20 was administered to 63 subjects prior to the Safety Follow-up period for a median treatment duration of 669 days (range: 60 to 729 days) and a mean (± standard deviation [SD]) of 565.9 ± 211.8 days. The mean (± SD) dose received per week, per body mass, was 0.156 ± 0.051 g/kg/week. Across all age groups, the median initial rate of IGSC, 10% infusion with rHuPH20 was 10 mL/hr (range: 5 to 300) and the median maximum rate of infusion achieved was 300 mL/hr (range: 10 to 350). Across all age groups and infusion intervals, a median number of 1.09 infusions/month (range: 0.3 to 2.1) was administered. IGSC, 10% with rHuPH20 treatment required a median number of 1.58 infusion sites/month (range 0.3 to 4.2) across all age groups and infusion intervals. For the majority of subjects in this study (41/66; 62.1%), the four-week infusion interval was the most frequently followed infusion interval. The two-week infusion interval was the most frequent interval for 15/66 subjects (22.7%), and 7/66 subjects (10.6%) followed a three-week infusion interval.

6.3.3.3 Efficacy

Analysis of the efficacy results in this study indicates that rHuPH20-facilitated SC treatment with IGI, 10% is efficacious in the treatment of adult and pediatric subjects with PIDD, in terms of IgG trough levels, infection rates, and patient-related outcomes.

Two validated acute serious bacterial infections (VASBIs) occurred in 66 subjects under IGSC, 10% treatment with rHuPH20. The annual rate of VASBIs was statistically significantly lower than the threshold specified as providing substantial evidence of efficacy.

The point estimate for the annualized rate of all infections was 2.86 (95% Confidence Interval [CI]: 2.36; 3.43) during IGSC, 10% with rHuPH20 treatment.

IgG trough levels maintained under IGSC, 10% with rHuPH20 treatment did not substantially vary with infusion interval changes and were lower with the longest (four-week) infusion interval (median steady-state trough level: 10.90 g/L [two-week interval], 12.30 g/L [three-week interval], and 9.76 g/L [four-week interval]).

Percent change of steady-state trough levels was 105.90% (mean and median) for subjects who switched from a three-week to a two-week infusion interval and a mean of 113.23% (median 112.44%) for subjects who switched from a four-week to a two-week infusion interval.

The point estimate for the annualized rate of days off school/work was less than eight days per year. The rate of days on antibiotics was less than 65 days per year. The rate of hospitalizations was less than one per year, and the rate of days hospitalized was less than one day per year. The rate of acute physician visits due to infection or other illness was less than five visits per year.

6.3.3.4 Safety

rHuPH20-facilitated SC treatment with IGI, 10% was safe and well-tolerated by adult and pediatric subjects with PIDD.

No SAEs occurred that were considered by the investigator to be related to either of the study drugs. In total, 11 subjects experienced SAEs during the study. One subject experienced an SAE after study completion.

Throughout the study, the proportion of infusions requiring adjustment for tolerability concerns or for AEs was low (0.1% of infusions stopped, 0.6% of infusions interrupted, 1% infusion rate reduced).

The most common related AEs under IGSC, 10% treatment facilitated by rHuPH20 were infusion site pain, infusion site pruritus, nausea, myalgia, infusion site erythema, headache, fatigue, asthenia, chills, infusion site discomfort, and pain.

The rate of all AEs related to IGI, 10%, by infusion, was 0.13 during rHuPH20-facilitated IGSC, 10% treatment administration, and 0.22 during the Safety Follow-up period. During rHuPH20-facilitated IGSC, 10% treatment, the rate of all AEs related to rHuPH20, by infusion, was 0.01, and the rate of all AEs related to both IGI, 10% and rHuPH20 by infusion, was 0.06.

The rate of all causally related AEs by infusion was 0.20 during rHuPH20-facilitated IGSC, 10% treatment administration. The rate of all causally-related local AEs, by infusion, was 0.10 during rHuPH20-facilitated IGSC, 10% treatment administration. During rHuPH20-facilitated IGSC, 10% treatment, the rate of related systemic AEs by infusion, including or excluding infections was 0.1.

The rate of all temporally-associated AEs by infusion was 0.28 during rHuPH20-facilitated IGSC, 10% treatment. The rate of all temporally-associated local AEs by infusion was 0.10 during rHuPH20-facilitated IGSC, 10% treatment. During rHuPH20-facilitated IGSC, 10% treatment, the rate of temporally-associated systemic AEs by infusion including infections was 0.18 and excluding infections was 0.16.

Throughout the study, 7.4% of infusions were associated with one or more local AEs.

No subjects developed neutralizing antibodies in the entire duration of the follow-up including data obtained in Study 160603 starting with first exposure to IGSC, 10% facilitated by rHuPH20 and in Study 160902.

A total of 13/66 subjects had anti-rHuPH20 antibody titers ≥ 160 in Study 160902. Eleven subjects had developed anti-rHuPH20 antibody titers ≥ 160 in Study 160603. Two subjects each newly developed one anti-rHuPH20 antibody titer of ≥160 in Study 160902. In the majority of subjects with anti-rHuPH20 antibody titers ≥ 160, the titers declined over time during continued IGSC, 10% with rHuPH20 treatment.

Assessment of hematology parameters, clinical chemistry parameters, urinalysis and specific antibody tests, and viral pathogen serology did not raise any safety concerns with respect to the SC administration of IGI, 10% with rHuPH20.

6.3.4 Clinical Study 161101

Tolerability, Safety and Administration Mode Evaluation of rHuPH20 Facilitated Subcutaneous Treatment with Immune Globulin Infusion (Human), 10% in Subjects with Primary Immunodeficiency Diseases

This U.S. study was a Phase 2/3, prospective, non-controlled, multicenter study to evaluate tolerability, safety, and other parameters of SC treatment using IGI (Human), 10% (% is the same product as IGIV 10% licensed in the European Union [EU] as KIOVIG) with rHuPH20 in a total of approximately 60 PIDD subjects already pre-treated with immunoglobulin products (Gamunex administered IV, Hizentra or Privigen).

PIDD patients already on IV or SC treatment were enrolled and treated with IGI, 10% and rHuPH20 subcutaneously with a dose/interval ramp-up of three weeks. The ramp-up period was Epoch 1.

The ramp-up was followed by Epoch 2, a six month period of IGSC, 10% with rHuPH20 treatment:

- For IV-pre-treated subjects: every three weeks or four weeks, depending on the subject's previous IV dosing schedule
- For SC-pre-treated subjects: every three weeks or four weeks, at the discretion of investigator and subject

The rHuPH20 administration was discontinued as of 2012 August 01 at the request of the FDA. Those subjects who did not withdraw from the study completed the planned infusions using conventional IGIV or IGSC. The last subject completed the study on 2013 January 04.

A total of 37 subjects started the treatment. All but one of the subjects reached Epoch 2. During Epoch 2, nine subjects withdrew. At the time when rHuPH20 administration was stopped, one subject had completed Epoch 2. The remaining 26 were switched to Epoch 3. During Epoch 3, two subjects withdrew, and 24 completed Epoch 3. Thus, 25 subjects completed the study, including the one subject who completed Epoch 2 without ever reaching Epoch 3.

Analysis of the efficacy results in this study indicate that rHuPH20-facilitated SC treatment with IGI, 10% was efficacious in the treatment of adults and pediatric subjects with PIDD, in terms of IgG trough levels, infection-rates, and subject-related outcomes.

Trough levels of total IgG at the end of Epoch 2 (geometric mean: 9.21 g/L [95% CI: 8.28 to 10.25]) were comparable to the levels measured at screening (geometric mean: 10.53 g/L [95% CI: 9.46 to 11.73]).

No serious bacterial infections were reported in any subject throughout the study. The point estimate for the rate of all infections per year was 2.45 for Epoch 1 and Epoch 2 combined.

The point estimate for the rate per month of days off either from work, school, or daily activity was less than one day/month. The rate of days on antibiotics was less than three days/month. No subjects were hospitalized during the study period, and the rate of acute physician visit due to infection or other illness was less than one visit/month.

Analysis of the mode of infusion was inconclusive due to the premature stop of subject enrollment and early termination of Epoch 2; however, the following results were observed.

The median numbers of infusions per month were 2.90 in Epoch 1 and 1.09 in Epoch 2. The median number of infusion sites (needle sticks) per infusion/month were 2.90 in Epoch 1 and 1.12 in Epoch 2. The median duration of infusion was less than two hours. The median maximum infusion rate was 240mL/h in Epoch 1 and 300mL/h in Epoch 2.

Treatment with IGI, 10% when administrated either SC with rHuPH20 (Epochs 1 and 2) or SC without rHuPH20 or IV (Epoch 3) was safe and well tolerated. No SAEs occurred that were considered by the investigator to be related to either of the study drugs.

During Epoch 1 and Epoch 2 combined, 59 related systemic AEs occurred. The rate of related systemic AEs/infusion, excluding infections (primary outcome) was 0.326 (95% CI: 0.186 to 0.522) and the rate per number of subjects was 37.8% (14/37), for Epochs 1 and 2 combined. The rate per infusion of local AEs (including infections) related to IGI, 10% was 0.066 in Epoch 1, 0.028 in Epoch 2, and 0.006 in Epoch 3. The rate of local AEs related to rHuPH20 per infusion was 0.039 in Epoch 1 and 0.038 in Epoch 2. The rate of local AEs related to both rHuPH20 and IGI, 10% per infusion was 0.776 in Epoch 1 and 0.745 in Epoch 2.

According to MedDRA preferred term classification, the most common AEs related to IGI, 10% with rHuPH20 in both Epoch 1 and Epoch 2 were "infusion site pain", "infusion site erythema", and "infusion site swelling".

No patient developed neutralizing anti-rHuPH20 antibodies in the course of the study. Assessment of hematology parameters, clinical chemistry parameters, and urinalysis did not raise any safety concerns with respect to the SC administration of IGI, 10% with rHuPH20.

6.3.5 HYQVIA Pregnancy Registry 161301

Pregnancy Registry to collect Long-Term Safety Data from Women treated with HYQVIA

This study is an ongoing non-interventional, prospective, uncontrolled, two-arm, open-label, multicenter post-authorization pregnancy registry. Subjects who prior to the study received HYQVIA at enrollment receive a licensed human normal immunoglobulin other than HYQVIA or an alternative treatment during the study are assigned to Study Arm 1 (Alternative Product Arm). Subjects in countries where HYQVIA treatment during pregnancy is not indicated are enrolled in this arm. Subjects who continue treatment with HYQVIA during pregnancy are followed in Study Arm 2 (HYQVIA Arm).

The study is conducted in the European Economic Area and North America. This pregnancy registry with regular assessment of antibodies against rHuPH20 was a commitment to the Committee for Medicinal Products for Human Use (CHMP) and the FDA in the course of the HYQVIA Marketing Authorization Procedure. Further data shall be collected to evaluate safety of women who become pregnant during or after treatment with HYQVIA as well as the physical and neurological development of the infant during the first two years of life.

The primary objective is to collect and assess clinical safety data regarding the possible effects of HYQVIA on the course and outcome of the pregnancy, and on the growth and development of the fetus/infant. The secondary objectives are to collect any laboratory safety data and additional safety assessments obtained during the clinical management of the pregnancy or in the evaluation of the fetus in utero and the infant post-partum.

In this registry, pregnant women who were ever treated with HYQVIA were enrolled. In the EU, the therapeutic indications for HYQVIA are PIDD, CLL, and myeloma. In the U.S., HYQVIA is licensed for the treatment of PIDD. Although the target population consisted mainly of women treated for the approved indications in the respective country, any woman who became pregnant after being exposed to HYQVIA could participate in the registry.

Visits to the investigator (for example immunologist) and all other medical care were performed as was standard for the site and for the subject's healthcare. However, the pregnant subject was invited to return approximately every three months to the site for blood samples to be taken to assess antibodies against rHuPH20, as requested by the CHMP and the FDA.

As soon as the patient became aware of the pregnancy, she should have informed the treating physician. According to her treatment, the subject entered the study in one of the following two Study Arms.

Study Arm 1 (Alternative Product Arm): subjects who stopped treatment with HYQVIA were followed in Study Arm 1. The treating physician of the pregnant woman prescribed a licensed human normal immunoglobulin other than HYQVIA for IV or SC infusion or an alternative treatment, at his/her discretion. Subjects in countries where HYQVIA treatment during pregnancy was not indicated were enrolled in this arm.

Study Arm 2 (HYQVIA Arm): subjects who continued treatment with HYQVIA according to their treatment regimen were followed in Study Arm 2.

The overall duration of the study is approximately six years from study initiation to study completion (i.e., end data collection). The participation period for the pregnant woman was from enrollment to study completion/termination visit after the delivery/end of pregnancy. The participation period for the infant is from enrollment until the age of two years to assess the development, unless prematurely discontinued. Enrollment and participation of the mothers has been completed.

6.3.6 HYQVIA Post-Authorization Safety Study 161302

Non-Interventional Post-Authorization Safety Study on the Long-Term Safety of HYQVIA in Subjects treated with HYQVIA

This is an ongoing, non-interventional, prospective, uncontrolled, multicenter, open-label, post-authorization safety study in the European Economic Area. The Post-Authorization Safety Surveillance was a commitment to the CHMP in the course of the HYQVIA Marketing Authorization Procedure.

The purpose of the study is to acquire additional data (including the assessment of anti-rHuPH20 antibodies) on the long-term safety of HYQVIA and to assess the prescribed treatment regimens and treatment administration in routine clinical practice.

The primary objective is to collect and assess safety data, in particular the occurrence of long-term changes in incidence and severity of related AEs in patients treated with HYQVIA.

Secondary objectives are to collect data on the prescribed treatment regimen, anti-rHuPH20 antibodies and, as available, other laboratory safety assessments, total IgG, further safety assessments that are obtained during the routine clinical management of the subjects, treatment administration, and health-related quality of life (HRQoL), and health resource use assessments (optional).

Adult patients (≥ 18 years) who have been prescribed treatment with HYQVIA have been enrolled. Treatment regimens are prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care are performed as is standard for the site and for the subject´s healthcare. In addition, the subject is requested to have additional blood samples drawn at the time of routine laboratory assessments approximately every three months, but no more often than four times a year, for the measurement of antibodies against rHuPH20.

The overall duration of the study is approximately six years from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately three to six years from enrollment to subject completion (i.e., study termination/completion visit), depending on the time point of enrollment, unless prematurely discontinued. Enrollment started in Q3 2014 and ended in December 2016 with 110 subjects enrolled into the study.

6.3.7 HYQVIA Study 161406

Non-Interventional Post-Marketing Safety Study on the Long-Term Safety of HYQVIA (Global)

This prospective, non-interventional, uncontrolled, multicenter, open-label, post-HYQVIA marketing authorization surveillance study with assessment of anti-rHuPH20 antibodies was agreed upon with the FDA in the course of the HYQVIA Biologic License review and approval process and is designed to obtain additional safety and tolerability data on HYQVIA. Further data shall be collected in subjects with an anti-rHuPH20 antibody titer ≥ 160. Subject enrollment has been completed. The study is ongoing.

The purpose of the study is to acquire additional data (including the assessment of anti-rHuPH20 antibodies) on the long-term safety of HYQVIA and to assess the prescribed treatment regimens and treatment administration in a total of 250 adult evaluable subjects with PIDD under routine clinical conditions. Further data shall be collected in subjects with an anti-rHuPH20 antibody titer ≥ 160.

The primary objective is to collect and assess safety data, in particular the occurrence of long-term changes in incidence and severity of related AEs in patients treated with HYQVIA.

Secondary objectives are to collect data on anti-rHuPH20 antibodies and, as available, other laboratory safety assessments, total IgG, further safety assessments that are obtained during the routine clinical management of the subjects, the prescribed treatment regimen, treatment administration, HRQoL, and health resource use assessments.

Approximately 50% of the subjects enrolled will have received SC administered immunoglobulins prior to enrollment. The remaining subjects will have received immunoglobulins IV prior to enrollment or will be naïve to immunoglobulin treatment.

Treatment regimens will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care will be performed as is standard for the site and for the subject´s healthcare. In addition, the subject will be invited to have additional blood samples drawn at the time of routine laboratory assessments approximately every three months, but no more often than four times a year, for the measurement of anti- rHuPH20 antibodies. For subjects with an anti-rHuPH20 antibody titer ≥ 10,000, antibody characterization will be performed. Additional blood samples for anti-rHuPH20 antibody testing should be taken if the visit coincides with other routine laboratory assessments. If anti-rHuPH20 antibody testing is not done for any reason, all other laboratory data will be collected as available.

Epoch 1: Subjects will be treated in Epoch 1 for approximately one year with HYQVIA. Subjects who at no time during Epoch 1 test positive for anti-rHuPH20 antibodies ≥ 160, including subjects who did not undergo testing for anti-rHuPH20 antibodies at least once during Epoch 1, will exit the study at the end of Epoch 1. Subjects who at any time during Epoch 1 test positive ≥ 160 will continue in Study Epoch 2. Subjects in whom anti-rHuPH20 antibodies ≥ 160 were measured and documented at any time prior to enrollment will also continue in Epoch 2 regardless of any test results for anti-rHuPH20 antibodies that may be available from Epoch 1.

Epoch 2: Subjects who at any time during Epoch 1 had an anti-rHuPH20 antibody titer ≥ 160, or had an anti-rHuPH20 antibody titer ≥ 160 documented any time prior to enrollment, will remain in the study for additional two years from the time of completing Epoch 1. Treatment with HYQVIA, site visits and all other medical care will continue as in Epoch 1. If a subject who tested positive ≥ 160 at any time before or during the study discontinues treatment with HYQVIA, the subject will be asked to continue participation in the study, and will continue to be followed up for the occurrence of AEs and anti-rHuPH20 antibody titers through the completion of Epoch 2. For the remaining time in the study, the subject´s treating physician will prescribe an alternative licensed human normal immunoglobulin or any other alternative treatment. If the subject withdraws consent for further testing of anti-rHuPH20 antibodies, data on AEs will continue to be collected.

The overall duration of the study is approximately six years. The subject participation period is approximately one year for subjects who complete only Epoch 1, and approximately three years for subjects who complete Epochs 1 and 2, unless prematurely discontinued.

6.3.8 HYQVIA Study 161504

Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases

This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate the safety, tolerability, and other parameters of SC treatment using HYQVIA in approximately 40 pediatric subjects with PIDD in Europe. Subjects will have received immunoglobulin therapy before enrollment into this study, and will undergo regular anti-rHuPH20 antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study approximately every three months. The study is ongoing.

The purpose of the study is to acquire additional data on safety, tolerability, and immunogenicity of HYQVIA in pediatric (age < 18 years) subjects with PIDD.

The primary objective of the study will be to assess the safety of HYQVIA treatment in pediatric subjects with PIDD who have received prior immunoglobulin therapy before enrollment into the study. The secondary objective will be further safety assessments (e.g., immunogenicity), tolerability, characteristic of product administration, and efficacy (IgG trough levels).

Epoch 1: Pediatric patients with PIDD who are on non-HYQVIA IV or SC treatment with immunoglobulin (IV-pre-treated, SC pre-treated) will be enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. Epoch 1 infusions will be administered at the study site. Subjects already treated with HYQVIA (HYQVIA pre-treated) will be enrolled directly into Epoch 2.

Epoch 2: The ramp-up (Epoch 1) is followed by Epoch 2 with HYQVIA treatment at the following intervals. For IV-pre-treated subjects: treatment happens every three or four weeks, depending on the subject's previous IV dosing schedule. For SC-pre-treated subjects: every three or four weeks, at the discretion of the investigator and the subject. For HYQVIA pre-treated subjects: no change in frequency of administration. After one year in Epoch 2, the anti-rHuPH20 binding antibody assay results during that year will be used to decide the next steps in the study. Subjects with an anti-rHuPH20 antibody titer < 160 at all time points during the study will complete the study at the next possible occasion. Subjects with anti-rHuPH20 antibody titer ≥ 160 during the study and/or at the last measurement will continue in Epoch 2 for an additional two years of HYQVIA treatment and observation.

Epoch 3: Epoch 3 is up to one year safety follow-up for subjects whose anti-rHuPH20 antibody titer was ≥ 160 during Epoch 1 or Epoch 2 and who experience either a related SAE or a related severe AE. Subjects in Epoch 3 will be treated with KIOVIG IV or Cuvitru SC, at the discretion of the investigator and the subject.

In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or related severe AE without anti-rHuPH20 antibody titer ≥ 160, the subject can (at the discretion of the investigator and subject) either be: 1) terminated from the study; 2) change directly to Epoch 3; or, 3) continue in Epoch 1 or 2 with appropriate medical intervention such as decreasing the HYQVIA infusion rate and/or premedication.

Subjects with antibody titer of ≥ 160 when entering Epoch 3 continue regular anti-rHuPH20 antibody testing (approximately every three months) for approximately one year or until the anti-rHuPH20 antibody titer declines to < 2,560 for at least two consecutive measurements, whichever comes first. These subjects complete the study termination or completion visit when the AE or SAE resolves and the anti-rHuPH20 titer is < 2,560.

The maximum subject participation period is approximately four years.

6.4 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

6.4.1 HYQVIA

The clinical development program for HYQVIA has demonstrated that IGI, 10% administered via SC treatment with rHuPH20 is efficacious and safe in persons with PIDD. The safety, tolerability, efficacy, and bioavailability of HYQVIA were investigated in one pivotal Phase III study (160603 and an extension study (160902) in patients with PIDD. One supportive clinical study (160602) in patients with PIDD using Gammagard Liquid administered subcutaneously was also conducted. Further information is provided in the Investigational Brochure for IGI, 10% with rHuPH20 as well as Prescribing Information for HYQVIA and Summary of Product Characteristics (SPC) for HYQVIA.

The most common ARs observed in PIDD clinical trials in > 5% of subjects were: local reactions, headache, antibody formation against rHuPH20, fatigue, nausea, pyrexia, and vomiting.

The safety and efficacy of chronic use of the rHuPH20 solution in HYQVIA has not been established in conditions other than PIDD. Study 160603 compared the efficacy, PKs, safety and tolerability of IGIV, 10% and IGI, 10% administered subcutaneously following rHuPH20 solution. Study 160902, an extension to study 160603, assessed the long-term tolerability and safety of IGI, 10% following administration of rHuPH20 solution. Eighteen percent (15 of 83) of subjects with PIDD receiving IGI, 10% with rHuPH20 in Study 160603 and Study 160902 developed non-neutralizing antibodies to rHuPH20. The clinical significance of these antibodies is not known. The clinical data from Study 160603 and Study 160902 have shown no temporal association between ARs and the presence of anti-rHuPH20 antibodies, and there was no increase in incidence or severity of ARs in subjects who developed anti-rHuPH20 antibodies. In all subjects, antibody titers decreased despite continued treatment.

There is a theoretical potential risk for such antibodies to cross-react with human hyaluronidase which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may interfere with fertilization and fetal development in humans; nonclinical safety studies have demonstrated no such effect. Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study.

6.4.1.1 Pregnancy, Breast Feeding, Fertility

SCIG products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy or on the fetus and the neonate are to be expected. Development and reproductive toxicology studies have been conducted with rHuPH20 in mice and rabbits. No adverse effects on pregnancy and fetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20 were transferred to offspring in utero. The effects of antibodies to the rHuPH20 component of HYQVIA on the human embryo or on human fetal development are currently unknown. Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

The safety of HYQVIA for use in human pregnancy has not been established in controlled clinical trials, and therefore, should only be given with caution to pregnant or breastfeeding women.

There are currently no clinical safety data for HYQVIA on fertility available. Clinical experience with immunoglobulins suggests that no harmful effects of IGI 10% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 or anti-rHuPH20 antibodies with respect to reproductive potential at the doses used for facilitating administration of IG 10%.

Subjects who become pregnant during the study should be withdrawn from the study, see also Section 9.3.

6.4.2 GAMMAGARD LIQUID

The below information is derived from the Prescribing Information for GAMMAGARD LIQUID in the U.S. (Initial U.S. Approval: 2005, with changes of 09/2013). Local prescribing information should be consulted if the study is conducted in other areas.

GAMMAGARD LIQUID IGI (Human), 10% Solution administered via IV or SC is efficacious and safe in the particular fields of therapeutic use and approved indications, i.e., PIDD and MMN, as demonstrated in the clinical development program for GAMMAGARD LIQUID. Please see the Prescribing Information for further information.

IV administration in PIDD: The serious AR seen during IV treatment in the clinical trials for PIDD was aseptic meningitis. The most common ARs for PIDD (observed in ≥ 5% of subjects) were headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, edema peripheral, pruritus, and cardiac murmur.

SC administration in PIDD: No serious ARs were observed during the clinical trial for SC treatment. The most common ARs during SC treatment (observed in ≥ 5% of PI subjects) were infusion site (local) events, headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.

MMN: The serious ARs in the clinical trial for MMN were pulmonary embolism and blurred vision. The most common ARs for MMN (observed in ≥ 5% of subjects) were headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

GAMMAGARD LIQUID is contraindicated in patients who have a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin. GAMMAGARD LIQUID is also contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. Anaphylaxis has been reported with the IV use of GAMMAGARD LIQUID and is theoretically possible following SC administration.

Further information is provided in the Prescribing Information for GAMMAGARD LIQUID.

6.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP R2, November 2016), Title 21 of the US Code of Federal Regulations, the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to acquire additional data on efficacy, safety, tolerability, immunogenicity, PK and other parameters of HYQVIA in pediatric (age ≥ 2 to < 16 years) subjects with PIDD.

7.2 Primary Objective

The primary objective of the study is to assess the efficacy of HYQVIA treatment in pediatric subjects with PIDD who received prior IV or SC immunoglobulin therapy before enrollment into the study.

7.3 Secondary Objectives

Secondary objectives of the study are further efficacy and safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, and PK parameters.

The assessment of study objectives is described in detail in Section 11, Section 12, and Supplement 20.2.

8. STUDY DESIGN

8.1 Brief Summary

This is a Phase 3, open-label, prospective, non-controlled, multicenter study to evaluate efficacy, safety, tolerability, immunogenicity, PK, and other parameters of SC treatment using HYQVIA in approximately 40 pediatric subjects with PIDD who received IV or SC immunoglobulin therapy prior to study enrollment.

8.2 Overall Study Design

The overall study design is illustrated in Figure 1. Details on the procedures to be performed at each study visit can be found in Supplement 20.2 "Schedule of Study Procedures and Assessments" and Supplement 20.3 "Clinical Laboratory Assessments". In this study approximately 40 pediatric subjects with PIDD, who have received prior immunoglobulin therapy, will be enrolled. At least six subjects in each of the three age groups of 2 to < 6 years, 6 to < 12 years, and 12 to < 16 years will be enrolled. The study will be conducted in the United States.

All subjects will have regular testing for binding anti-rHuPH20 antibodies approximately every three months throughout the study. rHuPH20 neutralizing antibody testing and/or characterization of anti-rHuPH20 antibodies may also be done (see Section 12.7.6).

The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion during Epoch 1 and 2 to follow up on AEs that may have occurred during or after completion of the infusion, and to ensure appropriate, timely entry of data into the subject diary. If the subject is not reached, a call-back on Day 6 is acceptable. Efforts should be made to adhere to the infusion schedule. In case of deviation, the original schedule should be resumed with the next administration.

8.2.1 Epoch 1

Pediatric patients with PIDD who are on IV or non-HYQVIA SC treatment with immunoglobulin (IV-pre-treated, SC-pre-treated) will be enrolled and treated with HYQVIA subcutaneously with a dose or interval ramp-up period of up to six weeks.

Epoch 1 infusions will be administered at the study site.

8.2.2 Epoch 2

8.2.2.1 Treatment

The ramp-up (Epoch 1) is followed by Epoch 2 with HYQVIA treatment at the following intervals:

- For IV-pre-treated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.
- For SC-pre-treated subjects: every three or four weeks, at the discretion of investigator and subject.

Alternative treatment intervals, for example infusion every 2 weeks, may be considered for tolerability reasons, at the discretion of the investigator after informing the sponsor.

After one year in Epoch 2, the anti-rHuPH20 binding antibody assay results during that year will be used to decide the next steps in the study (see Figure 1 Study Flow Chart in Supplements 20.1):

- Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study completion visit at the next possible occasion following the 12-months visit.
- Subjects with anti-rHuPH20 antibody titer ≥ 160 during the study and/or at the last measurement will continue in Epoch 2 for an additional two years of HYQVIA treatment and observation, and complete the study completion visits at the next possible occasion following the 36-months visit

The first two to three infusions during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions (with the exception of the per-protocol planned study site visits approximately every 3 months (see Tables in Supplement 20.2) be performed at home (or equivalent site), by the subject/caregiver, if in the opinion of the investigator, such treatment is safe and appropriate. In that case, the investigator/designee must have trained the subject or caregiver and must be satisfied that the subject or caregiver is capable of self-administration of SC infusions at home before the subject or caregiver will be permitted to conduct the SC infusion at home.

The study termination/completion visit will be conducted at the study site.

8.2.2.2 Pharmacokinetic Assessment

At the six-month infusion visit, a PK assessment should be performed. If the PK assessment cannot be done at the six-month visit for any reason, it may alternatively be performed at the infusion before or after the six-month visit. For subjects who do not undergo the PK assessments at month 6, an additional infusion visit at the site may be required.

Serum samples will be collected at the following time points:

- Pre-infusion (i.e., trough level of previous infusion, within one hour of infusion start time) (Day 0 of PK);
- [Only for subjects 12 years of age and older: Day 2 (± one day, from infusion start time of Day 0)];
- Day 4 (± two days from infusion start time of Day 0);
- Day 10 (± two days);
- Day 21 (± three days = trough level blood draw before next infusion). (end of PK assessment for three-week treatment interval), and,
- Day 28 (± three days = trough level blood draw before next infusion) (end of PK assessment for four-week treatment interval).

Subjects will return to the site for the required blood draws during the PK assessment period as outlined above. Alternatively, the samples for PK assessments (except Day 0) may be taken at the subject's home, if a health care professional is available.

8.2.3 Epoch 3

Epoch 3 is approximately one year safety follow-up, if needed: subjects whose anti-rHuPH20 antibody titer was ≥ 160 during Epoch 1 or Epoch 2 and who experience either a study drug- related SAE or a related severe AE will be followed accordingly.

Subjects in Epoch 3 continue regular anti-rHuPH20 antibody testing (approximately every three months) for approximately one year. These subjects complete the study termination/completion visit when the AE/SAE resolves and the anti-rHuPH20 titer is < 2,560.

Subjects in Epoch 3 will be treated with GAMMAGARD LIQUID intravenously or subcutaneously, at the discretion of the investigator and the subject (see Section 8.7.2.2).

In the event that a subject in Epoch 1 or in Epoch 2 experiences a study drug-related SAE or related severe AE **without** anti-rHuPH20 antibody titer ≥ 160, the subject can (at the discretion of the investigator and subject): 1) be terminated from the study; or, 2) change directly to Epoch 3; or, 3) continue in Epoch 1 or 2 with appropriate medical intervention such as decreasing the HYQVIA infusion rate and/or premedication.

Infusions in Study Epoch 3 will be administered at home or at the study site (for Site Visits see Supplement 20.2, Table 6).

The study termination/completion visit will be conducted at the study site.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately six years from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately two years. The end of the study is defined as the end of follow-up of the last subject to enter the study.

The maximum subject participation period is approximately four years from enrollment to subject completion (i.e., study termination/completion visit), unless prematurely discontinued.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The rate of acute serious bacterial infections defined as the mean number of acute serious bacterial infections per subject per year in the intent-to-treat population. Acute serious bacterial infections will include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, diagnosed according to the Diagnostic Criteria for Acute Serious Bacterial Infections (see Section 12.9).

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

1. Number of all infections per patient-year
2. Trough levels of IgG and IgG subclasses for Study Epoch 2
3. Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and Hepatitis B Virus [HBV]) for Study Epoch 2

8.4.2.2 Pharmacokinetics

1. For the PK assessment in Epoch 2 the following PK parameters will be determined: area under the curve (AUC), clearance (CL), maximum concentration (C_{max}), minimum concentration (C_{min}), time to maximum concentration (T_{max}), and terminal half-life

8.4.2.3 Safety

1. Number and rate per infusion (excluding infections) of SAEs, related and not related
2. Number and rate per infusion (excluding infections) of all AEs, related and not related
3. Number and rate per infusion (excluding infections) of local AEs, related and not related
4. Number and rate per infusion (excluding infections) of systemic AEs, related and not related
5. Number and rate per infusion (excluding infections) of all temporally associated AEs (begin during or within 72 hours of completion of infusion)
6. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
7. Rates of all AEs (excluding infections) defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of infusions
8. Number/proportion of subjects who develop positive titer (≥ 160) of binding or neutralizing antibodies to rHuPH20

8.4.2.4 Mode of Product Administration

1. Infusions (Study Epoch 2)
    a. Number of infusions per month
    b. Number of infusion sites (needle sticks) per infusion/month
    c. Duration of infusion
    d. Maximum infusion rate / site
    e. Infusion volume / site

f. Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE

2. Number of weeks to reach final dose interval (three weeks or four weeks) (Epoch 1)
3. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
4. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months

8.4.2.5 Health-related Quality of Life (HRQoL)

Assessment of Health-related Quality of Life (HRQoL) Questionnaires:

1. Pediatric Quality of Life Inventory (Peds-QL)
2. EuroQol five dimensions questionnaire (EQ-5D)

8.4.2.6 Treatment Preference and Satisfaction

1. Assessment of Life Quality Index (LQI)
2. Assessment of Treatment Satisfaction and Medication Questionnaire (TSQM-9)
3. Assessment of Treatment Preference Questionnaire

8.4.2.7 Health Resource Utilization

1. Days not able to go to school or work, or to perform normal daily activities due to infection or other illnesses per patient-year
2. Days on antibiotics per patient-year
3. Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized per patient-year
4. Number of acute physician visits (office and emergency room) due to infection or other illnesses per patient-year

8.5 Randomization and Blinding

Not applicable. This is a non-randomized, open-label, active treatment clinical study.

8.6 Study Stopping Rules

The study will be stopped in case one death of a subject is attributed to the study drug. The study may also be terminated by the sponsor for any safety or medical concerns.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 rHuPH20

Dosage Form: Injection, solution

Packaging: rHuPH20 drug product (160 U/mL) will be supplied as a clear, colorless, ready-for-use sterile liquid preparation in single-use glass vials. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Labeling: The product will be labeled according to the regulatory requirements for clinical studies.

Storage: rHuPH20 drug product must be stored under refrigerated conditions (2° to 8°C or 36° to 46°F). Do not freeze the product. Do not use if expiration date is exceeded.

8.7.1.2 Immune Globulin Infusion 10% (Human) [IGI, 10%]

Dosage Form: Injection, solution.

Packaging: IGI, 10% will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials. IGI, 10% is a clear or slightly opalescent and colorless or pale yellow solution. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Labeling: IGI, 10% will be labeled according to regulatory requirements for clinical studies.

Storage: IGI, 10% must be stored under refrigerated conditions (2°C to 8°C or 36°F to 46°F). Do not freeze the product. Do not use if expiration date is exceeded.

Prior to use, the vials must be removed from refrigeration and placed at room temperature for a minimum of 90 minutes to a maximum of 24 hours to equilibrate and should be kept at room temperature during administration.

If IGI, 10% is pooled in a bag, it must be used as soon as possible, but no longer than three hours from the time of pooling.

8.7.1.3 GAMMAGARD LIQUID [IGI 10%]

Dosage Form: Injection, solution

Packaging: GAMMAGARD LIQUID is supplied in single use bottles containing the labeled amount of functionally active IgG. The packaging of this product is not made with natural rubber latex.

Labeling: The study product will be labeled according to the valid regulatory requirements for clinical studies.

Storage and Shelf Life: Do not freeze. Store GAMMAGARD LIQUID in the refrigerator or at room temperature. Refrigeration: 2° to 8°C [36° to 46°F] for up to 36 months. Room Temperature: up to 25°C [77°F] for up to 24 months. Expiration dates for both storage conditions are printed on the outer carton and vial label. Do not use past the applicable expiration date. Note: Storage and Shelf Life described above is valid for U.S. only. Refer to the relevant section of the local Prescription Information, if the study is conducted in areas other than U.S.

8.7.2 Administration

8.7.2.1 HYQVIA

rHuPH20 will be administered at a dose ratio of approximately 80 U/g IgG before the infusion of IGI, 10%.

rHuPH20 should be injected at a rate of approximately 1 to 2 mL/min, or faster if tolerated, through the same SC needle that will be used to infuse the IGI, 10%. As soon as the rHuPH20 infusion is completed, but no longer than ten minutes after it is completed, the administration tubing to deliver IGI, 10% should be connected to the same SC needle set used to administer rHuPH20 in order to flush the remaining rHuPH20 into the SC tissue and start the infusion of immunoglobulin.

Subjects will be treated with HYQVIA in Study Epoch 1 and Study Epoch 2 (Table 2).

Dosage Form: Injection

Mode of Administration: SC

Dosage Frequency:

Study Epoch 1 (Ramp-up):
The first HYQVIA infusion will be given at baseline, The second infusion will be given after an interval of one week. For subjects planned to receive HYQVIA in three-week treatment intervals, the second infusion will be the last infusion in Epoch 1 (see Table 2).

Subjects planned to receive HYQVIA in four-week treatment intervals will receive the third infusion two weeks after the second, which will be their last infusion in Epoch 1 (see Table 2).

Study Epoch 2 (Final dosing):
Once every three or four weeks:
For IV-pre-treated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.

For SC-pre-treated subjects: every three or four weeks, at the discretion of investigator and subject.

Subjects on a three-week treatment interval will administer the first infusion in Epoch 2 two weeks after the last infusion in Epoch 1, and in intervals of three weeks thereafter. Subjects on a four-week treatment interval will administer the first infusion in Epoch 2 three weeks after the last infusion in Epoch 1, and in intervals of four weeks thereafter.

Dose: HYQVIA weekly dose will be equivalent to 100% (±5%) of pre-study treatment.

To calculate the required HYQVIA dose, for example for a 3-week treatment interval, the investigator will divide the total monthly dose (g/kg BW per 4 weeks) administered prior to enrollment by 4, and then multiply by 3 for a three-week treatment interval. Dosing for other treatment intervals (e.g., as required in Study Epoch 1) will be calculated analogously. Thus, the monthly dose of HYQVIA will be equivalent to the dose administered before the study, notwithstanding of the treatment interval adhered to prior to enrollment.

Table 2
Example for IgG dosing

Pre-Study		Epoch 1 (Ramp-Up)			Epoch 2 (Final Dose)
Admin. Route	**Dose**	**First Infusion at Baseline: one-Week Dose**	**Second Infusion at Week 1: two-Week Dose**	**Third Infusion at Week 3: three-Week Dose**	
IV	0.6 g/kg every three weeks	0.2 g/kg	0.4 g/kg	-	0.6 g/kg every three weeks
IV	0.6 g/kg every four weeks	0.15 g/kg	0.3 g/kg	0.45 g/kg	0.6 g/kg every four weeks
SC	0.1 g/kg every week	0.1 g/kg	0.2 g/kg	-	0.3 g/kg every three weeks
SC	0.1 g/kg every week	0.1 g/kg	0.2 g/kg	0.3 g/kg	0.4 g/kg every four weeks

The dose (in grams IgG per kg body weight) should remain stable throughout the study. In order to maintain the same dose in g/kg when there has been an increase in body weight (kg), it will be necessary to increase the absolute dose (in g or mg) administered. The HYQVIA dose should be based on the most current weight measurement (taken at a site visit) - if the subject´s weight has increased by more than 5%, the absolute dose (in g or mg) should be adjusted at the next possible infusion. If there is a weight decrease, regardless of the percentage, the HYQVIA dose should not be changed.

The final dose in g/kg may be increased if clinically indicated (e.g. increased incidence of infections, low IgG trough level (<5 g/L)) at the investigator´s discretion. If such an event arises, the sponsor should be informed, the rationale for such dose adjustment should be documented in the patient file, and the adjusted dose should be entered in the case report forms (CRFs).

Infusion Rate:

Study Epoch 1 (Ramp-up):

- For subjects with a BW of < 40 kg: 5 mL/h/site (at start) to 80 mL/h/site (maximum, if tolerated)
- For subjects with a BW of ≥ 40 kg: 10 mL/h/site (at start) to 240 mL/h/site (maximum, if tolerated)

Study Epoch 2 (Final dosing):

- For subjects with a BW of < 40 kg: 10 mL/h/site (at start) to 160 mL/h/site (maximum, if tolerated)
- For subjects with a BW of ≥ 40 kg: 10 mL/h/site (at start) to 300 mL/h/site (maximum, if tolerated)

If infusions have been tolerated after the subject has received two HYQVIA infusions at the dose for the final infusion interval (three or four week dose), then the investigator may choose an infusion rate schedule at his/her own discretion.

Infusion Volume:

Administer up to 600 mL per infusion site for subjects with a BW ≥ 40 kg, and up to 300 mL per site for subjects with a BW < 40 kg. A second site can be used at the discretion of the physician and subject based on tolerability and total volume. If a second site is used, administer half the total volume of rHuPH20 of HYQVIA in each site.

8.7.2.2 GAMMAGARD LIQUID

Subjects may be treated with GAMMAGARD LIQUID in **Study Epoch 3** (Safety Follow-up). Treatment will follow the guidance of the GAMMAGARD LIQUID product information and the site´s standard of care.

Dosage form: Injection

Mode of Administration: IV or SC

The infusion rate and infusion volume per site will follow the suggestions of the GAMMAGARD LIQUID product information.

Dosage frequency: Once every three or four weeks (IV), once a week (SC).

Dose: For IV administration, the weekly dose will be equivalent to 100% (± 5%) of the dose in the previous study epoch. For SC administration, the weekly dose will be equivalent to 137% (± 5%) of the weekly dose equivalent in the previous study epoch.

8.7.3 Investigational Product Accountability

The investigator will ensure that the investigational product(s) (IP[s]) are stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per the ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise, but are not limited to, the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly into the electronic case report form (eCRF).

For additional information on study documentation and eCRFs, see Section 17.2. The use of subject diaries is described in Section 10.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject must have a documented diagnosis of a form of primary immunodeficiency (PI) involving a defect in antibody formation and requiring gammaglobulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Scientific Committee 2015 (Picard et al., 2015) prior to enrollment. The diagnosis must be confirmed by the sponsor´s Medical Director prior to first treatment with IP in the study.
2. Subject is at least two and below 16 years of age at the time of screening.
3. Subject has been receiving a consistent dose of IgG, administered in compliance with the respective product information for a period of at least three months prior to screening. The average minimum pre-study dose over that interval was equivalent to 300 mg/kg BW / 4 weeks and a maximum dose equivalent to 1000 mg/kg BW / 4 weeks.
4. Subject has a serum trough level of IgG > 5 g/L at screening.
5. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study.
6. Subject/legally authorized representative is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has a known history of or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
   a. Persistent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) for the testing laboratory
   b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] $\leq 500/mm^3$)

3. Subject has anemia that would preclude phlebotomy for laboratory studies, according to standard practice at the site.
4. Subject has an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or Immune Serum Globulin (ISG) infusions.
5. Subject has severe IgA deficiency (less than 7.0 mg/dL) with known anti-IgA antibodies and a history of hypersensitivity.
6. Subject has a known allergy to hyaluronidase.
7. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening.
8. Subject has a bleeding disorder or a platelet count less than 20,000/µL, or who, in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of SC therapy.
9. Subject has severe dermatitis that would preclude adequate sites for safe product administration in the opinion of the investigator.
10. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
11. Subject is a family member or employee of the investigator.
12. If female, subject is pregnant or lactating at the time of enrollment.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study eCRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Supplement 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to one year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
- The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
- The subject twice consecutively misses administration of IP.
- The subject does not comply with the protocol (per the investigator's discretion).
- The subject develops severe hypersensitivity reactions related to IP administration.
- The subject uses prohibited medications (see Section 10.4) during the course of this study.
- The subject participates in another clinical study involving an IP or device during the course of this study.

10. STUDY PROCEDURES

10.1 Informed Consent

Any patient who provides informed consent (i.e., signs and dates the informed consent form [ICF] and assent form, if applicable (see Section 16.3), is considered enrolled in the study, and thus becomes a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 161503) to be provided by the sponsor, three-digit number study site number (e.g., 002) to be provided by the sponsor, and three-digit subject number (e.g., 003) reflecting the order of providing informed consent. For example, the third subject who signed an ICF at study site 002 will be identified as Subject 161503-002003. All study documents (e.g., case report forms [CRFs], clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

Screening will comprise all procedures to confirm subject eligibility. The investigator is responsible for maintaining a patient identification list that includes all enrolled subjects and which includes the following information: subject´s full name, subject number, and site number. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in eCRFs, regardless of screening outcome. A subject may be re-screened. All screening procedures must be completed up to 31 days after enrollment and prior to the first HYQVIA infusion in the study. If a subject is re-screened, the End of Study eCRF for the prior screening should be completed, and a new ICF, new SIC and new eCRF are required for that subject. If a subject is scheduled to receive a dose of immunoglobulin before eligibility is fully confirmed (e.g., due to the unavailability of lab results), the subject may – on a case-by-case basis – be allowed to continue receiving the IG product used prior to enrollment.

A screening failure is a patient who was screened and provided informed consent but did not fulfill the study admission criteria.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

Details on the treatment regimen including dose (total dose in mg/kg BW/week) and the infusion interval will be collected. Changes to the treatment regimen, including the reason for the change, will also be collected.

In addition, details on product administration such as infusion date and start/stop time, lot number, actual volume infused, maximum infusion rate achieved, and number and location of infusion sites (needle sticks) per infusion, will be collected.

Details of the treatment regimen and product administration, if performed at the site, should be recorded on the CRF. Administration details for home treatment should be recorded by the subject/subject´s legally authorized representative in the subject diary.

10.3.1 Epoch 1

Table 3 in Supplement 20.2 describes the schedule of study procedures and assessments for Epoch 1. At the screening/enrollment visit, informed consent will be signed prior to any study-specific procedures. Eligibility criteria will be reviewed and the subjects' medical history will be attained at the screening/enrollment visit. The list of concomitant medications and non-drug therapies, as well as vital signs, will be reviewed at each visit in Epoch 1.

At screening/enrollment and subsequent scheduled study visits, a physical examination will be performed on the following body systems being described as normal or absent: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening/enrollment, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease, not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

HRQoL questionnaires (see Section 11.2) and Treatment Preference and Satisfaction Questionnaires (see Section 11.3) are also completed at the baseline visit, with the exception of the Treatment Preference Questionnaire.

AEs are assessed at the treatment visits in Epoch 1. AEs are further described in Section 12.

10.3.2 Epoch 2

Table 4 and Table 5 in Supplement 20.2 describe the schedule of study procedures, including infusion visits, and assessments for Epoch 2. The list of concomitant medications and non-drug therapies will be reviewed at each visit in Epoch 2. The physical exam (see Section 12.6), AEs (Section 12.1), laboratories (see Section 12.7 and Supplement 20.3) and vital signs (see Section 12.8) will be completed at each scheduled visit in Epoch 2. The HRQoL/Treatment Preference and Satisfaction questionnaires as described in Section 11.2 and Section 11.3 will be completed at the Month 12 visit, and also at the Month 24 and Month 36 visits (for subjects who continue in the study for additional 2 years). Subjects who prematurely exit the study will complete the questionnaires at the study termination visit.

HYQVIA treatment is described in Section 8.2.2.1.

PK assessments

Subjects will return to the site for the required blood draws (see Section 8.2.2.2) during the PK assessment period. Alternatively, the samples for PK assessments (except Day 0) may be taken at the subject´s home, if a health care professional is available.

If the PK assessment cannot be done at the six-month visit for any reason, it may alternatively be performed at the infusion before or after the six-month visit. For subjects who do not undergo the PK assessments at Month 6, an additional infusion visit at the site may be required.

10.3.3 Epoch 3

Table 5 and Table 6 in Supplement 20.2 describe the schedule of study procedures and assessments, Section 8.7.2.2 describes product treatment for Epoch 3. Infusion visits will be performed at Month 0, 3, 6, and 9. The list of concomitant medications and non-drug therapies will be reviewed at each visit in Epoch 3. The physical exam (see Section 12.6), AEs (see Section 12.1), laboratories (see Section 12.7 and Supplement 20.3) and vital signs (see Section 12.8) will be completed at each visit in Epoch 3. The HRQoL questionnaires (Peds-QL, EQ-5D) will be completed at the Month 0 visit as well as at the study completion/termination visit. Treatment Preference and Satisfaction questionnaires will not be done in Epoch 3.

10.4 Medications and Non-Drug Therapies

The use of all antibiotic therapy must be associated with a corresponding AE, and documented accordingly.

The following medications and non-drug therapies are **not** permitted during the course of the study:

- Prophylactic treatment with systemic antibacterial antibiotics is not allowed during the study. The use of systemic prophylactic antibacterial antibiotics by a subject will be considered a protocol deviation. However, prophylaxis for viral infections, fungi, and parasites (including pneumocystis pneumonia) which are not treated by immunoglobulin, can be used and should be recorded as concomitant medication. Use of Trimethoprim-Sulfamethoxazole for pneumocystis prophylaxis is acceptable in doses typical for pneumocystis pneumonia, but not low dose daily therapy that can also be used for antibacterial prophylaxis. Brief (less than 72 hours), prophylaxis for surgery (including dental procedures) or injury is permitted but treatment and indication must be recorded.
- Other IGIV or IGSC products
- Pre-medication on the day of product administration:
  - In this study, subjects should not receive pre-medication for SC infusions unless an AR of at least moderate severity, not resolving with a reduction in the infusion rate, occurs during or after at least two infusions. Should this occur, subjects may be pre-treated with antipyretics, corticosteroids, or antihistamines at the discretion of the investigator. Topical anesthetics (e.g., EMLA) may be used if the needle insertion was intolerable in prior infusions. Subjects who have a history of using topical anesthetics (e.g., EMLA) may use these topical anesthetics for SC infusions. The use of such pre-medications should be recorded on the concomitant medication record.

10.5 Subject Diary

A paper subject diary will be provided to each subject/caregiver at enrollment to record the following information:

- Occurrence of AEs (including infections). The investigator will provide guidance for the subject/caregiver regarding identification and documentation of AEs
- Concomitant medication use
- Details of the product administration as specified in Section 10.3
- Days not able to go to school or work, or to perform normal daily activities due to infection or other illnesses

- Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized
- Number of acute physician visits (office and emergency room) due to infection or other illnesses

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in paper format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

The subject diary will serve as a source record and remain at the study site after the study completion visit. Entries in the subject diary will be transferred into the appropriate collection device. Any entry in the collection device that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according to the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation eCRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as three documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

Every effort will be made to have discontinued subjects complete the study completion/ termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit.
If a subject terminates participation in the study and does not return for the completion/ termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of

withdrawal or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

For study procedures that are to be performed under the direct supervision of the investigator/healthcare professional (e.g., infusion nurse) at the study site or infusion center, no separate procedures will be used to monitor subject compliance.

Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions. A healthcare professional (e.g., infusion nurse) may be present to observe the subject's self-administration. The subject (and/or caregiver) may be asked to return to the study site during the study so the investigator/designee can further assess and document the subject (and/or caregiver) is capable of continuing to independently perform self-infusion procedures.

10.8 Post-trial patient treatment and IMP supply

At the conclusion of the study, the sponsor will not maintain the IMP supply. The investigator will transition the subject to a commercially available drug/treatment after the end of the study.

10.9 Contraception and Pregnancy Avoidance Procedure

No clinical studies have been conducted with GAMMAGARD LIQUID/KIOVIG or HYQVIA in pregnant women.

Animal reproduction studies have not been conducted with GAMMAGARD LIQUID/KIOVIG (IGI 10%) and IGI 10% component of HYQVIA. It is also not known whether IGI 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, clinical experience with immunoglobulins suggests that no harmful effects of IGI 10% on fertility are to be expected.

Developmental and reproductive toxicology studies have been conducted with rHuPH20 in mice and rabbits. No adverse effects on pregnancy were associated with anti-rHuPH20 antibodies.
In these studies, maternal antibodies to rHuPH20 were transferred to offspring in utero. The effects of antibodies to the rHuPH20 component of HYQVIA on the human embryo or on human fetal development are unknown.

In this study, female subjects of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration of investigational product. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15), birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[vii]
- Intrauterine device (IUD)[vii]
- Intrauterine hormone-releasing system (IUS)[vii]
- Bilateral tubal occlusion[vii]
- Vasectomised partner(s)[vii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not

be used together.[vii]

11. ASSESSMENT OF EFFICACY

11.1 Trough Levels of IgG, IgG Subclasses and Specific Antibodies

Trough levels of IgG total, IgG subclasses and specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and HBV) will be determined on all subjects at several time points by using standard assay methods.

11.2 Health-related Quality of Life (HRQoL) Questionnaires

Patient reported outcomes will be collected electronically (ePRO), at the site, for the assessment of QoL (Peds-QL, EQ-5D) and treatment satisfaction and preference (LQI, TSQM-9, Treatment Preference Questionnaire). For administration time points refer to Section 10.3 and Supplement 20.2.

11.2.1 PedsQL

The PedsQL is a validated questionnaire designed to measure generic HRQoL among a pediatric population. Both patient and proxy versions of the questionnaire are available. This questionnaire measures four domains, including; physical functioning, emotional functioning, social functioning, and school functioning. A total score and domain scores can be calculated. Higher scores indicate better health status (Varni et al., 1999).

Quality of life will be assessed separately for the age groups two to four years, five to seven years, eight to 12 years (PEDS-QL, observer: parent/legal guardian), and 13 to <16 years (PEDS-QL, observer: subject). The same observer should be employed for the duration of subject participation.

Age will be defined as the age at screening, in order to determine which age-specific assessment is to be used. The same age-specific assessment is to be used for the duration of the study. In the event that the language or age group is not available, the assessment in the closest age group will be used. In the event that the appropriate language is not available, the questionnaire will not be administered for that subject. For detailed administration time points, see Supplement 20.2 Schedule of Study Procedures and Assessments.

11.2.2 EQ-5D

The EQ-5D is a validated, self-administered assessment of overall health designed by the EuroQol Group (Rabin and de Charro, 2001). It is a descriptive system of HRQoL

[vii] Contraception methods that are considered to have low user dependency.

states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression). Subjects are asked to describe their health state that day by choosing one of three responses that reflect the levels of severity for each of the five dimensions: no problems, some or moderate problems, or extreme problems.
The EQ-5D also includes a standard vertical 20-cm visual analogue scale (similar to a thermometer) for recording a subject's rating of their current HRQoL state.

The EuroQol five dimensions questionnaire (EQ-5D) will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <16 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent/legal guardian should complete the questionnaire on behalf of their child (observer: parent/legal guardian). In the event that the appropriate language is not available, the questionnaire will not be administered for that subject. For detailed administration time points, see Supplement 20.2 Schedule of Study Procedures and Assessments.

11.3 Treatment Preference and Satisfaction Questionnaires

For administration time points refer to Section 10.3 and Supplement 20.2.

11.3.1 Assessment of Life Quality Index (LQI)

The LQI is validated questionnaire assessing patient perceptions of their HRQoL and their treatment specifically among patients who use immunoglobulin therapy. This questionnaire covers 4 domains: Treatment Interferences, Therapy-related Problems, Therapy Setting, and Treatment Costs. A score can be calculated for each domain, with higher scores indicating higher satisfaction (Daly et al., 1991, Nicolay et al., 2005).
Age will be defined as the age at screening, in order to determine which age-specific assessment is to be used. The same age-specific assessment is to be used for the duration of the study. In the event that the language/age group is not available, the assessment in the closest language/ age group will be used. For the age group 2 to 12 years the observer will be a parent, for the age group 13 years and older the observer will be the subject. The same observer should be employed for the duration of subject participation.

11.3.2 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a nine-item, validated, self-administered instrument to assess patients' satisfaction with medication. The three domains assessed are effectiveness, convenience, and global satisfaction.

The TSQM-9 will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject completes the assessment using the same translated version throughout the course of the study. For subjects aged 13 to < 16 years, the subject should complete the questionnaire themselves (observer: subject).

For subjects under the age of 13, the parent/legal guardian should complete the questionnaire on behalf of their child (observer: parent/legal guardian). The same observer should be employed for the duration of subject participation.

11.3.3 Treatment Preference Questionnaire

The treatment preference questionnaire, internally developed at Baxalta, is a self-administered, non-validated scale assessing patient preference for various attributes of IgG therapy, such as ease of administration, frequency and duration of administration, and convenience.

The treatment preference questionnaire will be administered at the study site using a translated version, as applicable. It is recommended that the subject completes the assessment using the same translated version throughout the course of the study. For subjects aged 13 to < 16 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent/legal guardian should complete the questionnaire on behalf of their child (observer: parent/legal guardian). The same observer should be employed for the duration of subject participation.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. Therefore, an AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

Temporally associated AEs are all AEs which occur during the infusion or within 72 hours of completion of infusion.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

1. Outcome is fatal/results in death (including fetal death)
2. Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
4. Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
5. Is a congenital anomaly/birth defect
6. Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are the following:
   - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
- Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accidents [e.g., stroke, transient ischemic event])
- Hemolytic anemia

Uncomplicated pregnancies, following maternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information. “Unexpected” also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the IB and/or prescribing information as the RSI.

This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

12.1.1.5 Preexisting Diseases

Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study completion/discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. Follow-up information will be recorded in the appropriate CRF(s) as applicable, unless the database has already locked. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing or underdosing by more than 20%, abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and one year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.

If an investigator becomes aware of an SAE occurring in a subject within 30 days after study completion, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on CREs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

1. Mild
   - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
   - The AE resolves spontaneously or may require minimal therapeutic intervention.
2. Moderate
   - The AE produces limited impairment of function and may require therapeutic intervention.
   - The AE produces no sequela/sequelae.
3. Severe
   - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
   - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge / rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

1. Not related (both circumstances must be met)
   - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
   - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
2. Unlikely related (either one or both circumstances are met)
   - Has little or no temporal relationship to the IP
   - A more likely alternative etiology exists
3. Possibly related (both circumstances must be met)
   - Follows a reasonable temporal relationship to the administration of IP
   - An alternative etiology is equally or less likely compared to the potential relationship to the IP
4. Probably related (both circumstances must be met)
   - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
     - Reappearance of a similar reaction upon re-administration (positive rechallenge)
     - Positive results in a drug sensitivity test (skin test, etc.)
     - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid

- Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 hours after completion of IP administration, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within one calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC(s)) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF and on the SAE Report Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be reported to the sponsor/designee within one business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent scheduled study visits (as described in Supplement 20.2), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

For detailed sampling time points see Supplement 20.3 Clinical Laboratory Assessments. Blood and urine collection will occur pre-infusion (unless stated otherwise), and should be collected within one hour before the start of the infusion procedure, if possible.

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin [Hgb], hematocrit, erythrocytes [i.e., red blood cell (RBC) count], and leukocytes [i.e., white blood cell count [WBC]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate amino transferase (AST), total bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), serum creatinine, lactate dehydrogenase (LDH) and glucose. If the LDH is $\geq$ 2 times the upper limit of normal, the sample should reflexively be sent for isoenzyme analysis.

Hematology and clinical chemistry assessments will be performed on Ethylenediamine tetracetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.7.2 Urine Tests

Urinalysis will include color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination. Urinalysis tests will be conducted at the central laboratory.

12.7.3 Pregnancy Test

For female subjects of childbearing potential, urine pregnancy test will be performed at a central laboratory, unless a serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

12.7.4 Hemolysis Test

Hemolysis test will consist of Hgb, lactate dehydrogenase (LDH), serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coomb's) test (antibody elution to be performed if direct Coomb's test is positive), reticulocyte count, as well as urine hemosiderin. If the LDH is ≥ 2 times the upper limit of normal, the sample should reflexively be sent for isoenzyme analysis.

If there is a reduction in Hgb of 2 g/dL or more compared to baseline Hgb, every effort is to be made to perform a repeat test consisting of the hemolysis tests described above within 72 hours; if it is not feasible to do so, the hemolytic panel must be performed as soon as possible. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia.

Hemolysis test will be performed at the central laboratory or other laboratories as appropriate (e.g., antibody elution in the event of positive direct Coomb's test). Complete hematology and clinical chemistry assessments may be performed in order to obtain laboratory results required for a hemolytic panel.

12.7.5 Trough Levels of IgG, IgG Subclasses and Specific Antibodies

IgG total and IgG subclass trough levels and trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and HBV) will be determined on all subjects at the time points specified in Supplement 20.3 Clinical Laboratory Assessments. Measurements will be performed at the central laboratory and by using standard assay methods. The IgG serum trough level at screening should be the most recent pre-study serum IgG trough level on the stable (unchanged) dose administered prior to enrollment, and should not be older than six months. For PK assessments, only IgG (total) will be measured (refer to Section 8.2.2.2).

12.7.6 Anti-rHuPH20 Antibodies

All subjects will have regular anti-rHuPH20 antibody testing in pre-identified central laboratories for binding anti-rHuPH20 antibodies throughout the study approximately every three months (see Supplement 20.3). For subjects with an anti-rHuPH20 antibody titer ≥ 160, neutralizing antibodies will also be measured.

If a subject has a positive titer ≥ 10,000 at any time during the study, characterization of antibodies may be performed (to include neutralizing antibodies and antibodies cross-reacting with Hyal 1, 2, and 4).

At any time during the course of study, subjects who have 1) two consecutive anti-rHuPH20 antibody titers of ≥ 1:160 that are elevated from the subject's baseline titers; and 2) a moderate or severe AE that may be a result of immune-mediated response to either immunoglobulin or rHuPH20 will be asked to return to the study site as soon as possible to undergo an additional panel of testing. That panel assesses:

- 50% hemolytic complement activity of serum;
- serum complement component 3;
- serum complement component 4;
- Complement 1q (C1q) binding ; and,
- circulating immune complex Raji cells.

12.7.7 Viral Pathogen Serology

Tests for viral pathogen serology include: HBsAg by enzyme-linked immunosorbent assay, PCR for HCV, and PCR for HIV-1/2. These assessments will be performed at the central laboratory at the time points specified in Supplement 20.3 Clinical Laboratory Assessments.

12.7.8 Assessment of Laboratory Values

12.7.8.1 Toxicity Grading Scale

The following laboratory values will be evaluated by the sponsor/sponsor's representative according to the Common Toxicity Criteria of the Eastern Cooperative Oncology Group (ECOG), published by Oken et al., 1982:

- ALP, ALT, AST, BUN, Hgb, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and WBC. Grading for LDH will use the same thresholds as defined for ALT and AST.
- Sodium and potassium will be graded using the thresholds taken from the World Health Organization toxicity grading system (World Health Organization, 2003). The laboratory parameters and the corresponding grading scale are provided in Section 12.7. The toxicity scale is defined as: zero = none, one = mild, two = moderate, three = severe, four = life-threatening. Laboratory parameters not listed in Table 11 will not be graded. However, clinical significance of those abnormal laboratory values will be assessed as described in Section 12.7.8.2.

12.7.8.2 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value (with the exception of total IgG, IgG subclasses and specific antibodies) will be recorded on the eCRF laboratory form. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for HIV, HAV, HBV, HCV, HEV, or B19V shall be re-tested.

12.7.9 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used, for example, for re-testing, follow-up of an AE(s) or other test results, and/or assay development. After study testing is completed, the remaining samples may be stored in a coded form for no more than two years after the final study report has been completed and then the samples will subsequently be destroyed.

For this study, no samples will be taken or stored long-term in a biobank for future analyses.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths / minute), pulse rate (beats / minute), and systolic and diastolic blood pressure (mm Hg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured as described below at scheduled site visits (see also Supplement 20.2):

12.8.1 Screening

- All vital signs

12.8.2 Infusion at Study Site

1. Within 30 minutes prior to infusion:
   - All vital signs. Height and weight can be taken at any time at this visit.
2. 30 minutes (± 5) after initiation of infusion:
   - All vital signs, except height and weight
3. During the infusion if a systemic AE occurs, to be assessed as needed:
   - All vital signs, except height and weight
4. Within 30 minutes of completion of the infusion:
   - All vital signs, except height and weight

12.8.3 Infusion at Home

- No assessment of vital signs

12.8.4 End-of-Study

- All vital signs

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether to report an AE (see definition in Section 12.1) and record the medical diagnosis [preferably], symptom, or sign on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Acute Serious Bacterial Infections

Acute serious bacterial infections will be defined as follows based on the U.S. FDA Guidance for Industry to Support Marketing of Human IGIV as Replacement Therapy for Primary Humoral Immunodeficiency (U.S.Department of Health and Human Services 2008) and the European Medicines Agency guideline on the clinical investigation of human normal immunoglobulin for SC and /or intramuscular administration (Committee for Medicinal Products for Human Use, 2015).

12.9.1 Infection: Bacteremia/Sepsis[(a)]

1. Symptoms: chills, rigors
2. Physical findings: fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure < 90 mm Hg or a reduction of > 40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oliguria, cutaneous vasodilation/vasoconstriction
3. Laboratory tests: positive blood culture[(b)], leukocytosis (WBC count > 12,000/mm^3), differential WBC count demonstrating > 10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis

[(a)] Two of the following should be present to make the diagnosis of sepsis in adults: temperature > 38°C oral / > 39°C rectal or < 36°C oral or < 37°C rectal; heart rate > 90 beats / minute; respiratory rate > 20 breaths / minute, or partial pressure of carbon dioxide ($PaCO_2$) < 32 mm Hg; WBC > 12,000/mm^3, < 4,000/mm^3, or > 10% immature (band) forms. For pediatric patients, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (Goldstein et al., 2005).

[(b)] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGI 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 two or more of the sepsis criteria listed above will be classified as having bacteremia.

12.9.2 Infection: Bacterial Meningitis

1. Symptoms: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea / vomiting, rigors, seizures
2. Physical findings: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of > 38°C oral or > 39°C rectal
3. Laboratory tests: positive cerebrospinal fluid (CSF) Gram stain and / or culture and / or positive CSF bacterial antigen assay, positive blood culture[(c)], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose

[c] A blood culture positive for growth of Streptococcus pneumoniae, Neisseria meningitides, or Haemophilus influenzae, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis.

12.9.3 Infection: Osteomyelitis/Septic Arthritis

1. Symptoms: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults)
2. 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
3. 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
4. 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, involucre

12.9.4 Infections: Bacterial Pneumonia[d]

1. Symptoms: productive cough / change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias
2. 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)
3. Laboratory tests: leukocytosis; differential WBC count of >10% band neutrophils; leukopenia; hypoxemia (PaO2 < 60 mm Hg on room air); positive blood culture; Gram stain and culture of deep expectorated sputum[e], positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with Bronchoscopic Alveolar Lavage (BAL), or protected brush sampling,
4. Imaging studies: Pulmonary infiltrate with consolidation on chest X-Ray ([CXR]; new in comparison with baseline or previous CXR)

(d) For the diagnosis of pneumonia in adults, commonly at least two of the listed symptoms and / or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element[viii]. However, for the purposes of counting serious infection episodes in a clinical study of IGI, 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 ages three to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature > 38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature > 38°C (100.4°F). In pediatric patients, elevations of WBC counts > 15,000 / mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count < 5000 / mm^3 may be observed, usually associated with severe infection.

(e) We recommend a deep expectorated sputum Gram stain demonstrate the presence of microorganisms on examination of 10 to 20 oil immersion microscopic fields and < 10 squamous epithelial cells and > 25 polymorphonuclear leukocytes at tenX low power magnification to determine suitability of sputum culture.

12.9.5 Infection: Visceral Abscess

1. Symptoms: abdominal pain, anorexia, weight loss, cough / pleuritic chest pain (hepatic abscess), rigors (seldom present)
2. Physical findings: intermittent fevers (temperature > 38°C oral or > 39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice
3. 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 of > 10% immature (band) neutrophils; elevated serum amylase concentration (pancreatic abscess); elevated ALP concentration (hepatic abscess) pyuria in renal abscess
4. Imaging studies: typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan

[viii] Further evaluation, in particular laboratory evaluation (culture and WBC count with differential to evaluate for the presence of immature neutrophils) and CXRs, should be aggressively pursued whenever a bacterial pneumonia is suspected.

13. STATISTICS

13.1 Sample Size and Power Calculations

13.1.1 Evaluation of Efficacy

The planned sample size for this study is 40 subjects.

The primary objective of this study is to evaluate the efficacy of HYQVIA in terms of the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year. A sample size of 35 provides 83% power to reject the null hypothesis (H_0) of an acute serious bacterial infection rate greater or equal 1.0 ($H_0 \geq 1.0$), by means of a 1-sided test and a significance level of 0.01, versus the alternative hypothesis (H_1) of less than 1.0 ($H_1 < 1.0$), assuming a true rate of 0.5/year. Based on previous clinical experience, a dropout rate of 12% is assumed. Allowing for 12% dropouts, approximately 40 subjects will be enrolled in the study. Subjects who prematurely discontinued the study will not be replaced.

The sample size (40), power (at least 80%) and hypothesis testing (significance level of 0.01, 1-sided) are consistent with the FDA's guidance ("Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency").

Summarized below are sample size and power estimates under 2 scenarios of the rate of acute serious bacterial infections: 0.5/year and 0.4/year, which are in line with the FDA guidance, which indicates that IGIV administration to individuals with primary immunodeficiency has observed acute serious bacterial infection rates of 0.5/year. The sample size and power estimates were derived using nQuery software (version 4.0), with the following specifications: One Poisson Mean, $\alpha = 0.01$ (type 1 error), 1-sided.

	Rate under H_0	Rate under H_1	Sample Size [a]		Power [b]
			Subjects Enroll	Subjects Complete	
ASBI	1.0/year	0.5/year	34	30	75%
			36	32	81%
			40	35	83%
		0.4/year	34	30	94%
			36	32	96%
			40	35	97%

ASBI = Acute serious bacterial infections.
[a] Subjects Enroll = Number of Subjects Complete after adjusting for the assumed 12% dropout rate.
[b] Power is study power based on Subjects Complete.

13.1.2 Evaluation of Safety

For evaluation of AEs (treatment-emergent AEs), the FDA's guidance ("Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency") recommends a minimum sample size of 30 subjects for evaluation of safety. The planned sample size for this study is 40 subjects. For AEs that occur with a frequency of 10% ($\theta = 10\%$), the probability of observing at least 1 AE in this sample size is 98.5%. Displayed below are probabilities of observing at least 1 AE in this sample size under varying scenarios of θ, the frequency is AEs.

Sample Size	$\theta = 1\%$	$\theta = 5\%$	$\theta = 10\%$
34	28.9%	82.5%	97.2%
36	30.4%	84.2%	97.7%
40	33.1%	87.1%	98.5%

13.2 Analysis Sets

13.2.1 Full Analysis Set (FAS)

All patients who provide informed consent (i.e., sign and date the ICF, if applicable), and meet enrollment eligibility (i.e., meets all inclusion criteria and do not meet any exclusion criteria) will be included in the FAS. The FAS is defined as in pivotal study 160603 and other studies in the HYQVIA program. All efficacy analyses will be based on the FAS.

13.2.2 Per-Protocol Analysis Set (PPS)

All patients in the FAS who have no major protocol deviations will be included in the PPS. Major protocol deviations will be determined before study clinical database lock. Sensitivity analysis of efficacy will be based on the PPS.

13.2.3 Safety Analysis Set

All subjects who receive at least one dose of HYQVIA. All safety analyses will be based on the Safety Analysis Set.

13.2.4 Pharmacokinetic Analysis Set (PKAS)

All subjects in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. All PK summaries will be based on the PKAS.

13.3 Handling of Missing, Unused, and Spurious Data

All data for the primary and secondary outcome measures will be analyzed and provided in subject data listings. The primary analysis of the primary outcome measure (defined in Section 13.4.1) will be based on observed data, with no imputation for missing data. That analysis accounts for different lengths of the observation periods per subject. Additional information regarding the handling of missing, unused, or spurious data will be discussed in the study Statistical Analysis Plan (SAP), which will be finalized before study clinical database lock.

13.4 Methods of Analysis

Analysis details will be provided in the study SAP.

For the primary and secondary outcome measures, statistical hypothesis testing will be performed only if specified. For all outcome measures, descriptive analysis will be performed. The following summaries will be presented:

- For continuous outcome measures: number of subjects (n), mean, standard deviation (SD), median, minimum value, and maximum value. Raw (actual) values and changes from baseline will be summarized. Geometric mean and coefficient of variation will be presented for PK parameters as appropriate. Baseline is defined below.
- For categorical outcomes: counts and percentages. Summaries will include, but are not limited to: number and proportion of subjects with treatment-emergent AEs, and variants (e.g. AE seriousness, severity, and relationship); number and proportion of subjects with an outcome, and shift tables (categorical change from baseline). Treatment-emergent AE is defined below.

Summaries of primary and secondary outcome measures will be presented, as appropriate, by Epoch, by Epoch and time point (scheduled visit), and overall. Note that HYQVIA is administered subcutaneously in Epoch 1 (ramp-up) and Epoch 2. GAMMAGARD LIQUID is administered intravenously or subcutaneously only in Epoch 3, the 1-year follow-up period.

All data analyzed, including derived data, will be presented in subject data listings.

Definitions

TEAE (treatment-emergent adverse event): Any event not present prior to the initiation of study drug in the core study, or any AE due to a condition already present that worsens in either intensity or frequency following exposure to study drug. **Note**: Hereafter, treatment-emergent AEs are referred to simply as AEs (i.e. without "treatment-emergent").

Baseline: Last non-missing value prior to initial dose of HYQVIA.

13.4.1 Primary Outcome Measure

The primary objective of the study is to evaluate efficacy of HYQVIA, and the primary outcome measure is the rate of acute serious bacterial infection, defined as the mean number of acute serious bacterial infections per subject per year . Number of infections will be counted from start of initial dose of HYQVIA (start of Epoch 1) through end of Epoch 2. HYQVIA is administered in Epoch 1 and Epoch 2, and GAMMAGARD LIQUID only in Epoch 3.

The primary analysis of the primary outcome measure will be based on a Poisson model (details below), accounting for the length of the observation periods per subject. No imputation will be made for missing data, if any. The Full Analysis Set will be used. The null hypothesis of an acute serious bacterial infection rate greater or equal 1.0 ($H_0 \geq 1.0$) will be tested against the alternative hypothesis of less than 1.0 ($H_1 < 1.0$) at the 0.01 significance level (1-sided). The mean number of acute serious bacterial infections per subject per year and the corresponding 99% upper confidence limit will be provided. This approach is consistent with the FDA guidance, which states that a statistical demonstration of an acute serious bacterial infection rate per subject-year less than 1.0 is adequate to provide substantial evidence of efficacy. The null hypothesis is: the infection rate is greater than or equal to 1.0 per subject-year at the 0.01 level of significance or, equivalently, the upper 1-sided 99% confidence limit is less than 1.0.

A generalized linear model assuming the Poisson distribution for the number of acute serious bacterial infections, with the logarithm as link function, will be used via the SAS procedure PROC GENMOD. The Poisson model will include the natural logarithm of the length of the observation period in years as an offset to account for the (possibly) different lengths of the observation periods per subject. To handle over-dispersion, the exponential distribution dispersion parameter will be assumed to be given by the deviance divided by the degrees of freedom and all statistics will be adjusted accordingly.

The null hypothesis will be rejected in favor of the alternative hypothesis if the resulting p-value is less than 0.01; equivalently, if the upper bound of the 99% confidence limit is less than 1. Efficacy of HYQVIA will be claimed if the null hypothesis is rejected.

13.4.1.1 Subgroup Analysis of Primary Outcome Measure

For exploratory analysis purposes, the primary outcome measure will be summarized by clinically meaningful subgroups: sex and age groups, in years at screening (2 to <6, 6 to <12, 12 to <16). No statistical hypothesis testing will be performed. Note: The targeted enrollment is at least six subjects in each of the three age groups.

13.4.1.2 Sensitivity Analysis of Primary Outcome Measure

The primary analysis of the primary outcome measure will be based on a Poisson model and the FAS. To assess robustness of inference from the primary analysis, the following sensitivity analyses will be performed by repeating the primary analysis as follows:

- Replacing FAS with PPS. This is, only subjects with no major protocol deviations will be included in the analysis. The primary analysis was based on FAS.
- Excluding Epoch 1 from analysis. Number of infections will be counted from start of Epoch 2 through end of Epoch 2. For the primary analysis, the number will be counted from start of Epoch 1 through end of Epoch 2.

13.4.2 Secondary Outcome Measures

13.4.2.1 Efficacy

13.4.2.1.1 Number of all infections per patient-year

The annual rate of infection under HYQVIA treatment will be computed using a Poisson model and presented as point estimate and 95% confidence interval (CI). The Poisson model will include the natural logarithm of the length of the observation period in years as an offset to account for the different lengths of the observation periods per subject and handle over-dispersion by the deviance method (as for the primary endpoint).

13.4.2.1.2 Trough levels of IgG, IgG subclasses

Trough levels of IgG total and IgG subclasses will be analyzed via descriptive statistics defined in Section 13.4.

13.4.2.1.3 Trough levels of specific antibodies to clinically relevant pathogens

Trough levels of specific antibodies to clinically relevant pathogens will be analyzed using descriptive statistics defined in Section 13.4.

13.4.2.2 Pharmacokinetics

Analysis of pharmacokinetics (PK) will use the actual observed sample drawing times, not the nominal times specified in the protocol. A deviation from the protocol-specified drawing time window will not be a reason for exclusion of an observation. However, samples with unknown drawing time and/or where the concentration could not be determined will be eliminated before the calculations.

For the PK assessment in Epoch 2, the PK parameters AUC, CL, C_{max}, C_{min}, T_{max}, and terminal half-life will be determined for IgG total.

A listing of PK blood sample collection times and derived sampling time deviations will be provided. Tabular summaries and figures of IgG concentrations and PK parameters will be summarized and presented by age group, in years (2 to <6, 6 to <12, ≥12).

To facilitate comparisons across different dosing intervals (three and four weeks), IgG exposure (AUC) will be normalized by week.

Descriptive statistics (defined in Section 13.4) will be provided, as appropriate; parameter derivations and potential exploratory analyses will be outlined in the study SAP.

Analysis of PK will be based on the PKAS, unless otherwise specified in the SAP.

13.4.2.3 Safety

Safety outcome measures are defined in Section 8.4.2.3. In addition to the per-infusion outcomes, per-subject outcomes will be assessed as appropriate.

All safety outcomes will be analyzed using descriptive statistics defined in Section 13.4. In addition, safety outcomes will be summarized in terms of subject-years as appropriate, to adjust for differences in subjects' durations in the study. All safety summaries will be based on the Safety Analysis Set. No statistical hypothesis testing will be performed.

13.4.2.4 Mode of Product Administration

Mode of production administration outcome measures are defined in Section 8.4.2.4. All outcomes will be analyzed using descriptive statistics defined in Section 13.4. In addition, outcomes will be summarized in terms of subject-years as appropriate, to adjust for differences in subjects' durations in the study.

13.4.2.5 Health-related Quality of Life

Health-related quality of life outcome measures are defined in Section 8.4.2.5. Total scores and domain scores will be calculated for each subject at each data collection time point, and analyzed using descriptive statistics defined in Section 13.4.

13.4.2.6 Treatment Preference and Satisfaction

Treatment preference and satisfaction outcome measures are defined in Section 8.4.2.6. Total scores and domain scores will be calculated, if applicable, for each subject at each data collection time point, and analyzed using descriptive statistics defined in Section 13.4.

In addition to descriptive statistics at each time point, statistical hypothesis testing will be performed, limited to 4 domains: Treatment Interferences and Therapy Setting (a Life Quality Index domain), and Convenience and Global Satisfaction (a Treatment Satisfaction and Medication Questionnaire domain). Change from baseline in each domain score at Month 36 (end of Epoch 2) will be analyzed using Wilcoxon signed rank test at significance level of 0.05, 2-sided.

Analysis details will be provided in the study SAP. In addition, the study SAP will document any modifications from the protocol-specified statistical methodology and analysis.

13.4.2.7 Healthcare Resource Utilization

Healthcare resource utilization outcome measures are defined in Section 8.4.2.7. All outcomes will be analyzed using descriptive statistics defined in Section 13.4. In addition, mean and median days off school or work, mean and median days on antibiotics, mean and median days in hospital, and mean and median number of acute physician visits will be provided along with the corresponding 95% CIs.

13.5 Planned Interim Analysis of the Study

Analysis details will be provided in the interim analysis (IA) SAP, which will be finalized prior data cut-off for interim analysis.

The primary objective of this study is to evaluate the efficacy of HYQVIA. HYQVIA is administered in Epoch 1 (ramp-up period of up to 6 weeks) and Epoch 2 (final dosing period of up to 3 years), and GAMMAGARD LIQUID is administered only in Epoch 3 (safety follow-up period of approximately 1 year).

A single, formal IA will be performed, for planned submission to regulatory authorities in support of HYQVIA label expansion to pediatric population. All of the following will apply to the IA:

- Analysis will include all efficacy, safety and other study outcome measures.
- Analysis will be performed when all subjects have completed 12 months of participation (1 year observation period) in Epoch 2.

  Definition of completed 12 months of participation: Any subject who completes 12 months in Epoch 2, or discontinues prematurely from Epoch 2, irrespective of reason for withdrawal, is considered as having completed 12 months of participation in Epoch 2.
- Statistical hypothesis testing will be performed as indicated for the final analysis.
- No early stopping of study for efficacy or futility is planned.
- Multiplicity will be adjusted.

  For the primary analysis of the primary outcome measure, the null hypothesis of an acute serious bacterial infection rate greater than or equal to 1.0 ($H_0 \geq 1.0$) will be tested against the alternative hypothesis of less than 1.0 ($H_1 < 1.0$), at the interim analysis and at the final analysis. While no early stopping of study is planned, the Lan-DeMets alpha spending function approach will be used to preserve the overall type 1 error.
- Analysis results will be reported in an interim clinical study report.

The final analysis of all study data will be performed after database lock. Details will be provided in the final analysis SAP, which will be finalized prior to end of study.

In addition to the IA, the safety of HYQVIA in study subjects will be monitored by an Internal Safety Monitoring Committee (ISMC) comprising of individuals who have product experience and substantial expertise in the review and evaluation of safety data generated from study participants within Immunology and in the monitoring subject safety during study. Safety and safety-supported data will be provided in the ISMC. Details and procedural information will be provided in the ISMC Charter.

13.6 Statistical Analysis Plan Deviations

Any deviations from the analyses planned in this protocol will be documented in the study SAP, and changes in analysis after the original SAP is approved will be documented in an SAP amendment or in the Clinical Study Report, as appropriate.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored by an internal safety monitoring committee (ISMC).

The ISMC is a group of individuals with pertinent expertise within the sponsor that reviews on a regular basis accumulating data from an ongoing clinical study.

For this study, the ISMC will be composed of appropriate sponsor representatives from the relevant functions (e.g., Global Drug Safety, Clinical Research, Medical Affairs, and Clinical Development) with expertise/specialization in PIDD clinical care and research. The ISMC may recommend to stop a trial if it finds toxicities or if treatment is proven to be not beneficial.

15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within one calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, ICF, any promotional material/advertisements, and any other written information will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The Investigational Brochure will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval.

16.3 Informed Consent

Investigators will choose patients for participation considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an ICF before entering into the study according to national and local applicable regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients enrolled in the study. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited. The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If eCRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

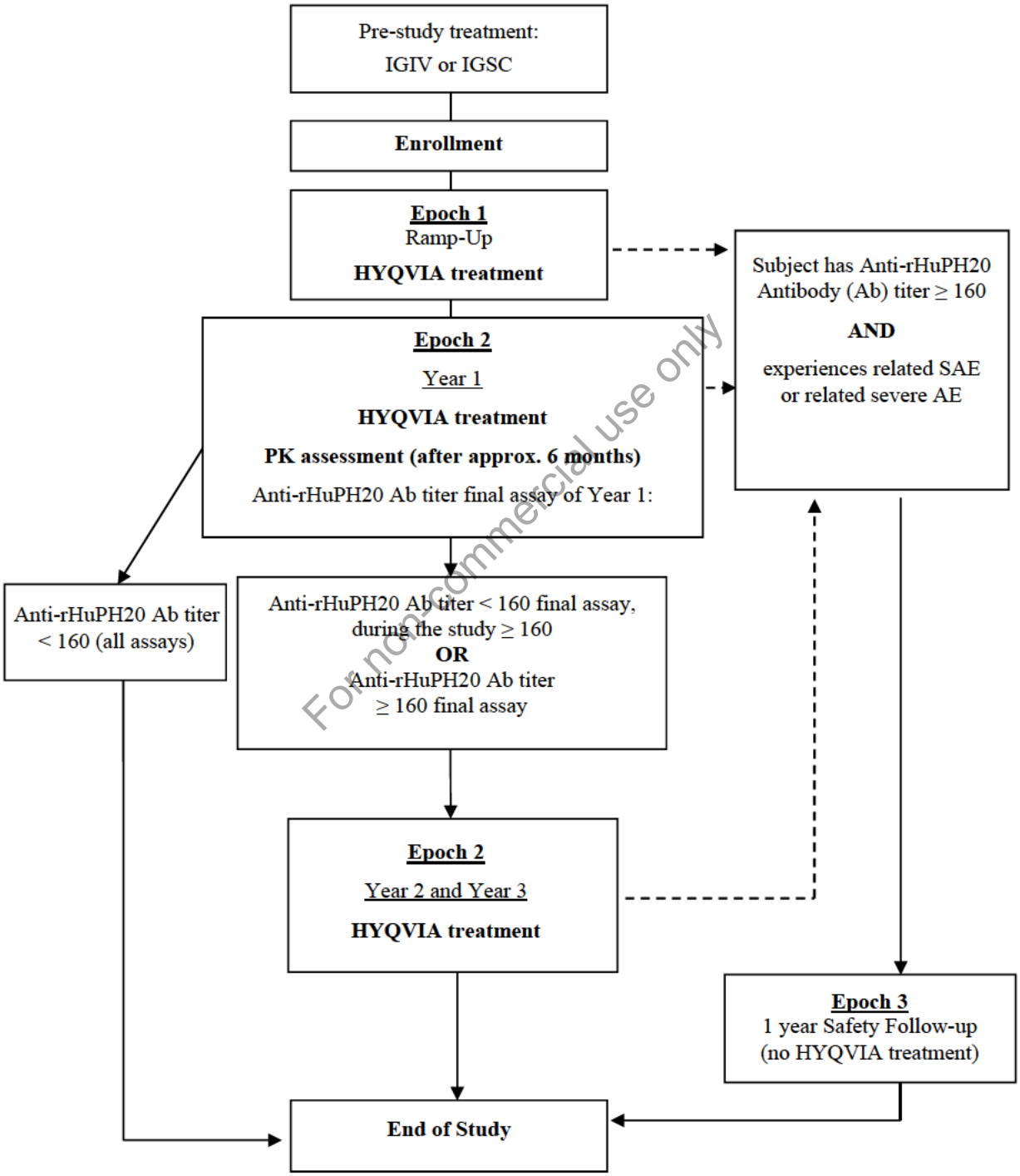
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Clinical Study 161503



20.2 Schedule of Study Procedures and Assessments

Table 3
STUDY EPOCH 1 – Ramp Up
Schedule of Study Procedures and Assessments

Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	**Screening/ Enrollment**	**First Infusion: Baseline**	**Treatment Visit in Study Epoch 1 (Visit +/- 1 Day)**	
			Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for three-Week Treatment Intervals) [c]	**Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to four-Week Treatment Intervals) [d]**
Location	Site	Site	Site	Site
Informed Consent [a]	x			
Eligibility Criteria	x			
Infusion		x	x	x
Follow-up call after infusion [e]		x	x	x
Medical History	x			
Concomitant Medications	x	x	x	x
Non-drug Therapies	x	x	x	x
Physical Exam	x	x	x	x
Adverse Events		x	x	x
Laboratories – see Lab Table [b]	x	x		
Vital Signs	x	x	x	x
HRQoL (PedsQL, EQ-5D)		x		
Treatment Preference and Satisfaction Questionnaires: LQI and TSQM-9 only		x [f]		

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[a] Occurs prior to any study-specific procedure.

[b] For laboratory assessments, see Supplement 20.3

[c] For subjects planning for three-week intervals: The first infusion in Epoch 2 will be given two weeks after the second infusion (Week 1) in Epoch 1. See also Section 8.7.2.1

[d] For subjects planning for four-week intervals: The first infusion in Epoch 2 will be given three weeks after the third infusion (Week 3) in Epoch 1. See also Section 8.7.2.1

[e] The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion (including home infusions) during Epoch 1 and 2 (see Section 8.2)

[f] At baseline, only LQI and TSQM-9 will be done. Treatment Preference Questionnaire will not be administered.

Table 4
STUDY EPOCH 2 – Year 1
Schedule of Study Procedures and Assessments

Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Month 0[g]	Visit in Study Epoch 2[g] - (Visit +/- 2 Weeks)				
		Month 3	Month 6	Month 9	Month 12[a]	Study Completion/ Termination Visit (at Next Infusion), if Applicable[h]
Location	Site	Site	Site	Site	Site	Site
Informed Consent						
Infusion [f]	x	x	x	x	x	
Follow-up call after infusion [b]	x	x	x	x	x	
Concomitant Medications	x	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x	x
Physical Exam	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x
Laboratories [i]	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x
HRQoL (PedsQL, EQ-5D)					x	(x)[d]
Treatment Preference and Satisfaction Questionnaires [c] (LQI, TSQM-9, Treatment Preference Questionnaire)					x	(x)[d]
PK assessment [e]			x			

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[a] Further (additional) infusions may be administered after the 12 months visit until anti-rHuPH20-antibody results become available to determine the subject´s continuation in the study. AEs, concomitant medications, and non-drug therapies will continue to be recorded until End of Study or continuation of Epoch 2 dependent on antibody assay result.

[b] The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion (including home infusions) during Epoch 1 and 2 (see Section 8.2)

[c] All Treatment Preference and Satisfaction Questionnaires, including LQI, TSQM-9 and Treatment Preference Questionnaire as described in Section 10.3.1 and Section 11.3 will be applied.

[d] All subjects will complete assessments at the Month 12 visit. Only subjects who prematurely exit the study will complete the questionnaires at the study termination visit. Refer to Section 10.3.1.

[e] For details of PK assessments refer to Section 8.2.2.2 and Section 10.3.2.

[f] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule

[g] Site Visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

[h] In case a subject moves to Study Epoch 3, he/she will have the Study Completion/Termination Visit at the end of Epoch 3.

[i] For laboratory assessments, see Supplement 20.3

Table 5
STUDY EPOCH 2 – Year 2 and Year 3
Schedule of Study Procedures and Assessments

Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	**Visit in Study Epoch 2[e] - (Visit +/- 2 Weeks)**							
	Month 15	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**	**Month 36/ Study Completion/ Termination Visit, if Applicable[a]**
Location	Site	Site	Site	Site	Site	Site	Site	Site
Infusion [d]	x	x	x	x	x	x	x	
Follow-up call after infusion [b]	x	x	x	x	x	x	x	
Concomitant Medications	x	x	x	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x	x	x	x
Physical Exam	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x
Laboratories [f]	x	x	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x	x	x
HRQoL (PedsQL, EQ-5D) [c]				x				x
Treatment Preference and Satisfaction Questionnaires[c] (LQI, TSQM-9, Treatment Preference Questionnaire)				x				x

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[a] In case a subject moves to Study Epoch 3, he/she will have the Study Completion/Termination Visit at the end of Epoch 3.

[b] The investigator/designee will contact the subject 3-5 days after completion of each HYQVIA infusion (including home infusions) during Epoch 1 and 2 (see Section 8.2).

[c] Refer to Section 10.3.2 and Section 11.3. Subjects who prematurely exit the study will complete assessments at the Study Termination Visit.

[d] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.

[e] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

[f] For laboratory assessments, see Supplement 20.3

Table 6
STUDY EPOCH 3
Schedule of Study Procedures and Assessments

Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	Month 0	Visit in Study Epoch 3[f] (Visit +/- 2 Weeks)			
		Month 3	Month 6	Months 9	Month 12/ Study Completion/ Termination Visit[a]
Location	Site	Site	Site	Site	Site
Infusion [b, e]	x	x	x	x	
Concomitant Medications	x	x	x	x	x
Non-drug Therapies	x	x	x	x	x
Physical Exam	x	x	x	x	x
Adverse Events	x	x	x	x	x
Laboratories [c]	x	x	x	x	x
Vital Signs	x	x	x	x	x
HRQoL questionnaires (PedsQL, EQ-5D) [d]	x				x

[a] Includes cases of withdrawal or discontinuation.

[b] Follow-up calls by the investigator/designee will not be required following infusion with GAMMAGARD LIQUID

[c] For laboratory assessments, see Supplement 20.3.

[d] Treatment Satisfaction Questionnaires (Treatment Preference Questionnaire, TSQM 9 Assessment) will not be done in Epoch 3.

[e] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule

[f] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

20.3 Clinical Laboratory Assessments

Table 7
STUDY EPOCH 1 – Ramp Up
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	**Screening/ Enrollment**	**First Infusion: Baseline** [a]	**Treatment Visit in Study Epoch 1 (Visit +/- 1 Day)**	
			Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for three-Week Treatment Intervals)	**Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to four-Week Treatment Intervals)**
Location	Site	Site	Site	Site
Hematology	x			
Clinical Chemistry	x			
Urinalysis	x			
Pregnancy Test in females of childbearing potential – Urine	x			
Viral Pathogen Serology	x			
Hemolysis Test				
Specific Antibody Tests		x		
IgG Trough Levels and IgG Subclasses		x		
Antibodies to rHuPH20		x		
Retention Samples [b]		x		

[a] See Section 12.7

[b] Approximately 1 mL serum will be taken and stored frozen at -70°C or below at the central laboratory in the event further safety testing is needed.

Table 8
STUDY EPOCH 2 – Year 1
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	**Month 0**	**Visit in Study Epoch 2[c] (Visit +/- 2 Weeks)**				
		Month 3	**Month 6**	**Month 9**	**Month 12**	**Study Completion/ Termination Visit (at Next Infusion), if Applicable**
Location	Site	Site	Site	Site	Site	Site
Hematology	x		x		x	
Clinical Chemistry	x		x		x	
Urinalysis	x		x		x	
Pregnancy Test in females of childbearing potential– Urine						x
Viral Pathogen Serology						x
Hemolysis Test [b]	x				x	
Specific Antibody Tests						x
IgG Trough Levels and IgG Subclasses	x		x		x	
Antibodies to rHuPH20	x	x	x	x	x	
PK assessment [a]			x			

[a] For details of PK assessments refer to Section 8.2.2.2 and Section 10.3.2.

[b] If there is a reduction in Hgb of 2 g/dL or more compared to baseline Hgb, hemolysis tests should be repeated within 72 hours. Also, an unscheduled hemolytic panel may be performed if hemolytic anemia is suspected. If clinical hematology/chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once. For details see Section 12.7.4.

[c] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

Table 9
STUDY EPOCH 2 – Year 2 and Year 3
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	**Visit in Study Epoch 2[c] (Visit +/- 2 Weeks)**							
	Month 15	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**	**Month 36/ Study Completion/ Termination Visit, if Applicable [a]**
Location	Site	Site	Site	Site	Site	Site	Site	Site
Hematology		x		x		x		x
Clinical Chemistry		x		x		x		x
Urinalysis		x		x		x		x
Pregnancy Test in females of childbearing potential – Urine								x
Viral Pathogen Serology								x
Hemolysis Test [b]				x				
Specific Antibody Tests				x				x
IgG Trough Levels and IgG Subclasses		x		x		x		x
Antibodies to rHuPH20	x	x	x	x	x	x	x	x

[a] In case a subject moves to Study Epoch 3, he/she will have the Study Completion/Termination Visit at the end of Epoch 3.

[b] If there is a reduction in Hgb of 2 g/dL or more compared to baseline Hgb, hemolysis tests should be repeated within 72 hours. Also, an unscheduled hemolytic panel may be performed if hemolytic anemia is suspected. If clinical hematology/chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once. For details see Section 12.7.4.

[c] Site Visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

Table 10
STUDY EPOCH 3
Clinical Laboratory Assessments

Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise	**Month 0**	**Visit in Study Epoch 3[b] (Visit +/- 2 Weeks)**			
		Month 3	**Month 6**	**Months 9**	**Month 12/ Study Completion/ Termination Visit**
Location	Site	Site	Site	Site	Site
Hematology	x		x		x
Clinical Chemistry	x		x		x
Urinalysis	x		x		x
Pregnancy Test in females of childbearing potential – Urine					x
Viral Pathogen Serology					x
Hemolysis Test[a]			x		
Specific Antibody Tests					x
IgG Trough Levels and IgG Subclasses	x		x		x
Antibodies to rHuPH20	x	x	x	x	x

[a] If there is a reduction in Hgb of 2 g/dL or more compared to baseline Hgb, hemolysis tests should be repeated within 72 hours. Also, an unscheduled hemolytic panel may be performed if hemolytic anemia is suspected. If clinical hematology/chemistry testing coincides with hemolysis tests, overlapping tests need to be performed only once. For details see Section 12.7.4.

[b] Site visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)

20.4 Toxicity Grading Scale for Laboratory Values

Table 11
Grading of Laboratory Parameters

Analyte	Direction	WNL is Grade 0	No Grade 1	Units	Grade 0[a]		Grade 1[a]		Grade 2[a]		Grade 3[a]		Grade 4[a]		Source
					Low	High	Low	High	Low	High	Low	High	Low	High	
ALP	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
ALT	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
AST	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
LDH	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	N/A
BUN	Increase	NO	NO	ULN	0.0	1.4	1.5	2.5	2.6	5.0	5.1	10	10.1	.	ECOG
Hemoglobin	Decrease	YES	NO	g/dL	.	.	10.0.	Normal	8.0	9.9	6.5	7.9	0.0	6.4	ECOG
Lymphocytes	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Neutrophils	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Platelet Count	Decrease	YES	NO	x10^3/uL	.	.	75.0	Normal	50.0	74.9	25	49.9	0.0	24.9	ECOG
Potassium	Decrease	NO	NO	mmol/L	3.5	.	3.0	3.4	2.5	2.9	2.0	2.4	0.0	1.9	WHO
Potassium	Increase	NO	NO	mmol/L	0.0	5.5	5.6	6.0	6.1	6.5	6.6	7.0	7.1	.	WHO
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	1.4	1.5	3.0	3.1	6.0	6.1	.	ECOG
Sodium	Decrease	NO	NO	mmol/L	136	.	130	135	123	129	116	122	0.0	115	WHO
Sodium	Increase	NO	NO	mmol/L	0.0	145	146	150	151	157	158	165	166	.	WHO

Table 11
Grading of Laboratory Parameters

Analyte	Direction	WNL is Grade 0	No Grade 1	Units	Grade 0[a]		Grade 1[a]		Grade 2[a]		Grade 3[a]		Grade 4[a]		Source
					Low	High	Low	High	Low	High	Low	High	Low	High	
Serum Total Bilirubin	Increase	YES	YES	ULN	.	.	.	.	.	1.4	1.5	3.0	3.1	.	ECOG
WBC	Decrease	NO	NO	x10^3/uL	4.0	.	3.0	3.9	2.0	2.9	1.0	1.9	0.0	0.9	ECOG

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; N/A=not applicable; ULN=upper limit of normal; WBC=white blood cell; WHO=World Health Organization; WNL=within normal limits.

[a] Grade refers to severity: one = mild, two = moderate, three = severe, four = life-threatening or disabling, and five (not shown in the table) = death. Grading scale criteria taken from ECOG (Oken et al., 1982) and WHO (World Health Organization, 2003) guidelines, with the exception of LDH that uses the same thresholds as defined for ALT and AST.

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22. SUMMARY OF CHANGES

Protocol 161503: Amendment 2: 2019 MAR 25

Replaces: Amendment 1: 2017 JUL 20

In this section, changes from the previous version of the Protocol 161503, Amendment 1, dated 2017 JUL 20, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Minor grammatical, editorial and/or administrative changes have been made.
   Rationale for Change: To improve the readability and/or clarity of the protocol.

2. **Title Page**
   Description of Change: The address of the US Sponsor and the format of the cover page have changed.
   Rationale for Change: Administrative. Adjustment to Shire template.

3. **Protocol Signature Page**
   Description of Change: The format and location of the investigator and sponsor signature pages was changed.
   Rationale for Change: Administrative. Adjustment to Shire template.

4. **Synopsis and Section 8.2.3 Epoch 3**
   Description of change: Emphasize that Epoch 3 should last approximately 1 year and the removal of " or until the anti-rHuPH20 antibody titer declines to < 2,560 for at least two consecutive measurements, whichever comes first ."
   Rationale for Change: To clarify that safety follow up and the antibody testing continue for one year, not less, for all subjects who switch to Epoch 3.

5. **Section 6.1.4 Immunoglobulin and Hyaluronidase Treatment**
   Description of Change: Addition of more recent references regarding rHuPH20.
   Purpose of Change: Update on the rHuPH20 product e.g. latest references.

6. **Section 6.3.5, 6.4.1, 9.3 12.1.2 HYQVIA Pregnancy Registry 161301**
   Description of Change: Description of the current study status, wording was updated to reflect the most recent study status, the pregnancy registry has closed enrollment.
   Rationale for Change: Update on the current study status.

7. **Section 6.3.7 HYQVIA Study 161406**
   Description of Change: Description of the current study status, wording was updated to reflect the most recent study status, the study has closed for enrollment.
   Rationale for Change: Update on the current study status.

8. **Section 6.3.8 HYQVIA Study 161504**
   Description of Change: Replacement of *Subcuvia* with *Cuvitru* in the description of Study 161504 (in Europe).
   Rationale for Change: Cuvitru is approved for pediatric patients in Europe, and is a study medication in Study 161504.

9. **Section 6.5 Compliance Statement**
   Description of Change: Update compliance statement according to the clinical trial regulations.
   Rationale for Change: Updated according to the ICH GCP R2, November 2016.

10. **Section 8.2.2.1 Treatment Epoch** 2
    Description of Change: Addition of description to allow shorter infusion intervals (e.g. 2 weeks) if preferable due to tolerability, at the discretion of the investigator, after informing the sponsor.
    Rationale for Change: Infusion intervals to allow more flexibility if needed for pediatric patients.

11. **Synopsis and Section 8.3 Duration of Study Period(s) and Subject Participation**
    Description of Change: Study status changed.
    Rationale for Change: Update on study status.

12. **Section 8.7.2.1 HYQVIA**
    Description of Change: Removal of the sentence "The full vial of rHuPH20 associated with each vial of IG, 10% should be used." and accordingly adding "*approximately*" for the dose ratio of 80 U/g IgG.
    Rationale for Change: For these pediatric subjects, the full vial will not always be needed.

13. **Section 8.7.2.1 HYQVIA**
Description of Change: Additional clarification that the mg/kg dose of each subject should remain stable during the study, and that in the event of weight gain the absolute dose (g or mg) should be increased to maintain the mg/kg dose stable. In the event of increased infections or low trough level, the mg/kg dose may be increased, after documentation is provided in the medical file.
Rationale for Change: Clarify when dose adjustments are required.

14. **Sections 10.3.1, 10.3.2, 12.6, 12.8 Study Procedures, Physical Examination and Vital Signs**
Description of Change: Addition of the wording "*Scheduled*" to study visits
Rationale for Change: Clarification of study procedures to be performed at site visits, in particular for physical examination and vital signs during site visits which are outside of the *scheduled* site visits.

15. **Section 12.7 Clinical Laboratory Parameters**
Description of Change: Text change
from: "Blood and urine collection, if appropriate, will occur within one hour before the start of the infusion procedure."
to: "Blood and urine collection, will occur pre-infusion (unless stated otherwise), and should be collected within one hour before the start of the infusion procedure, if possible."
Rationale for Change: Additional clarification that sample collection should occur pre-infusion but may be performed outside the specified time if required, to accommodate needs of young children.

16. **Section 12.7.5 Trough levels of IgG, IgG Subclasses and Specific Antibodies**
Description of Change: Addition of the text: "The IgG serum trough level at screening should be the most recent pre-study serum IgG trough level on the stable (unchanged) dose administered prior to enrollment and should not be older than six months."
Purpose for Change: To confirm the IgG trough level at study entry without additional blood sampling for the pediatric subjects .

17. **Section 13.4.2.6 Treatment Preference and Satisfaction**
Description of Change: Addition of Therapy Setting domain (a Life Quality Index domain), and Global Satisfaction questionnaire domain. And "In addition, the study SAP will document any modifications from the protocol-specified statistical methodology and analysis."
Rationale for Change: Changes to the HRQoL SAP part to include two additional domains.

18. **Section 13.4.2.7 Healthcare Resource Utilization**
Description of Change: Addition of "median"
i.e. ". .. . mean *and median* days . . . " and "… mean *and median* number …"
Rationale for Change: Additional descriptive statistics.

19. **Sections 20.2 and 20.3 Schedule of Study Procedures and Assessments Table 4, Table 5, Table 6, Table 8, Table 9, Table 10:**
Description of Change: Addition of a footnote:
"Site Visits are to occur at an infusion in the corresponding calendar month following the initial infusion in Month 0 (e.g. if Epoch 2 Year 1 first visit is January, then Month 0 is January, Month 3 is April, Month 6 is July, and so on). Site visits can occur at any time an infusion is due within the target calendar month. To calculate target dates, the calendar month is calculated with 30 days and a window of +/- 2 weeks (from the Epoch´s Month 0) is also allowed (except for Month 0)".
Rationale for Change: To clarify the guidance regarding when the scheduled visits to the study site should take place, while allowing limited flexibility in the scheduling of study site visits. Visits should occur approximately every 3 calendar months - e.g. in the 3rd, 6th etc. calendar month after month 0.

Table 7:
Description of Change: Test time point for IgG trough level and IgG subclasses is moved from screening enrollment to first infusion baseline, to be done immediately pre-infusion/baseline.
Rationale for Change: To better distribute the blood samples and to ensure a baseline IgG trough level and IgG subclasses is taken during the study.

22. SUMMARY OF CHANGES

Protocol 161503: Amendment 1 2017 JUL 20

Replaces: Original: 2016 JUL 22

In this section, changes from the previous version of the Protocol, dated 2016 JUL 22, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Minor grammatical, editorial and/or administrative changes have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. **Throughout the document**
   Description of Change: The study title and short study title were updated to include "efficacy".
   Purpose for Change: To respond to a request of the FDA to revise the study outcome measures.

3. **Title Page**
   Description of Change: The address of the US Sponsor has changed.
   Purpose for Change: Administrative.

4. **Section 1.1 Authorized Representative (Signatory)/Responsible Party; Investigator Acknowledgement Page**
   Description of Change: Name and title of the authorized representative were changed.
   Purpose for Change: Administrative.

5. **Section 3 Synopsis**
   Description of Change: Section 3. Synopsis was updated to match changes in the main body of the protocol.
   Purpose for Change: To reflect main changes made to text in the main body of the document. Changes in Sections 6 – 21are described below in detail.

   Description of Change: Study completion was updated from 2021 to 2021/2022.
   Purpose for Change: Accuracy.

6. **Section 6.1.1 HYQVIA; Section 6.1.2 GAMMAGARD LIQUID**
   Description of Change: References to the approval dates of the Prescribing Information were removed. In Section 6.1.2 text was added to explicitely reference the Prescribing Information for GAMMAGARD *in the U.S.*
   Purpose for Change: For purposes of the protocol, the latest approved version of the Prescribing Information for the U.S.A. will be applicable.

7. **Section 6.3.6 HYQVIA Study 161302**
   Description of Change: Subject recruitment was completed in December 2016. Text was updated accordingly
   Purpose for Change: Update on study status.

8. **Section 6.3.8 HYQVIA Study 161504**
   Description of Change: Study status changed from "planned" to "ongoing".
   Purpose for Change: Update on study status.

9. **Section 7. Study Purpose and Objectives**
   Description of Change: Changes as listed below.
   Purpose for Changes: To align the study purpose and objectives with the FDA´s request to revise the study outcome measures. Upon the FDA´s request to assess efficacy (measured as the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year in the intent-to-treat population) as primary endpoint, instead of number and rate per infusion (excluding infections) of related SAEs and of all severe related AEs. Tertiary outcome measures were changed to secondary.

   Section 7.1 Study Purpose:
   Description of Change: "Efficacy" was added to the description of the study purpose.
   Purpose for Change: see above

   Section 7.2 Primary Objective:
   Description of Change: "safety" was replaced by "efficacy"
   Purpose for Change: see above

Section 7.3 Secondary Objectives:
Description of Change: The description of the secondary objectives was modified to emphasize efficacy assesments; specific mention of IgG trough levels was removed.
Purpose for Change: see above

Description of Change: The tertiary objectives (formerly Section 7.4) of the study were included in secondary objectives.
Purpose for Change: see above

Description of Change: A reference to the relevant sections for details on the assessment of study objectives was added.
Purpose for Change: To enhance clarity.

10. **Section 8.1 Brief Summary**
Description of Change: "Efficacy" was added to the description of the study.
Purpose for Change: To align the study summary information with the FDA´s request to revise the study outcome measures.

11. **Section 8.2. Overall Study Design**
Description of Change: Information on testing of anti-rHuPH20 antibodies was added.
Purpose for Change: To provide specific information on the testing of neutralizing anti-rHuPH20 antibodies and characterization of anti-rHuPH20 antibodies.

Description of Change: Instructions to the investigator/designeed to follow up with the subject/caregiver after completion of each HYQVIA study infusion, and to maintain the originally planned infusion schedule, were added.
Purpose for Change: To follow up on AEs that may have occurred during or after completion of the infusion, to ensure appropriate, timely entry of data into the subject diary and to maintain a regular infusion schedule.

12. **Section 8.2.2.1 Treatment**
Description of Change: Additional information on the time point and location to perform the study completion visit in Study Epoch 2 was provided.
Purpose for Change: To clarify the time point and location of the study completion visit.

13. **8.2.2.2 Pharmacokinetic Assessment**
Description of Change: An additional blood sample should be drawn on Day 2 from subjects of 12 years of age and older. For the sample taken on Day 10, a maximum deviation of two days (previously: three) will be acceptable.
Purpose for Change: Both changes were made following a request of the FDA.

14. **Section 8.4 Outcome Measures**
Description of Change: Changes as listed below.
Purpose for Change: The below changes were made to align the study purpose and objectives with the FDA´s request to revise the study outcome measures. Upon the FDA´s request to assess efficacy (measured as the rate of acute serious bacterial infections, defined as the mean number of acute serious bacterial infections per subject per year in the intent-to-treat population) as primary endpoint, instead of number and rate per infusion (excluding infections) of related SAEs and of all severe related AEs. Tertiary outcome measures were changed to secondary.

Section 8.4.1 Primary Outcome Measure
Description of Change: The primary outcome measure was changed from safety to efficacy.
Purpose for Change: see above.

Section 8.4.2 Secondary Outcome Measures
Description of Change: The secondary outcome measures were re-grouped. Tertiary outcome measures were included in secondary. An additional assessment, LQI, was added to "Treatment Preference and Satisfaction".
Purpose for Change: see above. Secondary endpoints were re-grouped for better readability. The LQI assessment was added to obtain further QoL data from patients.

Description of Change: Tertiary outcome measures (former Section 8.4.3) were included secondary outcome measures.
Purpose for Change: see above.

15. **Section 8.6 Study Stopping rules**
Description of Change: Stopping rules were introduced to stop the study in case one death of a subject is attributed to the study drug.
Purpose for Change: The stopping rules were revised due to a request of the FDA.

16. **Section 8.7.1.3 GAMMAGARD LIQUID**
Description of Change: Information on the administration of Gammagard Liquid was moved to section 8.7.2.2 Administration, and the text changed to state that treatment will follow the GAMMAGARD LIQUID product information and the site´s standard of care.
Purpose for Change: To move administration instructions to the applicable section

17. **Section 8.7.2.1 HYQVIA**
Description of Change: Additional information regarding dosing frequency and infusion intervals during Study Epoch 1 and Epoch 2, and on dose calculation and infusion volume was provided.
Purpose for Change: To provide additional guidance on the administration of study product.

18. **Section 8.7.2.2 GAMMAGARD LIQUID**
Description of Change: A statement was added that treatment with GAMMAGARD LIQUID will follow the guidance of the product information and the site´s standard of care.
Purpose for Change: To provide additional clarification.

19. **Section 8.8 Source data**
Description of Change: Text (in italics) was added: "… Source data for this study comprise*, but are not limited to, ….*".
Purpose for Change: To widen the range of potential source data documents.

20. **Section 9.2 Exclusion criteria**
Description of Change: "…*in the opinion of the investigator"* was added to it. 16
Purpose for Change: To further define the exclusion criterion.

21. **Section 10.1. Informed Consent**
Description of Change: Text was modified to specifically describe subject enrollment.
Purpose for Change: To clarify the definition of "enrollment".

22. **Section 10.3. Screening and Study Visits**
Description of Change: A definition of screening and a description of re-screening procedures were added. The term "screening log" was replaced by "patient identification list" and it´s description.
Purpose for Change: To define screening, and to clarify screening/re-screening procedures.

Description of Change: A time limit to complete screening procedues was defined. Provisions were added for subjects to be allowed a dose of the IG administered prior to enrolment on a case-by-case basis before eligibility is fully confirmed.
Purpose for Change: To avoid study termination due to e.g., late availability of screening lab results.

23. **Sections 10.3.1 Epoch 1, 10.3.2 Epoch 2, 10.3.3 Epoch 3**

Section 10.3.1 Epoch 1
Description of Change: The Treatment Preference Questionnaire will not be completed at Baseline (Epoch 1).

Section 10.3.2 Epoch 2
Description of Change: Instructions were added to administer the HRQoL and Treatment Preference and Satisfaction questionnaires at Month 24 and Month 36, and for subjects who prematurely exit the study.

Section 10.3.2 Epoch 2
Description of Change: A statement was added that Treatment Preference and Satisfaction qustionnaires will not be done in Epoch 3.

Purpose for Changes: To provide additional information regarding the timepoints of administration of the QoL questionnaires and Treatment Preference and Satisfaction assessments.

24. **Section 10.3.2 Epoch 2 – PK assessments**
Description of Change: Time points for PK assessments were removed.
Purpose for Change: Removed for redundancy. Identical information is provided in section 8.2.2.2.

25. **Section 10.5 Subject Diary**
Description of Change: The section was revised to describe the use of a paper subject diary, instead of an electronic subject diary.
Purpose for Change: Operational change; a paper subject diary will be used in the study instead of an electronic diary.

Description of Change: The text on non-study required out-patient visits was replaced by text on hospitalizations, a bullet point on acute physician visits was added.
Purpose for Change: To accurately match Secondary Outcome Measures as in Section 8.4.2.7.

26. **Section 11.2 Assessment of Efficacy through Section 11.4 HRQoL Questionnaire**
Description of Change: Text was added that patient reported outcomes will be collected electronically. The order of the questionnaires was re-arranged. LQI was added to Section 11.3.
Purpose for Change: Clarification of data collection method. To match secondary outcome measures as described in Sections 8.4.2.5 and8.4.2.6. LQI was added to allow for the collection of additional QoL data.

27. **Section 12.1.1.2 SUSAR**
Description of Change: The definition of SUSAR was edited.
Purpose for Change: To reflect an update made to Baxalta´s standard protocol template.

28. **Section 12.1.2 Assessment of Adverse Events**
Description of Change: SAE reporting after study completion was limited to 30 days after study completion.
Purpose for Change: To limit the investigator´s responsibility to report SAEs after study completion.

29. **Section 12.4 Non-Medical Complaints**
Description of Change: The requirement to use a NMC form was deleted.
Purpose for Change: To match a change in the respective Shire procedures (SOP), and to allow for reporting to the sponsor´s designee.

30. **Section 12.7.1 Hematology and Clinical Chemistry**
Description of Change: The clinical chemistry panel was updated (new text in *italics*) to read: "*total* protein, *total* bilirubin, *serum* creatinine". AST, LDH and LDH isoenzyme measurement was added.
Purpose for Change: To accurately define tests, and to monitor for potential hemolysis.

31. **Section 12.7. Hemolysis Test**
Description of Change: LDH isoenzyme testing was added.
Purpose for Change: Consistency.

32. **Section 12.7.6 Anti-rHuPH20 Antibodies**
Description of Change: Text was changed to separately describe testing for neutralizing and for binding anti-rHuPH20 antibodies.
Purpose for Change: Clarity.

33. **Section 13. Statistics**
Description of Change: The entire section was revised.
Purpose for Change: To match the revisions made to the study outcomes as agreed with the FDA. Refer also to point 14 in this Section 22.

34. **Section 15.4 Safety Monitoring**
Description of Change: "Internal Safety Review Board (ISRB)" was updated to "Internal Safety Monitoring Committee (ISMC)"
Purpose for Change: To match with terms used in the Sponsor´s applicable standard operation procedures (SOPs) that currently undergo harmonization following Baxalta´s acquisition by Shire.

35. **Section 20.2 Schedule of Study Procedures and Assessments**
Description of Change: A deviation of ±1 day will be allowed for Treatment Visits in Study Epoch 1.
Purpose for Change: To improve compliance.

Table 3
Description of Change: A margin of ±1 day for the scheduling of treatment visits in Epoch 1 was defined.
Purpose for Change: To allow a limited amount of flexibility in the scheduling of study drug infusions, and to prevent related protocol deviations.

Tables 3, 4 and 5

Description of Change: A new line "Follow-up call after infusion" and a corresponding explanatory footnote were added.
Purpose for Change: To remind investigators/designee to perform follow-up after each HYQvia infusion.

Description of Change: The line for Questionnaires was separated into two, including 1) HRQoL and 2) Treatment Preference and Satisfaction Questionnaires. Lines will appear in the tables as applicable for the relevant time period. Footnotes with instructions on the administration of the questionnaires were added to each table.
Purpose for Change: To clarify administration time points and align with text sections of protocol.

Table 4

Description of Change: Footnotes on PK were replaced by references to the relevant sections of the protocol.
Purpose for Change: To reduce redundancy.

Tables 4, 5

Description of Change: A margin for the administration of infusions (incl. home infusions) between site visits/infusions was defined.
Purpose for Change: To allow a limited amount of flexibility in the scheduling of study drug infusions, and to prevent related protocol deviations.

Table 6

Description of Change: A footnote was added that follow-up calls by the investigator/designee will not be required after infusion with GAMMAGARD LIQUID.
Purpose for Change: To clarify follow-up requirements after infusion of IP in Epoch 3.

Description of Change: Only HRQoL will be done in Epoch 3. An explanatory footnote was added.
Purpose for Change: To clarify administration time points and align with text sections of protocol.

Description of Change: A margin for the administration of infusions between site visits/infusions was defined.
Purpose for Change: To allow a limited amount of flexibility in the scheduling of study drug infusions, and to prevent related protocol deviations

36. **Section 20.3 Clinical Laboratory Assessments**

Table 7
Description of Change: A margin of ±1 day for the scheduling of treatment visits in Epoch 1 was defined.
Purpose for Change: To allow a limited amount of flexibility in the scheduling of study drug infusions, and to prevent related protocol deviations.

Description of Change: Requirements for retention samples were specified.
Purpose for Change: To provide specific guidance on sample taking for retention samples.

Table 8
Description of Change: An additional time point for hemolysis testing was added to the Month 12 visit (Year 1/Epoch 2).
Purpose for Change: To perform additional monitoring for potential hemolysis.

Description of Change: Footnotes on PK were replaced by references to the relevant sections of the protocol.
Purpose for Change: To reduce redundancy.

Tables 8, 9, 10
Description of Change: Explanatory footnotes on hemolysis testing requirements was added to Tables 8, 9 and 10.
Purpose for Change: Hemolysis testing at Month 12 /Epoch 2 was added on request of the FDA. Footnotes were added to emphasize the importance to monitor potential hemolytic events and reference relevant text sections of the protocol.