**CLINICAL STUDY PROTOCOL**

NCT Number: NCT03116347

Study Title: Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

Study Number: 161504

Protocol Version and Date:

Original Protocol: 16-MAR-2016

Protocol Amendment 1: 07-OCT-2016

Protocol Amendment 2: 04-DEC-2019

# CLINICAL STUDY PROTOCOL

**PRODUCT: HyQvia**

**STUDY TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

**STUDY SHORT TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD subjects

**PROTOCOL IDENTIFIER: 161504**

**CLINICAL TRIAL PHASE 4**

**ORIGINAL: 2016 MAR 16**



**OTHER ID(s)**
**NCT Number:** Not Yet Available
**EudraCT Number:** Not Yet Available
**IND NUMBER:** Not Applicable


| **Study Sponsor(s):** | **Baxalta US Inc.** | **Baxalta Innovations GmbH** |
|---|---|---|
| | One Baxter Way<br>Westlake Village, CA 91362,<br>UNITED STATES | Industriestrasse 67<br>A-1221 Vienna,<br>AUSTRIA |

# 1. STUDY PERSONNEL

## 1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Clinical Development
Baxalta US Inc.

## 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 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.**

**See SAE Protocol Sections for further information and SAER form for contact information.**

**Further details are also available in the study team roster.**



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

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

## 3. SYNOPSIS

| | |
|---|---|
| **INVESTIGATIONAL PRODUCT** | |
| **Name of Investigational Product (IP)** | 1. HyQvia<br>2. KIOVIG 100 mg/ml solution for infusion<br>3. SUBCUVIA 160 g/l solution for infusion<br>(For better readability the names KIOVIG and SUBCUVIA will be used throughout the document.) |
| **Name(s) of Active Ingredient(s)** | Human Normal Immunoglobulin |
| **CLINICAL CONDITION(S)/INDICATION(S)**<br>• Primary Immunodeficiency Diseases (PIDD) | |
| **PROTOCOL ID** | 161504 |
| **PROTOCOL TITLE** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases |
| **Short Title** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD subjects |
| **STUDY PHASE** | Ph4 (post-authorization) |
| **PLANNED STUDY PERIOD** | |
| **Initiation** | 2016 |
| **Primary Completion** | 2021 |
| **Study Completion** | 2021 |
| **Duration** | Approximately five years |
| **STUDY OBJECTIVES AND PURPOSE** | |
| **Study Purpose**<br>The purpose of the study is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age <18 years) subjects with Primary Immunodeficiency Diseases (PIDD). | |
| **Primary Objective**<br>Safety of HyQvia treatment in pediatric subjects with PIDD who have received prior immunoglobulin therapy before enrollment into the study. | |
| **Secondary Objective(s)**<br>Further safety assessments (e.g. immunogenicity), tolerability, characteristic of product administration and efficacy (immunoglobulin G [IgG] trough levels) | |

| STUDY DESIGN | |
|---|---|
| **Study Type/ Classification/ Discipline** | Safety, Immunogenicity |
| **Control Type** | No control |
| **Study Indication Type** | Treatment |
| **Intervention Model** | Single-group |
| **Blinding/Masking** | Open-label |
| **Study Design** | This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate the safety, tolerability, and other parameters of subcutaneous (SC) treatment using HyQvia in approximately 40 pediatric subjects with PIDD who have received immunoglobulin therapy before enrollment into this study. Subjects will have regular anti-recombinant human hyaluronidase PH20 (rHuPH20) antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months).<br><br>**Epoch 1:** Pediatric patients with PIDD who are on non-HyQvia intravenous (IV) or SC treatment with immunoglobulin (IV-pretreated, SC pretreated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks. Subjects already treated with HyQvia (HyQvia pretreated) will be enrolled directly into Epoch 2. Epoch 1 infusions will be administered at the study site.<br><br>**Epoch 2:** The ramp-up (Epoch 1) is followed by Epoch 2 with HyQvia treatment at the following intervals. For IV-pretreated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule. For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and subject. For HyQvia pretreated 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 (see Figure 1: Study Flow Chart in Supplements). Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study termination/completion visit 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.<br><br>The first two or three infusion(s) during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions be performed at home (or equivalent site) by the subject or 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.<br><br>**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 Serious Adverse Event (SAE) or a related severe Adverse Event (AE).<br><br>Subjects in Epoch 3 will be treated with KIOVIG intravenously or SUBCUVIA subcutaneously, at the discretion of the investigator and the subject.<br><br>In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or 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 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.<br><br>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 anti-rHuPH20 antibody titer declines to <2560 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 <2560.<br><br>Infusions in Study Epoch 3 will be administered at home or at the study site.<br><br>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 for HyQvia-naïve subjects<br>Study Epoch 2 (Final dosing): Up to three years<br>Study Epoch 3 (Safety Follow-up): Up to one year<br>The maximum subject participation period is approximately four years. |

**Primary Outcome Measure**

1. Number and rate per infusion (excluding infections) of all severe related AEs
2. Number and rate per infusion (excluding infections) of related SAEs

**Secondary Outcome Measure(s)**

**Efficacy**

1. Trough levels of IgG (for Study Epoch 1 and 2)

**Safety**

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and Adverse Reactions (ARs)
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs
7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

**Mode of Product Administration** (For Study Epoch 1 and 2)

1. Infusions
   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)
3. Assessment of Treatment Preference Questionnaire
4. Assessment of Treatment Satisfaction with Medication Questionnaire: TSQM-9
5. Assessment of Health-related Quality of Life Questionnaires: Peds-QL, EQ-5D

**Tertiary Outcome Measure(s)**

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

**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**: injectable

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

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

Example for IgG dosing:

| Pre-Study | | Epoch 1 (Ramp-Up) | | | Epoch 2 (Final Dose) |
|---|---|---|---|---|---|
| **Admin. Route** | **Dose** | **First Infusion at Baseline: 1-Week Dose** | **Second Infusion at Week 1: 2-Week Dose** | **Third Infusion at Week 3: 3-Week Dose** | |
| IV | 0.6 g/kg every 3 weeks | 0.2 g/kg | 0.4 g/kg | - | 0.6 g/kg every 3 weeks |
| IV | 0.6 g/kg every 4 weeks | 0.15 g/kg | 0.3 g/kg | 0.45 g/kg | 0.6 g/kg every 4 weeks |
| SC | 0.1 g/kg every week | 0.1 g/kg | 0.2 g/kg | - | 0.3 g/kg every 3 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 4 weeks |

**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):<br>• For subjects with a BW of < 40 kg: 10 ml/h/site (at start) to 160 ml/h/site (maximum, if tolerated)<br>• For subjects with a BW of ≥ 40 kg: 10 ml/h/site (at start) to 300 ml/h/site (maximum, if tolerated)<br>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.<br><br>**2. KIOVIG**<br>Subjects may be treated with KIOVIG in **Study Epoch 3** (Safety Follow-up).<br>**Dosage form**: injectable<br>**Mode of Administration:** intravenous<br>The infusion rate and infusion volume per site will follow the suggestions of the KIOVIG product information.<br>**Dosage frequency**: Once every three or four weeks<br>**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch<br><br>**3. SUBCUVIA**<br>Subjects may be treated with SUBCUVIA in **Study Epoch 3** (Safety Follow-up).<br>**Dosage form**: injectable<br>**Mode of Administration:** subcutaneous<br>The infusion rate and infusion volume per site will follow the suggestions of the SUBCUVIA product information.<br>**Dosage frequency**: Once every week or biweekly<br>**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch. |
| **SUBJECT SELECTION** | |
| **Targeted Accrual** | Sample size: Approximately 40 pediatric subjects already on IgG treatment pre-study will be enrolled. The study will enroll approximately six subjects two to less than six years of age, 12 subjects six to <12 years of age, 22 subjects 12 to <18 years of age. The study will be conducted in the European Economic Area.<br><br>Study sites: Approximately 20 |
| **Number of Groups/ Arms/Cohorts** | 1 |

**Inclusion Criteria**

1. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving a defect in antibody formation and requiring gammaglobulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Scientific Committee 2015 [1] and by diagnostic criteria according to Conley et al.[2] prior to enrollment. The diagnosis must be confirmed by the sponsor Medical Director prior to first treatment with investigational product (IP) in the study.
2. Subject is at least two and below 18 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.

Subject/legally authorized representative is willing and able to comply with the requirements of the protocol.

**Exclusion Criteria**

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 amino transferase (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/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 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.

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 the study is approximately 40 pediatric subjects.

**Planned Statistical Analysis**

Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. All SAEs and non-serious AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. All analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

## 4. TABLE OF CONTENTS

***Tables***

***Figures***

## 5. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADR | Adverse drug reaction (i.e., related AE) |
| AE | Adverse event |
| AR | Adverse reaction |
| AIDS | Acquired immune deficiency syndrome |
| ALP | Alkaline phosphatase |
| ALT | Alanine amino transferase (SGPT) |
| ANC | Absolute neutrophil count |
| AST | Aspartate amino transferase (SGOT) |
| AUC | Area under the curve |
| B19V | Parvovirus B19 |
| BUN | Blood urea nitrogen |
| BW | Body weight |
| CHMP | Committee for Medicinal Products for Human Use |
| CLL | Chronic lymphocytic leukemia |
| CI | Confidence interval |
| $C_{max}$ | Maximum concentration |
| $C_{min}$ | Minimum concentration |
| CRF | Case report form |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| CXR | Chest x-ray |
| EC | Ethics committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EPR | Electronic Patient Reported |
| EU | European Union |
| Fc | Crystallizable region of antibody |
| FDA | Food and Drug Administration |

| Abbreviation | Definition |
|---|---|
| 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 |
| ICH | International Council for Harmonization |
| IgA | Immunoglobulin A |
| IGIV, 10% | Immune Globulin Intravenous (Human) GAMMAGARD LIQUID/KIOVIG |
| IgG | Immunoglobulin G |
| IGI | Immunoglobulin |
| IGIV | Immune globulin intravenous (human) |
| IGSC | Immune globulin subcutaneous (human) |
| IP | Investigational Product |
| ISG | Immune serum globulin |
| ISRB | Internal safety review board |
| ITP | Idiopathic thrombocytopenic purpura |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | Minute(s) |
| mL | Milliliter(s) |
| MM | Multiple myeloma |
| MMN | Multi-focal motor neuropathy |
| MRI | Magnetic resonance imaging |

| Abbreviation | Definition |
|---|---|
| NMC | Non-medical complaint |
| $PaCO_2$ | Partial pressure (tension) of carbon dioxide |
| PASS | Post-authorization safety study |
| PCR | Polymerase chain reaction |
| PIDD | Primary immunodeficiency disease |
| PK | Pharmacokinetic(s) |
| RBC | Red blood cell (count) |
| rHuPH20 | Recombinant human hyaluronidase PH20<br>(active ingredient in the U.S. marketed product HYLENEX) |
| SAP | Statistical analysis plan |
| S/D | Solvent/detergent |
| SAE | Serious adverse event |
| SAER | Serious adverse event report |
| SC | Subcutaneous |
| SCIG | Subcutaneous immunoglobulin G |
| SIC | Subject identification code |
| SmPC | Summary of product characteristics |
| $T_{max}$ | Time to maximum concentration |
| TRALI | Transfusion related acute lung injury |
| ULN | Upper limit of normal |
| VASBI | Validated acute serious bacterial infection |
| WBC | White blood cell (count) |

## 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.[3;4] 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.[5;6;7;8] Immunoglobulins are also effective in the management of autoimmune disorders, such as idiopathic thrombocytopenic purpura (ITP) [9;10;11], Kawasaki syndrome [12;13], and multi-focal motor neuropathy (MMN).[14]



### 6.1 Description of Investigational Product

#### 6.1.1 HyQvia

HyQvia 100 mg/ml solution for infusion for subcutaneous (SC) use is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20).

The IG 10% component provides the therapeutic effect of this medicinal product. The rHuPH20 facilitates the dispersion and absorption of IG 10%.

Human normal immunoglobulin contains mainly IgG with a broad spectrum of opsonizing and neutralizing antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1,000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range.

rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan. Hyaluronan is a polysaccharide found in the intercellular matrix of connective tissue and of certain specialized tissues. It is degraded by naturally occurring hyaluronidase and has a very fast natural turnover in SC tissue.

As a permeation enhancer, rHuPH20 temporarily accelerates the break-down of hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates more rapid dispersion and absorption and improved bioavailability of the IG 10%.

HyQvia therapeutic indications include:

- Replacement therapy in adults (≥18 years) with primary immunodeficiency syndromes such as:
    a. congenital agammaglobulinaemia and hypogammaglobulinaemia
    b. common variable immunodeficiency
    c. severe combined immunodeficiency
    d. IgG subclass deficiencies with recurrent infections
- Replacement therapy in adults (≥18 years) with myeloma or CLL with severe secondary hypogammaglobulinaemia and recurrent infections

### 6.1.2 KIOVIG 100 mg/ml solution for infusion and SUBCUVIA 160 g/l solution for injection

**KIOVIG** is a liquid unmodified IgG preparation with an osmolality that is similar to physiologic osmolality and contains no added sugars, sodium, or preservatives. The manufacturing process includes three independent, validated viral inactivation or removal steps: solvent/detergent (S/D) treatment, nanofiltration and incubation at a low pH and elevated temperature. The product contains immunoglobulins with intact Fc regions (crystallizable region of the antibody) in isotonic solution including glycine for stabilization. KIOVIG is a ready-to-use 10% liquid preparation.



A detailed description of KIOVIG is provided in the Summary of Product Characteristics (SmPC) and the Investigator's Brochure for Immune Globulin Infusion (Human), 10% (IGI 10%) for intravenous (IV) and SC administration.

**SUBCUVIA** is a 16% ready to use solution of polyvalent human normal immunoglobulin for SC infusion in patients with primary and secondary immune deficiency syndromes.

Further information is provided in the respective SmPC.

### 6.1.3 Immunoglobulin Treatment

Defective antibody formation, 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 agammaglobulinemia, selective IgG subclass deficiency, common variable immunodeficiency, 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.[1]

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.[15] MM is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, hypercalcemia but also recurrent infections.[16]



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 US, 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 US are licensed for IV administration; though, in December 2005, the first SC preparation was licensed by ZLB-Behring.[17,18] 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.[19,20,21,22,23]

All of the gammaglobulin preparations licensed for SC use are formulated at 10-20%. 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, SC IgG leads to higher trough serum IgG concentrations than monthly IV infusions (at the same monthly dose).[24,25]

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.[26]

Immunoglobulin administered intravenously is immediately available in the blood, and slowly equilibrates to the extra-vascular compartment over three to five days.[27] 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 IM was 100% when compared to IV.[28] 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.[18,29] Accordingly, it is recommended that the dose of SC immunoglobulin be adjusted to 137-153% of the IV dose to provide a comparable IgG exposure.[18;30] Despite the technical difficulties of comparing AUC for two different routes and frequencies of administration, studies of intradermally administered immunoglobulin in rats[i] 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.[31]

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) thus 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.



[i] Halozyme Report Number R1005-0551.

### 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 sixty years to temporarily depolymerize the hyaluronan and facilitate SC infusions of fluids for re-hydration.[32] rHuPH20 is a 63 kd protein genetically engineered from the sequence of the naturally occurring human protein. It temporarily depolymerizes the 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 h, leaving no observable changes[ii]. Weekly infusions into cynomolgus monkeys in doses up to two mg/kg (> 1,000 fold higher than the HyQvia dose in humans) did not lead to adverse reactions during a follow-up of 39 weeks[iii]. Infusion of rHuPH20 improved 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.[33] 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 animals and thus, human studies were required. rHuPH20 can facilitate absorption of small molecules such as insulin and morphine in humans; in phase 1 trials rHuPH20 improved bioavailability of proteins such as infliximab[iv] and enabled drug dispensation and absorption at the administration site of rituximab and trastuzumab.[34] 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]. No positive skin reactions were observed when rHuPH20 was administered to 100 healthy volunteers in a skin allergy clinical trial.[35] 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 have declined during the long-term extension study despite continued exposure to rHuPH20.

---

ii Halozyme Report R08014.
iii Halozyme Report R09050.
iv Halozyme Report R05109.
v Halozyme Report Number 10059.

None of these samples contained neutralizing antibodies. No local or systemic reactions were attributed to the presence of 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, 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%.[36] 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.



### 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 IGIV 10% in a single SC site with good tolerability.[37] An infusion was defined as having been tolerated if it caused no more than mild local adverse drug reactions (ADRs) (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 comparison of PKparameters 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, multi-center, Phase III study.[38] 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/g IgG rHuPH20 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.

[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.

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 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. A comparison of data from the present 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 after a delay of approximately three to five days.

Data from the clinical trial of HyQvia show that serum IgG trough levels 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 PKs of HyQvia was evaluated in this Phase 3 efficacy and safety study in 60 patients with PIDD aged 12 years and older. The pharmacokinetic results are presented in the table 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) 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 have 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 01 August of 2012, the FDA requested administration of rHuPH20 drug product in all ongoing HyQvia clinical studies in the US to be suspended and patients were switched to treatment with KIOVIG/GAMMAGARD LIQUID only (Protocol Amendment 5). Subjects were treated with conventional IGIV or 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), seven subjects in the range of 12 to <16 years and four subjects in the range of two to <12 years. The median age was 43.0 years. Of the 66 subjects who met all inclusion/exclusion criteria, 50 (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: 60-729 days) and a mean (± 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: 5-300) and the median maximum rate of infusion achieved was 300 mL/hr (range: 10-350). Across all age groups and infusion intervals, a median number of 1.09 infusions/month (range: 0.3-2.1) was administered. IGSC, 10% with rHuPH20 treatment required a median number of 1.58 infusion sites/month (range 0.3-4.2) 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 (22.7%) subjects and 7/66 (10.6%) subjects most frequently 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), 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, 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 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 US study was a Phase 2/3, prospective, non-controlled, multicenter study to evaluate tolerability and safety and other parameters of SC treatment using Immune Globulin Infusion (Human), 10% (IGI, 10%. IGI, 10% is the same product as IGIV 10% licensed in the 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-pretreated subjects: every three weeks or four weeks, depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects: every three weeks or four weeks, at the discretion of investigator and subject

The rHuPH20 administration was discontinued as of 01 August 2012 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 04 January 2013.

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, 24 completed Epoch 3. Thus, 25 subjects including the one subject who completed Epoch 2 without ever reaching Epoch 3 completed the study.

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: 8.28-10.25]) were comparable to the levels measured at screening (geometric mean: 10.53 g/L [95% CI: 9.46-11.73]).

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.



Median number of infusions per month: 2.90 in Epoch 1; 1.09 in Epoch 2. Median number of infusion sites (needle sticks) per infusion/month: 2.90 in Epoch 1; 1.12 in Epoch 2. Median duration of infusion: less than two hours. Median maximum infusion rate: 240mL/h in Epoch 1; 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: 0.186-0.522) 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 (Immune Globulin (Human) 10% with rHuPH20**

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 and 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, North America, and other countries where the product is licensed, as needed. 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 ever treated with HyQvia will be enrolled. In the European Union (EU) the therapeutic indications for HyQvia are PIDD, CLL, and myeloma. In the USA, HyQvia is licensed for the treatment of PIDD. Although the target population consists mainly of women treated for the approved indications in the respective country, any woman who becomes pregnant after being exposed to HyQvia will be encouraged to participate in the registry.

Visits to the investigator (for example immunologist) and all other medical care will be performed as is standard for the site and for the subject's healthcare.

However, the pregnant subject will be 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 becomes aware of the pregnancy, she should inform the treating physician. According to her treatment, the subject enters the study in one of the following two Study Arms.

Study Arm 1 (Alternative Product Arm): Subjects who stop treatment with HyQvia will be followed in Study Arm 1. The treating physician of the pregnant woman prescribes a licensed human normal immunoglobulin other than HyQvia for IV or SC infusion or an alternative treatment, at his/her discretion.

Study Arm 2 (HyQvia Arm): Subjects who continue treatment with HyQvia according to their treatment regimen will be followed in Study Arm 2.

The overall duration of the study is approximately six years from study initiation (Registry ready to enroll) to study completion (i.e., end data collection). The enrollment period is expected to be three years. The participation period for the pregnant woman is 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.



### 6.3.6 HyQvia PASS 161302

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

This is a non-interventional, prospective, uncontrolled, multi-center, open-label, post-authorization safety study (PASS) 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 are 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, however, 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 recruitment period is expected to be approximately three years. Enrollment started in Q3 2014. 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. It is anticipated that approximately 80 to 120 subjects will be eligible for enrollment in this study.



### 6.3.7 HyQvia Study 161406

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

This prospective, uncontrolled, multi-center, 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.

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.

## 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), 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 IB for Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20) as well as Prescribing Information for HyQvia and SmPC 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 of patients 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. Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study.

#### 6.4.1.1 Pregnancy, Breast Feeding, Fertility

Subcutaneous immunoglobulin G (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 rHuPH20in mice and rabbits. No adverse effects on pregnancy and fetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20were transferred to offspring in utero. The effects of antibodies to the rHuPH20component 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 IG 10% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 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 and recommended to participate in the HyQvia Pregnancy Registry (Study 161301), if available in the respective country.

See Section 6.4.2 for the known risks associated with IGI, 10%.

### 6.4.2 KIOVIG

IGI, 10% administered via IV treatment (KIOVIG) is efficacious and safe in the particular fields of therapeutic use and approved indications, i.e., PIDD, ITP and MMN, as demonstrated in the clinical development program for KIOVIG. Please see the investigator's brochure for Immune Globulin Infusion (Human), 10% Solution (IGI, 10%) for further information, as well as SmPC for KIOVIG.

Serious ARs (defined as SAEs occurring during or within 72 hours of infusion or any casually related SAE occurring within the study period) which occurred in the clinical trials of KIOVIG were aseptic meningitis, pulmonary embolism, and blurred vision.

The most common ARs observed in ≥ 5% of patients were:

- PIDD, IV administration: 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.
- PIDD, SC administration: infusion site (local) event, 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, IV administration: headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

Rare but serious events may occur with IGI products, including hypersensitivity, thrombosis, renal dysfunction/failure, hyperproteinemia, increased serum viscosity, and hyponatremia hemolysis, hemolysis, transfusion related acute lung injury (TRALI), and aseptic meningitis syndrome.



Thrombosis may occur with immune globulin products, including IGI, 10%. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients receiving immune globulin intravenous (IGIV) products including IGI, 10%. Renal dysfunction and acute failure occur more commonly with IGIV products containing sucrose. IGI, 10% does not contain sucrose.

IGI, 10% contains blood group antibodies (isoagglutinins) that may cause hemolysis. Delayed hemolytic anemia can develop subsequent to IGI, 10% therapy due to enhanced red blood cell (RBC) sequestration. Acute hemolysis, consistent with intravascular hemolysis, has been reported. The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥ 2 g/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of hemolysis but its role is uncertain.

Contraindications to IGI treatment include anaphylactic or severe systemic hypersensitivity reactions to IG and IgA deficient patients with antibodies against IgA and a history of hypersensitivity.

IGI, 10% has a high margin of safety. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and preparation. Three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, further increasing the margin of safety. In addition, careful screening and monitoring of subjects in this study will be utilized to minimize the above and other known risks associated with IG therapy (e.g., exclusion criteria, blood group typing at baseline, and laboratory monitoring for hemolysis).

Further information is provided in the SmPC for KIOVIG, and the IB for Immune Globulin Infusion (Human), 10% Solution (IGI, 10%).

### 6.4.3 SUBCUVIA

Information about SUBCUVIA is provided in the SmPC.

### 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, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, 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 safety, tolerability and immunogenicity of HyQvia in pediatric (age <18 years) subjects with PIDD.

### 7.2 Primary Objective

The primary objective of the study is to assess the safety of HyQvia treatment in pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment.

### 7.3 Secondary Objectives

Secondary objectives of the study are further assessments (e.g. immunogenicity), tolerability, characteristic of product administration and efficacy (IgG trough levels).

### 7.4 Tertiary Objectives

Tertiary objectives are further safety and efficacy assessments. The study objectives are described in more detail in Section 11, Section 12, Supplement 20.2 and Figure 1.

# 8. STUDY DESIGN

## 8.1 Brief Summary

This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate safety, tolerability, and other parameters of SC treatment using HyQvia in approximately 40 pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment.

The purpose of the study is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric subjects.

## 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 Supplement 20.3 Clinical Laboratory Assessments. In this study approximately 40 pediatric subjects with PIDD will be enrolled, who have received prior immunoglobulin therapy. The study will enroll approximately six subjects aged 2 to <6 years, 12 subjects 6 to <12 years, and 22 subjects 12 to <18 years of age. The study will be conducted in the European Economic Area.

All subjects will have regular anti-rHuPH20 antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months).



### 8.2.1 Epoch 1

Pediatric patients with PIDD who are on non-HyQvia IV or SC treatment with immunoglobulin (IV-pretreated, SC-pretreated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks. Subjects already treated with HyQvia (HyQvia-pretreated) will be enrolled directly into Epoch 2.

Epoch 1 infusions will be administered at the study site.

### 8.2.2 Epoch 2

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

- For IV-pretreated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.
- For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and 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 (see Figure 1 Study Flow Chart in Supplements):

- Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study termination/completion visit 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.

The first two to three infusions during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions 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.



### 8.2.3 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.

In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or 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 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.

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 anti-rHuPH20 antibody titer declines to < 2560 for at least two consecutive measurements, whichever comes first. These subjects complete the study termination/completion visit when the AE/SAE resolves and the anti-rHuPH20 titer is < 2560.

Subjects in Epoch 3 will be treated with KIOVIG (IGI, 10%) intravenously or SUBCUVIA subcutaneously, at the discretion of the investigator and the subject.

Infusions in Study Epoch 3 will be administered at home or at the study site.

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 five 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 one year.

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

1. Number and rate per infusion (excluding infections) of all severe related AEs
2. Number and rate per infusion (excluding infections) of related SAEs

#### 8.4.2 Secondary Outcome Measures

##### 8.4.2.1 Efficacy

1. Trough levels of IgG (for Study Epoch 1 and 2)

##### 8.4.2.2 Safety/Tolerability

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and ARs
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs

7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

#### 8.4.2.3 Mode of Product Administration

For Study Epoch 1 and 2

1. Infusions
   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 (3 weeks or 4 weeks)
3. Assessment of Treatment Preference Questionnaire
4. Assessment of HRQoL Questionnaire: Peds-QL, EQ-5D



### 8.4.3 Tertiary Outcome Measures

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

### 8.4.4 Exploratory Outcomes Measure

Not applicable.

### 8.5 Randomization and Blinding

This is a nonrandomized, open-label, active treatment clinical study.

### 8.6 Study Stopping Rules

Stopping rules will not be established for this study as the pediatric subjects will be treated with a licensed human normal immunoglobulin, according to the routine standard at the study site, for the duration of the study.

### 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 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 KIOVIG

**Dosage Form:** Injection, solution

**Packaging:** IGIV, 10% will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials of 5 g (50 mL) and 10 g (100 mL).

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

**Storage**: Refrigeration. IGIV, 10% 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. Prior to use, the unopened 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.



#### 8.7.1.4 SUBCUVIA

**Dosage form:** Injection, solution

**Packaging:**
5 mL of solution in a vial (Type I glass) with a stopper (halogenobutyl rubber)
10 mL of solution in a vial (Type I glass) with a stopper (halogenobutyl rubber)

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

**Storage and Shelf Life**: Store in a refrigerator (2ºC - 8ºC). Do not freeze. Shelf Life: 30 months. Do not use if expiration date is exceeded. Keep the container in the outer carton in order to protect from light. Once opened: use immediately.

### 8.7.2 Administration

rHuPH20 will be administered at a dose ratio of 80 U/g IgG before the infusion of IGI, 10%. The full vial of rHuPH20 associated with each vial of IGI, 10% should be used.

rHuPH20 should be injected at a rate of approximately1-2 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.

### 8.7.3 Description of Treatment

#### 8.7.3.1 HyQvia

Subjects will be treated with HyQvia in Study Epoch 1 and Study Epoch 2.

**Dosage Form**: Injection

**Mode of Administration:** subcutaneous

**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 in whom treatment is expected to be every four weeks).

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

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

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

**Table 2**
**Example for IgG dosing**

| Pre-Study | | Epoch 1 (Ramp-Up) | | | Epoch 2 (Final Dose) |
|---|---|---|---|---|---|
| **Admin. Route** | **Dose** | **First Infusion at Baseline: 1-Week Dose** | **Second Infusion at Week 1: 2-Week Dose** | **Third Infusion at Week 3: 3-Week Dose** | |
| IV | 0.6 g/kg every 3 weeks | 0.2 g/kg | 0.4 g/kg | - | 0.6 g/kg every 3 weeks |
| IV | 0.6 g/kg every 4 weeks | 0.15 g/kg | 0.3 g/kg | 0.45 g/kg | 0.6 g/kg every 4 weeks |
| SC | 0.1 g/kg every week | 0.1 g/kg | 0.2 g/kg | - | 0.3 g/kg every 3 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 4 weeks |



**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.

#### 8.7.3.2 KIOVIG

Subjects may be treated with KIOVIG in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** intravenous

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

**Dosage frequency**: Once every three or four weeks

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study Epoch.

#### 8.7.3.3 SUBCUVIA 160 g/l

Subjects may be treated with SUBCUVIA in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** subcutaneous

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

**Dosage frequency**: Once every week or biweekly

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch.



### 8.7.4 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 International Council for Harmonization (ICH) Good Clinical Practice (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 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 humoral immunodeficiency involving a defect in antibody formation and requiring gammaglobulin replacement, as defined according to the IUIS (International Union of Immunological Societies) Scientific Committee 2015 [1] and by diagnostic criteria according to Conley et al.[2] prior to enrollment. The diagnosis must be confirmed by the sponsor Medical Director prior to first treatment with IP in the study.
2. Subject is at least two and below 18 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/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 amino transferase (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 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.
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. If the subject has been exposed to rHuPH20, she will be encouraged to participate in the HyQvia Pregnancy Registry (Study 161301), if available in the respective country. If the subject declines to enroll in the registry, attempts will be made to follow the subject through completion of the pregnancy and up to 1 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 and assent form, if applicable) and meets all inclusion and none of the exclusion criteria, is considered a subject in the study.

## 10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 090701) to be provided by the sponsor, three-digit number study site number (e.g., 02) to be provided by the sponsor, and three-digit subject number (e.g., 0003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. 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

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. 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. 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.

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, 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.

### 10.4 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 Trimethaprim-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 pretreated 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

An electronic 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 attend school/work or to perform normal daily activities due to illness/infection
- Non-study-required out-patient visits (including urgent care visits to see healthcare providers) and hospitalizations

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic 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.



Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Electronic Patient Reported (EPR) modules will be used to enable deployment of required subject diaries to subjects based on protocol requirements. EPRs can be programmed to allow a certain level of data validation at the time of data entry by the subject; this allows cleaning of subject reported data at the time of data collection. Additionally EPR compliance reports enable monitoring of patient compliance, and proactive follow up if required. EPRs can be deployed in local languages as needed. Automated reminder e-mails are sent to subjects who do not complete required EPRs. Following a certain number of reminder e-mails, the link to that particular EPR is disabled; this ensures that EPRs are collected in a timely manner during the study.

### 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 withdraw 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 that the investigator/designee can further assess and document that the subject (and/or caregiver) is capable of continuing to independently performing self-infusion procedures.

# 11. ASSESSMENT OF EFFICACY

## 11.1 IgG Trough Levels

IgG trough levels will be determined at several time points (see Supplement 20.3 Clinical Laboratory Assessments). Standard assay methods will be used for the determination of IgG and IgG subclasses. The measurement will be performed at the central laboratory.

## 11.2 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 complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

For detailed administration time points, see Supplement 20.2 Schedule of Study Procedures and Assessments.



## 11.3 Treatment Satisfaction Questionnaire for Medication

The Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a 9-item, validated, self-administered instrument to assess patients' satisfaction with medication. The 3 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 complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

For detailed administration time points, see Supplement 20.2 Schedule of Study Procedures and Assessments.

## 11.4 HRQoL Questionnaire

### 11.4.1 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.[39]

Quality of life (QoL) will be assessed separately for the age groups two to four years, and five to seven years, eight to 12 years (PEDS-QL, observer: parent), and 13 to <18 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.



### 11.4.2 EQ-5D

The EQ-5D is a validated, self-administered assessment of overall health designed by the EuroQol Group.[40] It is a descriptive system of HRQoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Subjects are asked to describe their health state that day by choosing 1 of 3 responses that reflect the levels of severity for each of the 5 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 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 <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). 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.

# 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. An AE can therefore 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

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

- Outcome is fatal/results in death (including fetal death)
- 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.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- 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:
  - 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 HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), 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 or paternal 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 Non-Serious Adverse Event

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

#### 12.1.1.3 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 investigator's brochure 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 investigator's brochure and/or prescribing information as the Reference Safety Information. 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.



#### 12.1.1.4 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 signing informed consent 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 Report Form. 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. Subjects who prematurely withdraw from the study because of pregnancy should be encouraged to participate in the pregnancy registry (Study 161301): Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia, if locally available.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness.

#### 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:

- 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.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- 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 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:

- 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).
- Unlikely related (either one or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- 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
- 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.

#### 12.1.2.3 Safety Reporting

AEs/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 5) and Section 12.1.2.

AEs/SAEs are to be recorded on the AE page of the eCRF or the SAE Report Form. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported using the paper SAE Report Form to meet the 24 hour timeline requirement (contacts and instructions to be provided in separate documentation).

The initial SAE information reported on the applicable SAE Report Formmust at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure (i.e., date, start-time, stop-time, infusion/infiltration rate, product identification)
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the Investigator
  - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)



Name, address, fax number, email, and telephone number of the reporting investigator (SAE Report Forms).

### 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(s) (ECs) 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 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 documented on an NMC form and reported to the sponsor 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 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 12.1.1.4), 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.

#### 12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin [Hgb], hematocrit, erythrocytes [i.e., RBC], 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, protein, albumin, ALT, bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, and glucose.

Hematology and clinical chemistry assessments will be performed on 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 there is a reduction in Hgb of two 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 IgG Trough Levels and IgG Subclasses and Specific Antibody Tests

IgG total and IgG subclass trough levels and levels of specific antibodies will be determined on all subjects by using standard assay methods (to be performed at the central laboratory).

At infusion visits where blood is drawn for trough levels, the blood drawing for the IgG determination will always take place before the infusion is administered.

### 12.7.6 Anti-rHuPH20 Antibodies

All subjects will have regular anti-rHuPH20 antibody testing in pre-identified central laboratories (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months, see Supplement 20.3). 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:

- 50% hemolytic complement activity of serum,
- serum complement component 3,
- serum complement component 4,
- C1q binding assay, and
- circulating immune complex Raji cell assay.



### 12.7.7 Viral Pathogen Serology

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

### 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.[41]:

- 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.[42] 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 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 12.1.1.4), 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/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured as described below:

### 12.8.1 Screening

- All vital signs

### 12.8.2 Infusion at Study Site

1. Within 30 min prior to infusion:
   - All vital signs. Height and weight can be taken at any time at this visit.
2. 30 (± 5) min 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 min 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 US FDA Guidance for Industry to Support Marketing of Human IGIV as Replacement Therapy for Primary Humoral Immunodeficiency [43] and the EMA guideline on the clinical investigation of human normal immunoglobulin for SC and /or intramuscular administration.[44]

### 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/min; respiratory rate >20 breaths/min, 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.[45]

[(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 ($PaO_2$ < 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 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[vii]. 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 age 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 >two 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 <ten 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 alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
4. Imaging studies: typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan

[vii] Further evaluation, in particular laboratory evaluation (culture and white blood count with differential to evaluate for the presence of immature neutrophils) and chest x-rays, should be aggressively pursued whenever a bacterial pneumonia is suspected

# 13. STATISTICS

## 13.1 Sample Size and Power Calculations

The sample size selected for the study is primarily determined by the objective to collect safety data in a sufficient number (about 40) of pediatric (age <18 years) subjects with PIDD who have received prior immunoglobulin therapy before enrollment into this study. In addition, the guideline of the CHMP on the clinical investigation of human normal immunoglobulin for SC and/or intramuscular administration [44] indicates that at least 40 patients should be included to evaluate replacement therapy in primary immunodeficiency syndromes.

## 13.2 Analysis Sets

### 13.2.1 Full Analysis Set

All patients who provide informed consent (i.e., sign and date the Informed Consent Form, if applicable), and meet enrollment eligibility (i.e., meets all inclusion criteria and do not meet any exclusion criteria) will be included in the full analysis set.

### 13.2.2 Per-Protocol Analysis Set

All patients in the full analysis set who have no major protocol deviations will be included in the per-protocol analysis set.

### 13.2.3 Safety Analysis Set

The safety analysis set will contain all subjects in the full analysis set who receive at least one dose of HyQvia.



## 13.3 Handling of Missing, Unused, and Spurious Data

The handling of missing, unused or spurious data will be described in the statistical analysis plan (SAP).

## 13.4 Methods of Analysis

In this study no hypothesis will be tested. Detailed statistical analysis methods will be described in the SAP. Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. If groups of sufficient sample size (such as age groups or PIDD types) are available, CIs may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class and preferred term. Tables will be prepared to list for each SAE and non-serious AE the number of events and the number of subjects who experienced one or more event. All analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

### 13.4.1 Primary Outcome Measure

- Number and rate per infusion (excluding infections) of all severe related AEs
- Number and rate per infusion (excluding infections) of related SAEs

For the endpoint of incidence of all severe related AEs and related SAEs, a point estimate and corresponding 95% CI (by the Wilson score method) for the proportion of subjects with one or more related SAEs will be provided. In addition, incidence of all severe related AEs and related SAEs will be calculated as rate per infusion and rate per subject-year, and will be analyzed for changes in frequency and for changes in severity over time. All SAEs will be listed. No statistical hypotheses will be tested.

### 13.4.2 Secondary Outcome Measures

#### 13.4.2.1 Efficacy

Trough levels of IgG (for Study Epoch 1 and 2): Descriptive statistics will be provided for the trough level of IgG for study Epoch 1 and 2.



#### 13.4.2.2 Safety

The following secondary safety endpoints will be analyzed:

- Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
- Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
- Number and rate per infusion (excluding infections) of local AEs and ARs
- Number and rate per infusion (excluding infections) of systemic AEs and ARs
- Number and rate per infusion (excluding infections) of all AEs and all ARs
- Number and rate per infusion (excluding infections) of all temporally associated AEs
- Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
- Number and rate per infusion (excluding infections) of all SAEs
- Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

Descriptive methods, mainly frequency tables, will be used for all secondary safety endpoints. In addition, incidence of all secondary safety endpoint will be calculates as rate per infusion and rate per subject-year.

#### 13.4.2.3 Mode of Product Administration (For Study Epoch 1 and 2)

- Number of Infusions
- Number of infusions per month
- Number of infusion sites (needle sticks) per infusion/month
- Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion)Maximum infusion rate/site
- Infusion volume/site
- Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE Number of weeks to reach final dose interval (defined as three or four weeks infusion interval)

Nonparametric descriptive statistics (median, quartiles, and range) will be calculated and reported for the infusion administration variables. Frequency table will show the number/proportion of infusions discontinued, slowed or interrupted due to AE and total observation time in subject-years.



#### 13.4.2.4 HRQoL

- Treatment Preference Questionnaire
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- HRQoL Questionnaire: Peds-QL, EQ-5D

Total and domain scores on each of the HRQoL measures will be calculated for each subject, at each data assessment time point. Descriptive statistics will be shown for each of the scores, at each data assessment time point.

### 13.4.3 Tertiary Outcome Measures

#### 13.4.3.1 Infections

- Number of acute serious bacterial infections
- Number of all infections
- Days on antibiotics

For the endpoint of incidence of acute serious bacterial infection and all infections a point estimate and 95% CI (by the Wilson score method) for the proportion of subjects with one or more infection will be calculated. In addition, incidence of all infection endpoints will be calculates as rate per infusion and rate per subject-year. Descriptive statistics will be performed and reported for the days on antibiotics.

#### 13.4.3.2 Healthcare Resource Utilization Endpoints

- Days not able to go to school/work or to perform normal daily activities
- 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

Healthcare resource utilization endpoints, including hospitalization, acute physician visits and days missed for school/work or normal daily activities, will be summed and annualized for reporting purposes. Descriptive statistics will be performed and reported.

### 13.5 Planned Interim Analysis of the Study

Annual reports will be prepared. Details will be described in the SAP.



## 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 Study Agreement. 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 Clinical Study Agreement.

# 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 regulatory requirements as described in the Clinical Study Agreement. 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. The coordinating investigator will be selected before study start.



## 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 regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. 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 review board (ISRB).

The ISRB 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 ISRB will be composed of appropriate sponsor representatives from the relevant functions (e.g., Global Drug Safety, Clinical Research, Medical Affairs, Clinical Development) with expertise/specialization in PIDD clinical care and research. The ISRB can 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 regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. 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 will also ensure the responsible EC 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

Inter-laboratory standardization methods will be described in the data management plan as needed.

# 16. ETHICS

## 16.1 Subject Privacy

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

## 16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, 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 IB 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 Clinical Study Agreement.

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 informed consent form before entering into the study according to 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 informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, 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 informed consent form 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 Clinical Study Agreement.

## 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 informed consent forms, 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 Clinical Study Agreement.

## 18. FINANCING AND INSURANCE

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

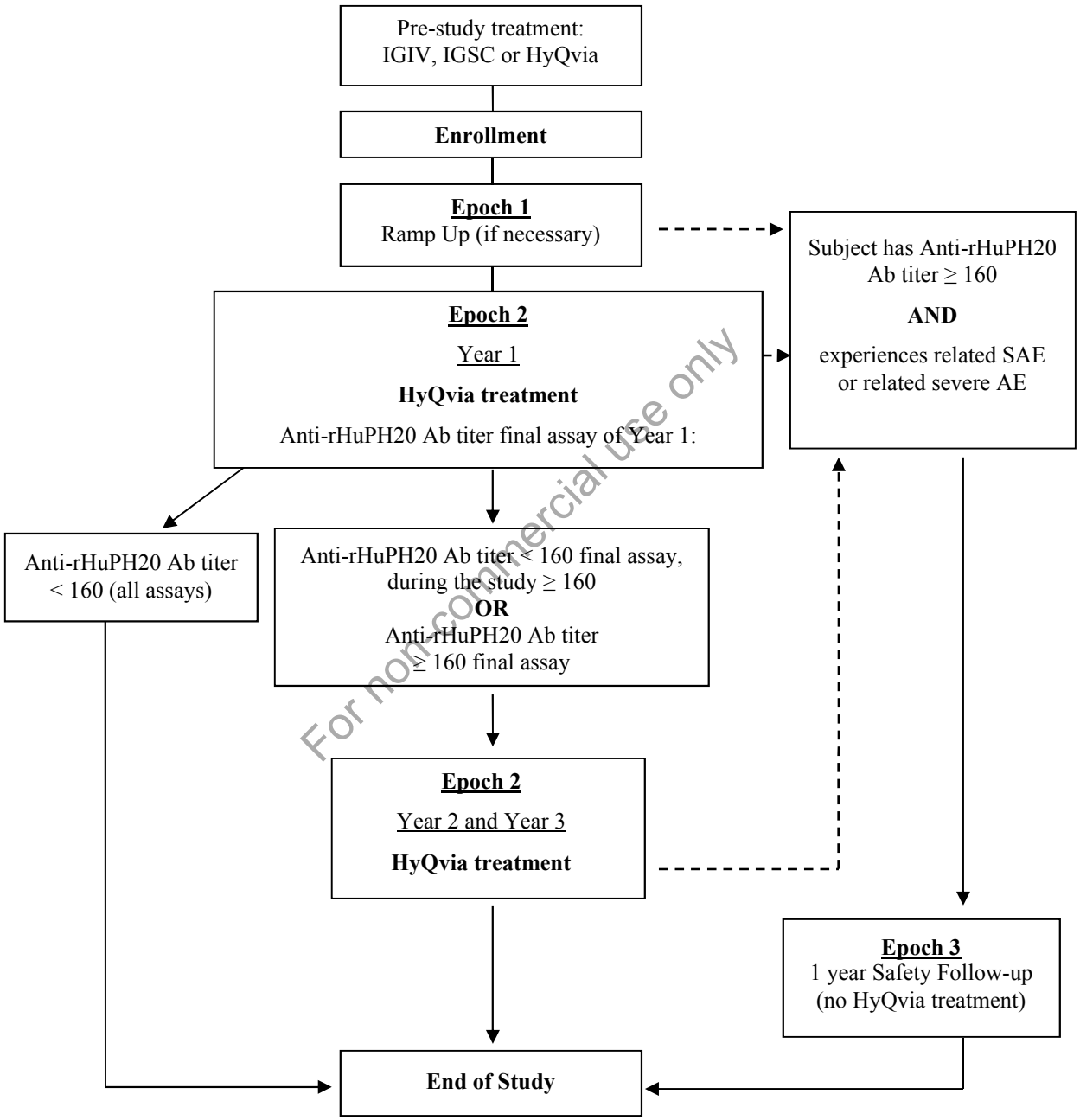
## 19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

## 20. SUPPLEMENTS

### 20.1 Study Flow Chart

**Figure 1**
**Study Design for Clinical Study 161504**



## 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 | Treatment Visit in Study Epoch 1 | | |
|---|---|---|---|---|
| | | First Infusion: Baseline | Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals) | Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-Week Treatment Intervals) |
| Location | Site | Site | Site | Site |
| Informed Consent[a] | x | | | |
| Eligibility Criteria | x | | | |
| Infusion | | 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)/ Treatment Preference questionnaire, TSQM-9 Assessment | | x | | |

[a] Occurs prior to any study-specific procedure.
[b] For laboratory assessments, see Supplement 20.3

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

| Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 2 (Visit +/- 2 weeks) | | | | | |
|---|---|---|---|---|---|---|
| | Month 0 | Month 3 | Month 6 | Month 9 | Month 12[a] | Study Completion/ Termination Visit (at Next Infusion), if Applicable |
| Location | Site | Site | Site | Site | Site | Site |
| Informed Consent | | | | | | |
| Infusion[a] | 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 | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x |
| HRQoL (PedsQL, EQ-5D), Treatment Preference questionnaire, TSQM-9 Assessment | | | | | x | x |

[a] Further (additional) infusions may be administered after 12 months if rHuPH20-antibody results not available. AEs, concomitant medications, and non-drug therapies will continue to be recorded until EOS or continuation of Epoch 2 (dependent on antibody assay result).

**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 (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 | 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 | x | x | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x | x | x |
| HRQoL (PedsQL, EQ-5D)/ Rx-Preference, TSQM-9 Assessment | | | | x | | | | x |

[a] In case a subject has an anti-rHuPH20 antibody titer ≥ 160 and experiences a related serious or severe AE, the subject may go to Study Epoch 3 and will have the Study Completion/Termination Visit at the end of this Epoch

**Table 6**
**STUDY EPOCH 3**
**Schedule of Study Procedures and Assessments**

| Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 3 (Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|
| | Month 0 | Month 3 | Month 6 | Months 9 | Month 12/ Study Completion/ Termination Visit[a] |
| Location | Site | Site | Site | Site | Site |
| Infusion | x | x | x | x | |
| Concomitant Medications | x | x | x | x | x |
| Non-drug Therapies | x | x | x | x | x |
| Physical Exam[b] | 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 (PedsQL, EQ-5D Treatment Preference questionnaire, TSQM-9 Assessment | x | | | | x |

[a] Includes for cases of withdrawal or discontinuation.
[b] Occurs prior to any study-specific procedure.
[c] For laboratory assessments, see Supplement 20.3.

## 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 | Treatment Visit in Study Epoch 1 | | |
|---|---|---|---|---|
| | | First Infusion: Baseline | Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals) | Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-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 | | x | | |

**Table 8**
**STUDY EPOCH 2 – Year 1**
**Clinical Laboratory Assessments**

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 2 (Visit +/- 2 Weeks) | | | | | |
|---|---|---|---|---|---|---|
| | Month 0 | 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 | x | | | | | |
| Specific Antibody Tests | | | x | | | |
| IgG Trough Levels and IgG Subclasses | x | | x | | x | |
| Antibodies to rHuPH20 | x | x | x | x | x | |

**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 (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 | | | | x[b] | | | | |
| Specific Antibody Tests | | | | | | | | 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 has an anti-rHuPH20 antibody titer ≥ 160 and experiences a related serious or severe AE, the subject may go to Study Epoch 3 and will have the Study Completion/Termination Visit at the end of this Epoch.

[b] If there is a reduction in Hgb of two 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

**Table 10**
**STUDY EPOCH 3**
**Clinical Laboratory Assessments**

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 3 (Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|
| | Month 0 | 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 | | | x | | |
| Specific Antibody Tests | | | | | x |
| IgG Trough Levels and IgG Subclasses | x | | x | | x |
| Antibodies to rHuPH20 | x | x | x | x | x |

## 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 |
| 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: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, 5 (not shown in the table)=death. Grading scale criteria taken from ECOG [41] and WHO [42] guidelines, with the exception of LDH that uses the same thresholds as defined for ALT and AST

## 21. REFERENCES

1. Picard C, Al-Herz W, Bousfiha A et al. Primary immunodeficiency diseases: An update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J.Clin.Immunol. 2015;35:696-726.

2. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin.Immunol. 1999;93:190-197.

3. Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9:722-728.

4. Rosen FS, Cooper MD, Wedgwood RJ. The primary immunodeficiencies. N.Engl.J.Med. 1995;333:431-440.

5. Wolin MJ, Gale RP. IVIG in bone marrow transplantation. In: Lee ML, Strand V, eds. Intravenous Immunoglobulins in Clinical Practice. New York: Marcel Dekker, Inc.; 1997:113-118.

6. Griffiths H, Chapel H. Prevention of infections in B-cell lymphoproliferative diseeases. In: Lee ML, Strand V, eds. Intravenous Immunoglobulins in Clinical Practice. New York: Marcel Dekker; 1997:203-223.

7. Rechtman DJ. Use of intravenous immune globulin in adults with HIV disease. In: Lee ML, Strand V, eds. Intravenous Immunoglobulins in Clinical Practice. New York: Marcel Dekker, Inc.; 1997:167-174.

8. Abdel-Mageed A, Graham-Pole J, Del Rosario ML et al. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplant. 1999;23:929-932.

9. George JN, Raskob GE. Idiopathic thrombocytopenic purpura: diagnosis and management. Am.J.Med.Sci. 1998;316:87-93.

10. Imbach P, Akatsuka J, Blanchette V et al. Immunthrombocytopenic purpura as a model for pathogenesis and treatment of autoimmunity. Eur.J.Pediatr. 1995;154:S60-S64.

11. McMillan R. The pathogenesis of chronic immune (idiopathic) thrombocytopenic purpura. Semin.Hematol. 2000;37:5-9.

12. Barron KS, Murphy DJ, Jr., Silverman ED et al. Treatment of Kawasaki syndrome: a comparison of two dosage regimens of intravenously administered immune globulin. J.Pediatr. 1990;117:638-644.

13. Rosenfeld EA, Shulman ST, Corydon KE et al. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. J.Pediatr. 1995;126:1000-1003.

14. Hahn AF, Beydoun SR, Lawson V et al. A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy. J.Peripher.Nerv.Syst. 2013;18:321-330.

15. Rozman C, Montserrat E. Chronic lymphocytic leukemia. N.Engl.J.Med. 1995;333:1052-1057.

16. Kyle RA, Rajkumar SV. Multiple myeloma. N.Engl.J.Med. 2004;351:1860-1873.

17. Gardulf A, Nicolay U, Asensio O et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies - A prospective multi-national study. J.Clin.Immunol. 2006;26:177-185.

18. Ochs HD, Gupta S, Kiessling P et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J.Clin.Immunol. 2006;26:265-273.

19. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann.Intern.Med. 1980;93:55-56.

20. Welch MJ, Stiehm ER. Slow subcutaneous immunoglobulin therapy in a patient with reactions to intramuscular immunglobulin. J.Clin.Immunol. 1983;3:285-286.

21. Roord JJ, van der Meer JW, Kuis W et al. Home treatment in patients with antibody deficiency by slow subcutaneous infusion of gammaglobulin. Lancet 1982;1:689-690.

22. Gardulf A, Björvell H, Gustafson R, Hammarström L, Smith CI. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. Immunodeficiency. 1993;4:81-84.

23. Gustafson R, Gardulf A, Hansen S et al. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. Clin.Exp.Immunol. 2008;152:274-279.

24. Gardulf A, Andersen V, Björkander J et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet 1995;345:365-369.

25. Gardulf A, Hammarström L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991;338:162-166.

26. Gardulf A, Hammarström L. Subcutaneous administration of immunoglobulins. What are the advantages? Clin.Immunother. 1996;6:108-116.

27. Schiff RI, Rudd C. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. J.Clin.Immunol. 1986;6:256-264.

28. Smith GN, Griffiths B, Mollison D, Mollison PL. Uptake of IgG after intramuscular and subcutaneous injection. Lancet 1972;1:1208-1212.

29. ZLB Behring. Immune Globulin Subcutaneous (Human), Vivaglobin®. US Label. 8. 2006.
Link to Publisher´s Site:
http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm070360.pdf

30. Wasserman RL, Melamed I, Nelson RP, Jr. et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin.Pharmacokinet. 2011;50:405-414.

31. Supersaxo A, Hein WR, Steffen H. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. Pharm.Res. 1990;7:167-169.

32. Olsson O, Löjgren O. Hyaluronidase as a factor hastening the spread and absorption of water-soluble radiopaque substances deposited intracutaneously, subcutaneously, or intramuscularly. Acta Radiol. 1949;31:250-256.

33. Thomas JR, Yocum RC, Haller MF, von Gunten CF. Assessing the role of human recombinant hyaluronidase in gravity-driven subcutaneous hydration: The INFUSE-LR Study. J.Palliat.Med. 2007;10:1312-1320.

34. Shpilberg O, Jackisch C. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. Br.J.Cancer 2013;109:1556-1561.

35. Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. J.Infus.Nurs. 2007;30:293-299.

36. Rosengren S, Dychter SS, Printz MA et al. Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. AAPS J. 2015;17:1144-1156.

37. Melamed IR, Stein MR, Wasserman RL et al. Recombinant human hyaluronidase facilitates dispersion of subcutaneously administered Gammagard Liquid and enables administration of a full monthly dose in a single site to patients with immunodeficiency diseases [abstract]. J.Allergy Clin.Immunol. 2008;121:S83.

38. Wasserman RL, Melamed I, Stein MR et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J.Allergy Clin.Immunol. 2012;30:951-957.

39. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med.Care 1999;37:126-139.

40. Rabin R, de Charro F. EQ-5D: A measure of health status from the EuroQol Group. Ann.Med. 2001;33:337-343.

41. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am.J.Clin.Oncol. 1982;5:649-655.

42. World Health Organization. Toxicity grading scale for determining the severity of adverse events. 96. 2-20-2003. World Health Organization (WHO).
Link to Publisher´s Site:
http://www.icssc.org/Documents/Resources/AEManual2003AppendicesFebruary_06_2003%20final.pdf

43. U.S.Department of Health and Human Services, Food and Drug Administration, and Center for Biologics Evaluation and Research. Guidance for industry: Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. 17. 2008. U.S. Department of Health and Human Services, Food and Drug Administration (FDA).

44. Committee for Medicinal Products for Human Use. Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg). EMA/CHMP/BPWP/410415/2011 rev 1, 10. 7-23-2015. European Medicines Agency (EMEA).
Link to Publisher´s Site:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500190211.pdf

45. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr.Crit.Care Med. 2005;6:2-8.

# INVESTIGATOR ACKNOWLEDGEMENT

**PRODUCT:** HyQvia

**STUDY TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

**PROTOCOL IDENTIFIER: 161504**

**CLINICAL TRIAL PHASE 4**

**ORIGINAL: 2016 MAR 16**



**OTHER ID(s)**
**NCT Number:** Not Yet Available
**EudraCT Number:** Not Yet Available
**IND NUMBER:** Not Applicable

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

## INVESTIGATOR ACKNOWLEDGEMENT

**PRODUCT:** HyQvia

**STUDY TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

**PROTOCOL IDENTIFIER: 161504**

**CLINICAL TRIAL PHASE 4**

**ORIGINAL: 2016 MAR 16**

**OTHER ID(s)**
**NCT Number:** Not Yet Available
**EudraCT Number:** Not Yet Available
**IND NUMBER:** Not Applicable



By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Development

# CLINICAL STUDY PROTOCOL

**PRODUCT: HyQvia**

**STUDY TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

**STUDY SHORT TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD subjects

**PROTOCOL IDENTIFIER: 161504**

**CLINICAL TRIAL PHASE 4**

**AMENDMENT 1: 2016 OCT 07**

**Replaces: ORIGINAL: 2016 MAR 16**



**ALL VERSIONS:**

**Amendment 1: 2016 OCT 07**
**Original: 2016 MAR 16**

**OTHER ID(s)**
**NCT Number:** Not Yet Available
**EudraCT Number:** 2016-003438-26
**IND NUMBER:** Not Applicable


| **Study Sponsor(s):** | **Baxalta US Inc.** | **Baxalta Innovations GmbH** |
|---|---|---|
| | One Baxter Way<br>Westlake Village, CA 91362,<br>UNITED STATES | Industriestrasse 67<br>A-1221 Vienna,<br>AUSTRIA |

# 1. STUDY PERSONNEL

## 1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH /Baxalta US Inc.

## 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 ANDTRANSMITTED 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 (IGI, 10% with rHuPH20).<br>2. KIOVIG 100 mg/ml solution for infusion<br>3. Cuvitru 200 mg/ml solution for subcutaneous injection<br><br>(For better readability the names HyQvia, KIOVIG and Cuvitru will be used throughout the document.) |
| **Name(s) of Active Ingredient(s)** | Human Normal Immunoglobulin |
| **CLINICAL CONDITION(S)/INDICATION(S)**<br>• Primary Immunodeficiency Diseases (PIDD) | |
| **PROTOCOL ID** | 161504 |
| **PROTOCOL TITLE** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases |
| **Short Title** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD subjects |
| **STUDY PHASE** | Ph4 (post-authorization) |
| **PLANNED STUDY PERIOD** | |
| **Initiation** | 2016 |
| **Primary Completion** | 2021 |
| **Study Completion** | 2021 |
| **Duration** | Approximately five years |
| **STUDY OBJECTIVES AND PURPOSE** | |
| **Study Purpose**<br>The purpose of the study is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age two to <18 years) subjects with Primary Immunodeficiency Diseases (PIDD). | |
| **Primary Objective**<br>Safety of HyQvia treatment in pediatric subjects with PIDD who have received prior immunoglobulin therapy before enrollment into the study. | |
| **Secondary Objective(s)**<br>Further safety assessments (e.g. immunogenicity), tolerability, characteristic of product administration and efficacy (immunoglobulin G [IgG] trough levels) | |

| STUDY DESIGN | |
|---|---|
| **Study Type/ Classification/ Discipline** | Safety, Immunogenicity |
| **Control Type** | No control |
| **Study Indication Type** | Treatment |
| **Intervention Model** | Single-group |
| **Blinding/Masking** | Open-label |
| **Study Design** | This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate the safety, tolerability, and other parameters of subcutaneous (SC) treatment using HyQvia in approximately 40 pediatric subjects with PIDD who have received immunoglobulin therapy before enrollment into this study. Subjects will have regular anti-recombinant human hyaluronidase PH20 (rHuPH20) antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months).<br><br>**Epoch 1:** Pediatric patients with PIDD who are on non-HyQvia intravenous (IV) or SC treatment with immunoglobulin (IV-pretreated, SC pretreated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks. Subjects already treated with HyQvia (HyQvia pretreated) will be enrolled directly into Epoch 2. Epoch 1 infusions will be administered at the study site.<br><br>**Epoch 2:** The ramp-up (Epoch 1) is followed by Epoch 2 with HyQvia treatment at the following intervals. For IV-pretreated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule. For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and subject. For HyQvia pretreated 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 (see Figure 1: Study Flow Chart in Supplements). Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study termination/completion visit 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.<br><br>The first two or three infusion(s) during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions be performed at home (or equivalent site) by the subject or 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.<br><br>**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 Serious Adverse Event (SAE) or a related severe Adverse Event (AE).<br><br>Subjects in Epoch 3 will be treated with KIOVIG intravenously or Cuvitru subcutaneously, at the discretion of the investigator and the subject.<br><br>In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or 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 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.<br><br>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 anti-rHuPH20 antibody titer declines to <2560 for at least two consecutive measurements, whichever comes first. These subjects complete the study termination or completion visit when the AE or SAE resolves or the anti-rHuPH20 titer is <2560.<br><br>Infusions in Study Epoch 3 will be administered at home or at the study site.<br><br>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 for HyQvia-naïve subjects<br>Study Epoch 2 (Final dosing): Up to three years<br>Study Epoch 3 (Safety Follow-up): Up to one year<br>The maximum subject participation period is approximately four years. |

**Primary Outcome Measure**

1. Number and rate per infusion (excluding infections) of all severe related AEs
2. Number and rate per infusion (excluding infections) of related SAEs

**Secondary Outcome Measure(s)**

**Efficacy**

1. Trough levels of IgG (for Study Epoch 1 and 2)

**Safety**

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and Adverse Reactions (ARs)
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs
7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

**Mode of Product Administration** (For Study Epoch 1 and 2)

1. Infusions
   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)
3. Assessment of Treatment Preference Questionnaire
4. Assessment of Treatment Satisfaction with Medication Questionnaire: TSQM-9
5. Assessment of Health-related Quality of Life Questionnaires: Peds-QL, EQ-5D

**Tertiary Outcome Measure(s)**

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

**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**: injectable

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

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

Example for IgG dosing:

| Pre-Study | | Epoch 1 (Ramp-Up) | | | Epoch 2 (Final Dose) |
|---|---|---|---|---|---|
| **Admin. Route** | **Dose** | **First Infusion at Baseline: 1-Week Dose** | **Second Infusion at Week 1: 2-Week Dose** | **Third Infusion at Week 3: 3-Week Dose** | |
| IV | 0.6 g/kg every 3 weeks | 0.2 g/kg | 0.4 g/kg | - | 0.6 g/kg every 3 weeks |
| IV | 0.6 g/kg every 4 weeks | 0.15 g/kg | 0.3 g/kg | 0.45 g/kg | 0.6 g/kg every 4 weeks |
| SC | 0.1 g/kg every week | 0.1 g/kg | 0.2 g/kg | - | 0.3 g/kg every 3 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 4 weeks |

**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):<br>• For subjects with a BW of < 40 kg: 10 ml/h/site (at start) to 160 ml/h/site (maximum, if tolerated)<br>• For subjects with a BW of ≥ 40 kg: 10 ml/h/site (at start) to 300 ml/h/site (maximum, if tolerated)<br>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.<br><br>**2. KIOVIG**<br>Subjects may be treated with KIOVIG in **Study Epoch 3** (Safety Follow-up).<br>**Dosage form**: injectable<br>**Mode of Administration:** intravenous<br>The infusion rate and infusion volume per site will follow the suggestions of the KIOVIG SmPC.<br>**Dosage frequency**: Once every three or four weeks<br>**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch<br><br>**3. Cuvitru**<br>Subjects may be treated with Cuvitru in **Study Epoch 3** (Safety Follow-up).<br>**Dosage form**: Solution for injection<br>**Mode of Administration:** subcutaneous injection<br>The infusion rate and infusion volume per site will follow the suggestions of the Cuvitru SmPC.<br>**Dosage frequency**: daily to once every two weeks, at the investigator´s discretion<br>**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch. |
| **SUBJECT SELECTION** | |
| **Targeted Accrual** | Sample size: Approximately 40 pediatric subjects already on IgG treatment pre-study will be enrolled. The study will enroll approximately six subjects two to less than six years of age, 12 subjects six to <12 years of age, 22 subjects 12 to <18 years of age. The study will be conducted in the European Economic Area.<br><br>Study sites: Approximately 20 |
| **Number of Groups/ Arms/Cohorts** | 1 |

**Inclusion Criteria**

1. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving a defect in antibody formation and requiring gammaglobulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Scientific Committee 2015 [1] 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 18 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.

**Exclusion Criteria**

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 amino transferase (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/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 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 the study is approximately 40 pediatric subjects.

**Planned Statistical Analysis**

Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. All SAEs and non-serious AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. All analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

## 4. TABLE OF CONTENTS

***Tables***



***Figures***

## 5. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADR | Adverse drug reaction (i.e., related AE) |
| AE | Adverse event |
| AR | Adverse reaction |
| AIDS | Acquired immune deficiency syndrome |
| ALP | Alkaline phosphatase |
| ALT | Alanine amino transferase (SGPT) |
| ANC | Absolute neutrophil count |
| AST | Aspartate amino transferase (SGOT) |
| AUC | Area under the curve |
| B19V | Parvovirus B19 |
| BUN | Blood urea nitrogen |
| BW | Body weight |
| CHMP | Committee for Medicinal Products for Human Use |
| CLL | Chronic lymphocytic leukemia |
| CI | Confidence interval |
| $C_{max}$ | Maximum concentration |
| $C_{min}$ | Minimum concentration |
| CRF | Case report form |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| CXR | Chest x-ray |
| EC | Ethics committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EPR | Electronic Patient Reported |
| EU | European Union |
| Fc | Crystallizable region of antibody |
| FDA | Food and Drug Administration |

| Abbreviation | Definition |
|---|---|
| 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 |
| ICH | International Council for Harmonization |
| IgA | Immunoglobulin A |
| IGIV, 10% | Immune Globulin Intravenous (Human) GAMMAGARD LIQUID/KIOVIG |
| IgG | Immunoglobulin G |
| IGI | Immunoglobulin |
| IGIV | Immune globulin intravenous (human) |
| IGSC | Immune globulin subcutaneous (human) |
| IP | Investigational Product |
| ISG | Immune serum globulin |
| ISRB | Internal safety review board |
| ITP | Idiopathic thrombocytopenic purpura |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | Minute(s) |
| mL | Milliliter(s) |
| MM | Multiple myeloma |
| MMN | Multi-focal motor neuropathy |
| MRI | Magnetic resonance imaging |

| Abbreviation | Definition |
|---|---|
| NMC | Non-medical complaint |
| $PaCO_2$ | Partial pressure (tension) of carbon dioxide |
| PASS | Post-authorization safety study |
| PCR | Polymerase chain reaction |
| PIDD | Primary immunodeficiency disease |
| PK | Pharmacokinetic(s) |
| RBC | Red blood cell (count) |
| rHuPH20 | Recombinant human hyaluronidase PH20<br>(active ingredient in the U.S. marketed product HYLENEX) |
| SAP | Statistical analysis plan |
| S/D | Solvent/detergent |
| SAE | Serious adverse event |
| SAER | Serious adverse event report |
| SC | Subcutaneous |
| SCIG | Subcutaneous immunoglobulin G |
| SIC | Subject identification code |
| SmPC | Summary of product characteristics |
| $T_{max}$ | Time to maximum concentration |
| TRALI | Transfusion related acute lung injury |
| ULN | Upper limit of normal |
| VASBI | Validated acute serious bacterial infection |
| WBC | White blood cell (count) |

# 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.[3,4] 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.[5,6,7,8] Immunoglobulins are also effective in the management of autoimmune disorders, such as idiopathic thrombocytopenic purpura (ITP) [9,10,11], Kawasaki syndrome [12,13], and multi-focal motor neuropathy (MMN).[14]



## 6.1 Description of Investigational Product

### 6.1.1 HyQvia

HyQvia 100 mg/ml solution for infusion for subcutaneous (SC) use is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20).

The IG 10% component provides the therapeutic effect of this medicinal product. The rHuPH20 facilitates the dispersion and absorption of IG 10%.

Human normal immunoglobulin contains mainly IgG with a broad spectrum of opsonizing and neutralizing antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1,000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range.

rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan. Hyaluronan is a polysaccharide found in the intercellular matrix of connective tissue and of certain specialized tissues. It is degraded by naturally occurring hyaluronidase and has a very fast natural turnover in SC tissue.

As a permeation enhancer, rHuPH20 temporarily accelerates the break-down of hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates more rapid dispersion and absorption and improved bioavailability of the IG 10%.

HyQvia therapeutic indications include:

- Replacement therapy in adults (≥18 years) with primary immunodeficiency syndromes such as:
    a. congenital agammaglobulinaemia and hypogammaglobulinaemia
    b. common variable immunodeficiency
    c. severe combined immunodeficiency
    d. IgG subclass deficiencies with recurrent infections
- Replacement therapy in adults (≥18 years) with myeloma or CLL with severe secondary hypogammaglobulinaemia and recurrent infections



### 6.1.2 KIOVIG 100 mg/ml solution for infusion and Cuvitru 200 mg/ml solution for subcutaneous injection

**KIOVIG** is a liquid unmodified IgG preparation with an osmolality that is similar to physiologic osmolality and contains no added sugars, sodium, or preservatives. The manufacturing process includes three independent, validated viral inactivation or removal steps: solvent/detergent (S/D) treatment, nanofiltration and incubation at a low pH and elevated temperature. The product contains immunoglobulins with intact Fc regions (crystallizable region of the antibody) in isotonic solution including glycine for stabilization. KIOVIG is a ready-to-use 10% liquid preparation.

A detailed description of KIOVIG is provided in the Summary of Product Characteristics (SmPC).

**Cuvitru** 200 mg/ml solution for subcutaneous injection is a ready-for-use sterile, liquid preparation of highly purified, concentrated, functionally intact human IgG.

Therapeutic indications include replacement therapy in adults, and children and adolescents (0-18 years) with

- primary immunodeficiency syndromes with impaired antibody production
- hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated

- hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients
- hypogammaglobulinaemia in patient's pre- and post- allogeneic haematopoietic stem cell transplantation (HSCT).

### 6.1.3 A detailed description of Cuvitru is provided in the SmPC. Immunoglobulin Treatment

Defective antibody formation, 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 agammaglobulinemia, selective IgG subclass deficiency, common variable immunodeficiency, 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.[1]



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.[15] MM is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, hypercalcemia but also recurrent infections.[16]

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 US, 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 US are licensed for IV administration; though, in December 2005, the first SC preparation was licensed by ZLB-Behring.[17,18] 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.[19,20,21,22,23]

All of the gammaglobulin preparations licensed for SC use are formulated at 10-20%. 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, SC IgG leads to higher trough serum IgG concentrations than monthly IV infusions (at the same monthly dose).[24,25] 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.[26]

Immunoglobulin administered intravenously is immediately available in the blood, and slowly equilibrates to the extra-vascular compartment over three to five days.[27] 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 IM was 100% when compared to IV.[28] 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.[18,29] Accordingly, it is recommended that the dose of SC immunoglobulin be adjusted to 137-153% of the IV dose to provide a comparable IgG exposure.[18,30] Despite the technical difficulties of comparing AUC for two different routes and frequencies of administration, studies of intradermally administered immunoglobulin in rats[i] 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.[31]

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) thus would require at least three sites per week or 12 sites per month.

[i] Halozyme Report Number R1005-0551.

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 sixty years to temporarily depolymerize the hyaluronan and facilitate SC infusions of fluids for re-hydration.[32] rHuPH20 is a 63 kd protein genetically engineered from the sequence of the naturally occurring human protein. It temporarily depolymerizes the 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 h, leaving no observable changes[ii]. Weekly infusions into cynomolgus monkeys in doses up to two mg/kg (> 1,000 fold higher than the HyQvia dose in humans) did not lead to adverse reactions during a follow-up of 39 weeks[iii]. Infusion of rHuPH20 improved 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.[33] 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 animals and thus, human studies were required. rHuPH20 can facilitate absorption of small molecules such as insulin and morphine in humans; in phase 1 trials rHuPH20 improved bioavailability of proteins such as infliximab[iv] and enabled drug dispensation and absorption at the administration site of rituximab and trastuzumab.[34]
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.



[ii] Halozyme Report R08014.
[iii] Halozyme Report R09050.
[iv] Halozyme Report R05109.

The immunogenicity of rHuPH20 has been monitored in a number of clinical trials[v]. No positive skin reactions were observed when rHuPH20 was administered to 100 healthy volunteers in a skin allergy clinical trial.[35] 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 have 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 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, 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%.[36] 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.



### 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.

[v] Halozyme Report Number 10059.

## 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 IGIV 10% in a single SC site with good tolerability.[37] An infusion was defined as having been tolerated if it caused no more than mild local adverse drug reactions (ADRs) (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 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, multi-center, Phase III study.[38] 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/g IgG rHuPH20 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.

[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.

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 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. A comparison of data from the present 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 after a delay of approximately three to five days.

Data from the clinical trial of HyQvia show that serum IgG trough levels 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 PKs of HyQvia was evaluated in this Phase 3 efficacy and safety study in 60 patients with PIDD aged 12 years and older. The pharmacokinetic results are presented in the table 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) 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 have 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 01 August of 2012, the FDA requested administration of rHuPH20 drug product in all ongoing HyQvia clinical studies in the US to be suspended and patients were switched to treatment with KIOVIG/GAMMAGARD LIQUID only (Protocol Amendment 5). Subjects were treated with conventional IGIV or 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), seven subjects in the range of 12 to <16 years and four subjects in the range of two to <12 years. The median age was 43.0 years. Of the 66 subjects who met all inclusion/exclusion criteria, 50 (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: 60-729 days) and a mean (± 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: 5-300) and the median maximum rate of infusion achieved was 300 mL/hr (range: 10-350). Across all age groups and infusion intervals, a median number of 1.09 infusions/month (range: 0.3-2.1) was administered. IGSC, 10% with rHuPH20 treatment required a median number of 1.58 infusion sites/month (range 0.3-4.2) 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 (22.7%) subjects and 7/66 (10.6%) subjects most frequently 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), 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, 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 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 US study was a Phase 2/3, prospective, non-controlled, multicenter study to evaluate tolerability and safety and other parameters of SC treatment using Immune Globulin Infusion (Human), 10% (IGI, 10%. IGI, 10% is the same product as IGIV 10% licensed in the 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-pretreated subjects: every three weeks or four weeks, depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects: every three weeks or four weeks, at the discretion of investigator and subject

The rHuPH20 administration was discontinued as of 01 August 2012 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 04 January 2013.

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, 24 completed Epoch 3. Thus, 25 subjects including the one subject who completed Epoch 2 without ever reaching Epoch 3 completed the study.

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: 8.28-10.25]) were comparable to the levels measured at screening (geometric mean: 10.53 g/L [95% CI: 9.46-11.73]).

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.



Median number of infusions per month: 2.90 in Epoch 1; 1.09 in Epoch 2. Median number of infusion sites (needle sticks) per infusion/month: 2.90 in Epoch 1; 1.12 in Epoch 2. Median duration of infusion: less than two hours. Median maximum infusion rate: 240mL/h in Epoch 1; 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: 0.186-0.522) 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 (Immune Globulin (Human) 10% with rHuPH20**

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 and 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, North America, and other countries where the product is licensed, as needed. 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 ever treated with HyQvia will be enrolled. In the European Union (EU) the therapeutic indications for HyQvia are PIDD, CLL, and myeloma. In the USA, HyQvia is licensed for the treatment of PIDD. Although the target population consists mainly of women treated for the approved indications in the respective country, any woman who becomes pregnant after being exposed to HyQvia will be encouraged to participate in the registry.

Visits to the investigator (for example immunologist) and all other medical care will be performed as is standard for the site and for the subject's healthcare.

However, the pregnant subject will be 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 becomes aware of the pregnancy, she should inform the treating physician. According to her treatment, the subject enters the study in one of the following two Study Arms.

Study Arm 1 (Alternative Product Arm): Subjects who stop treatment with HyQvia will be followed in Study Arm 1. The treating physician of the pregnant woman prescribes a licensed human normal immunoglobulin other than HyQvia for IV or SC infusion or an alternative treatment, at his/her discretion.

Study Arm 2 (HyQvia Arm): Subjects who continue treatment with HyQvia according to their treatment regimen will be followed in Study Arm 2.

The overall duration of the study is approximately six years from study initiation (Registry ready to enroll) to study completion (i.e., end data collection). The enrollment period is expected to be three years. The participation period for the pregnant woman is 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.



### 6.3.6 HyQvia PASS 161302

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

This is a non-interventional, prospective, uncontrolled, multi-center, open-label, post-authorization safety study (PASS) 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 are 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, however, 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 recruitment period is expected to be approximately three years. Enrollment started in Q3 2014. 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. It is anticipated that approximately 80 to 120 subjects will be eligible for enrollment in this study.



### 6.3.7 HyQvia Study 161406

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

This prospective, uncontrolled, multi-center, 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.

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.

## 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), 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 SmPC 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 of patients 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. Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study.

#### 6.4.1.1 Pregnancy, Breast Feeding, Fertility

Subcutaneous immunoglobulin G (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 rHuPH20in mice and rabbits. No adverse effects on pregnancy and fetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20were transferred to offspring in utero. The effects of antibodies to the rHuPH20component 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 IG 10% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 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 and recommended to participate in the HyQvia Pregnancy Registry (Study 161301), if available in the respective country.

See Section 6.4.2 for the known risks associated with IGI, 10%.

### 6.4.2 KIOVIG

IGI, 10% administered via IV treatment (KIOVIG) is efficacious and safe in the particular fields of therapeutic use and approved indications, i.e., PIDD, ITP and MMN, as demonstrated in the clinical development program for KIOVIG. Please see the SmPC for KIOVIG.

Serious ARs (defined as SAEs occurring during or within 72 hours of infusion or any casually related SAE occurring within the study period) which occurred in the clinical trials of KIOVIG were aseptic meningitis, pulmonary embolism, and blurred vision.

The most common ARs observed in ≥ 5% of patients were:

- PIDD, IV administration: 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.
- PIDD, SC administration: infusion site (local) event, 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, IV administration: headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

Rare but serious events may occur with IGI products, including hypersensitivity, thrombosis, renal dysfunction/failure, hyperproteinemia, increased serum viscosity, and hyponatremia hemolysis, hemolysis, transfusion related acute lung injury (TRALI), and aseptic meningitis syndrome.



Thrombosis may occur with immune globulin products, including IGI, 10%. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients receiving immune globulin intravenous (IGIV) products including IGI, 10%. Renal dysfunction and acute failure occur more commonly with IGIV products containing sucrose. IGI, 10% does not contain sucrose.

IGI, 10% contains blood group antibodies (isoagglutinins) that may cause hemolysis. Delayed hemolytic anemia can develop subsequent to IGI, 10% therapy due to enhanced red blood cell (RBC) sequestration. Acute hemolysis, consistent with intravascular hemolysis, has been reported. The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥ 2 g/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of hemolysis but its role is uncertain.

Contraindications to IGI treatment include anaphylactic or severe systemic hypersensitivity reactions to IG and IgA deficient patients with antibodies against IgA and a history of hypersensitivity.

IGI, 10% has a high margin of safety. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and preparation. Three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, further increasing the margin of safety. In addition, careful screening and monitoring of subjects in this study will be utilized to minimize the above and other known risks associated with IG therapy (e.g., exclusion criteria, blood group typing at baseline, and laboratory monitoring for hemolysis).

Further information is provided in the SmPC for KIOVIG.

### 6.4.3 Cuvitru

Information about Cuvitru is provided in the SmPC.

### 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, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, 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 safety, tolerability and immunogenicity of HyQvia in pediatric (age two to <18 years) subjects with PIDD.

### 7.2 Primary Objective

The primary objective of the study is to assess the safety of HyQvia treatment in pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment.

### 7.3 Secondary Objectives

Secondary objectives of the study are further assessments (e.g. immunogenicity), tolerability, characteristic of product administration and efficacy (IgG trough levels).

### 7.4 Tertiary Objectives

Tertiary objectives are further safety and efficacy assessments. The study objectives are described in more detail in Section 11, Section 12, Supplement 20.2 and Figure 1.

# 8. STUDY DESIGN

## 8.1 Brief Summary

This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate safety, tolerability, and other parameters of SC treatment using HyQvia in approximately 40 pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment.

The purpose of the study is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric subjects.

## 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 Supplement 20.3 Clinical Laboratory Assessments. In this study approximately 40 pediatric subjects with PIDD will be enrolled, who have received prior immunoglobulin therapy. The study will enroll approximately six subjects aged 2 to <6 years, 12 subjects 6 to <12 years, and 22 subjects 12 to <18 years of age. The study will be conducted in the European Economic Area.



All subjects will have regular anti-rHuPH20 antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months).

Female subjects of childbearing potential should employ birth control measures as advised by the investigator or per the site´s standard recommendations for the duration of the study.

### 8.2.1 Epoch 1

Pediatric patients with PIDD who are on non-HyQvia IV or SC treatment with immunoglobulin (IV-pretreated, SC-pretreated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks. Subjects already treated with HyQvia (HyQvia-pretreated) will be enrolled directly into Epoch 2.

Epoch 1 infusions will be administered at the study site.

### 8.2.2 Epoch 2

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

- For IV-pretreated subjects: every three or four weeks, depending on the subject’s previous IV dosing schedule.

- For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and 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 (see Figure 1 Study Flow Chart in Supplements):

- Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study termination/completion visit 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.

The first two to three infusions during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions 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.



### 8.2.3 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.

In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or 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 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.

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 anti-rHuPH20 antibody titer declines to < 2560 for at least two consecutive measurements, whichever comes first. These subjects complete the study termination/completion visit when the AE/SAE resolves or the anti-rHuPH20 titer is < 2560.

Subjects in Epoch 3 will be treated with KIOVIG (IGI, 10%) intravenously or Cuvitru subcutaneously, at the discretion of the investigator and the subject.

Infusions in Study Epoch 3 will be administered at home or at the study site.

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 five 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 one year.

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

1. Number and rate per infusion (excluding infections) of all severe related AEs
2. Number and rate per infusion (excluding infections) of related SAEs

#### 8.4.2 Secondary Outcome Measures

##### 8.4.2.1 Efficacy

1. Trough levels of IgG (for Study Epoch 1 and 2)

##### 8.4.2.2 Safety/Tolerability

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and ARs
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs
7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs

8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

#### 8.4.2.3 Mode of Product Administration

For Study Epoch 1 and 2

1. Infusions
   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 (3 weeks or 4 weeks)
3. Assessment of Treatment Preference Questionnaire
4. Assessment of HRQoL Questionnaire: Peds-QL, EQ-5D



### 8.4.3 Tertiary Outcome Measures

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

### 8.4.4 Exploratory Outcomes Measure

Not applicable.

### 8.5 Randomization and Blinding

This is a nonrandomized, open-label, active treatment clinical study.

### 8.6 Study Stopping Rules

Stopping rules will not be established for this study as the pediatric subjects will be treated with a licensed human normal immunoglobulin, according to the routine standard at the study site, for the duration of the study.

### 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 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 KIOVIG

**Dosage Form:** Injection, solution

**Packaging:** IGIV, 10% will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials of 5 g (50 mL) and 10 g (100 mL).

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

**Storage**: Refrigeration. IGIV, 10% 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. Prior to use, the unopened 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.



#### 8.7.1.4 Cuvitru

**Dosage form:** Solution for injection

**Packaging:**
5, 10, 20 or 40 ml of solution in a vial (Type I glass) with a stopper (bromobutyl).
Pack size: 1 vial. Not all pack sizes may be available.

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

**Storage and Shelf Life**: Do not store above 25°C. Do not freeze the product.
Shelf Life: 2 years. Do not use if expiration date is exceeded. Keep the container in the outer carton in order to protect from light. Once opened, use immediately.

### 8.7.2 Administration

rHuPH20 will be administered at a dose ratio of 80 U/g IgG before the infusion of IGI, 10%. The full vial of rHuPH20 associated with each vial of IGI, 10% should be used.

rHuPH20 should be injected at a rate of approximately1-2 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.

### 8.7.3 Description of Treatment

#### 8.7.3.1 HyQvia

Subjects will be treated with HyQvia in Study Epoch 1 and Study Epoch 2.

**Dosage Form**: Injection

**Mode of Administration:** subcutaneous

**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 in whom treatment is expected to be every four weeks).

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

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

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

**Table 2**
**Example for IgG dosing**

| Pre-Study | | Epoch 1 (Ramp-Up) | | | Epoch 2 (Final Dose) |
|---|---|---|---|---|---|
| **Admin. Route** | **Dose** | **First Infusion at Baseline: 1-Week Dose** | **Second Infusion at Week 1: 2-Week Dose** | **Third Infusion at Week 3: 3-Week Dose** | |
| IV | 0.6 g/kg every 3 weeks | 0.2 g/kg | 0.4 g/kg | - | 0.6 g/kg every 3 weeks |
| IV | 0.6 g/kg every 4 weeks | 0.15 g/kg | 0.3 g/kg | 0.45 g/kg | 0.6 g/kg every 4 weeks |
| SC | 0.1 g/kg every week | 0.1 g/kg | 0.2 g/kg | - | 0.3 g/kg every 3 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 4 weeks |



**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.

#### 8.7.3.2 KIOVIG

Subjects may be treated with KIOVIG in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** intravenous

The infusion rate and infusion volume per site will follow the suggestions of the KIOVIG SmPC.

**Dosage frequency**: Once every three or four weeks

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study Epoch.

#### 8.7.3.3 Cuvitru

Subjects may be treated with Cuvitru in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** subcutaneous

The infusion rate and infusion volume per site will follow the suggestions of the Cuvitru SmPC.

**Dosage frequency**: daily to once every two weeks, at the investigator´s discretion

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch.



### 8.7.4 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 International Council for Harmonization (ICH) Good Clinical Practice (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 humoral immunodeficiency involving a defect in antibody formation and requiring gammaglobulin replacement, as defined according to the IUIS (International Union of Immunological Societies) Scientific Committee 2015 [1] 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 18 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/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 amino transferase (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 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.



### 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. If the subject has been exposed to rHuPH20, she will be encouraged to participate in the HyQvia Pregnancy Registry (Study 161301), if available in the respective country. If the subject declines to enroll in the registry, attempts will be made to follow the subject through completion of the pregnancy and up to 1 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 and assent form, if applicable. See also Section 16.3) and meets all inclusion and none of the exclusion criteria, 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., 090701) 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., 0003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. 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 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. 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.

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.

All screening procedures must be completed up to 31 days prior to the first infusion. If a subject is scheduled to receive a dose of IgG before eligibility is fully confirmed (eg due to the unavailability of lab results), the subject may continue receiving the IgG product used prior to enrolment. Subjects may be re-screened once.

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, 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.

### 10.4 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 Trimethaprim-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 pretreated 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

An electronic 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 attend school/work or to perform normal daily activities due to illness/infection
- Non-study-required out-patient visits (including urgent care visits to see healthcare providers) and hospitalizations

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic 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.



Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Electronic Patient Reported (EPR) modules will be used to enable deployment of required subject diaries to subjects based on protocol requirements. EPRs can be programmed to allow a certain level of data validation at the time of data entry by the subject; this allows cleaning of subject reported data at the time of data collection. Additionally EPR compliance reports enable monitoring of patient compliance, and proactive follow up if required. EPRs can be deployed in local languages as needed. Automated reminder e-mails are sent to subjects who do not complete required EPRs. Following a certain number of reminder e-mails, the link to that particular EPR is disabled; this ensures that EPRs are collected in a timely manner during the study.

### 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 withdraw 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 that the investigator/designee can further assess and document that the subject (and/or caregiver) is capable of continuing to independently performing self-infusion procedures.

# 11. ASSESSMENT OF EFFICACY

## 11.1 IgG Trough Levels

IgG trough levels will be determined at several time points (see Supplement 20.3 Clinical Laboratory Assessments). Standard assay methods will be used for the determination of IgG and IgG subclasses. The measurement will be performed at the central laboratory.

## 11.2 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 complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

For detailed administration time points, see Supplement 20.2 Schedule of Study Procedures and Assessments.



## 11.3 Treatment Satisfaction Questionnaire for Medication

The Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a 9-item, validated, self-administered instrument to assess patients' satisfaction with medication. The 3 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 complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

For detailed administration time points, see Supplement 20.2 Schedule of Study Procedures and Assessments.

## 11.4 HRQoL Questionnaire

### 11.4.1 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.[39]

Quality of life (QoL) will be assessed separately for the age groups two to four years, and five to seven years, eight to 12 years (PEDS-QL, observer: parent), and 13 to <18 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.



### 11.4.2 EQ-5D

The EQ-5D is a validated, self-administered assessment of overall health designed by the EuroQol Group.[40] It is a descriptive system of HRQoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Subjects are asked to describe their health state that day by choosing 1 of 3 responses that reflect the levels of severity for each of the 5 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 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 <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). 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.

# 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. An AE can therefore 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

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

- Outcome is fatal/results in death (including fetal death)
- 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.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- 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:
  - 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 HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), 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 or paternal 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, a 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 investigator’s brochure 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 investigator’s brochure and/or prescribing information as the Reference Safety Information.

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 signing informed consent 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 Report Form. 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. Subjects who prematurely withdraw from the study because of pregnancy should be encouraged to participate in the pregnancy registry (Study 161301): Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia, if locally available.

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.



**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:

- 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.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- 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 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:

- 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).
- Unlikely related (either one or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- 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
- 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(s) (ECs) 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 documented on an NMC form and reported to the sponsor 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 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 drawing for trough levels will always take place before the infusion is administered.



#### 12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin [Hgb], hematocrit, erythrocytes [i.e., RBC], 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, protein, albumin, ALT, bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, and glucose.

Hematology and clinical chemistry assessments will be performed on 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 there is a reduction in Hgb of two 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 IgG Trough Levels and IgG Subclasses and Specific Antibody Tests

IgG total and IgG subclass trough levels and trough levels of specific antibodies against Clostridium tetani toxoid, Haemophilus influenzae, and HBV will be determined on all subjects.

Testing will be performed at the central laboratory using standard assay methods.

### 12.7.6 Anti-rHuPH20 Antibodies

All subjects will have regular anti-rHuPH20 antibody testing in pre-identified central laboratories (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months, see Supplement 20.3). At any time during the course of the 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:

- 50% hemolytic complement activity of serum,
- serum complement component 3,
- serum complement component 4,
- C1q binding assay, and
- circulating immune complex Raji cell assay.

### 12.7.7 Viral Pathogen Serology

Tests for viral pathogen serology include: HBsAg by enzyme-linked immunosorbent assay (ELISA), 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.

### 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.[41]:

- 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.[42] 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 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/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured as described below:



### 12.8.1 Screening

- All vital signs

### 12.8.2 Infusion at Study Site

1. Within 30 min prior to infusion:
    - All vital signs. Height and weight can be taken at any time at this visit.
2. 30 (± 5) min 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 min 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 US FDA Guidance for Industry to Support Marketing of Human IGIV as Replacement Therapy for Primary Humoral Immunodeficiency [43] and the EMA guideline on the clinical investigation of human normal immunoglobulin for SC and /or intramuscular administration.[44]



### 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/min; respiratory rate >20 breaths/min, 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.[45]

[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 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[vii]. 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 age 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 >two 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 <ten squamous epithelial cells and >25 polymorphonuclear leukocytes at tenX low power magnification to determine suitability of sputum culture.

[vii] Further evaluation, in particular laboratory evaluation (culture and white blood count with differential to evaluate for the presence of immature neutrophils) and chest x-rays, should be aggressively pursued whenever a bacterial pneumonia is suspected

### 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 alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
4. Imaging studies: typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan

# 13. STATISTICS

## 13.1 Sample Size and Power Calculations

The sample size selected for the study is primarily determined by the objective to collect safety data in a sufficient number (about 40) of pediatric (age two to <18 years) subjects with PIDD who have received prior immunoglobulin therapy before enrollment into this study. In addition, the guideline of the CHMP on the clinical investigation of human normal immunoglobulin for SC and/or intramuscular administration [44] indicates that at least 40 patients should be included to evaluate replacement therapy in primary immunodeficiency syndromes.

## 13.2 Analysis Sets

### 13.2.1 Full Analysis Set

All patients who provide informed consent (i.e., sign and date the Informed Consent Form, if applicable), and meet enrollment eligibility (i.e., meets all inclusion criteria and do not meet any exclusion criteria) will be included in the full analysis set.

### 13.2.2 Per-Protocol Analysis Set

All patients in the full analysis set who have no major protocol deviations will be included in the per-protocol analysis set.

### 13.2.3 Safety Analysis Set

The safety analysis set will contain all subjects in the full analysis set who receive at least one dose of HyQvia.



## 13.3 Handling of Missing, Unused, and Spurious Data

The handling of missing, unused or spurious data will be described in the statistical analysis plan (SAP).

## 13.4 Methods of Analysis

In this study no hypothesis will be tested. Detailed statistical analysis methods will be described in the SAP. Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. If groups of sufficient sample size (such as age groups or PIDD types) are available, CIs may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class and preferred term. Tables will be prepared to list for each SAE and non-serious AE the number of events and the number of subjects who experienced one or more event. All analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

### 13.4.1 Primary Outcome Measure

- Number and rate per infusion (excluding infections) of all severe related AEs
- Number and rate per infusion (excluding infections) of related SAEs

For the endpoint of incidence of all severe related AEs and related SAEs, a point estimate and corresponding 95% CI (by the Wilson score method) for the proportion of subjects with one or more related SAEs will be provided. In addition, incidence of all severe related AEs and related SAEs will be calculated as rate per infusion and rate per subject-year, and will be analyzed for changes in frequency and for changes in severity over time. All SAEs will be listed. No statistical hypotheses will be tested.

### 13.4.2 Secondary Outcome Measures

#### 13.4.2.1 Efficacy

Trough levels of IgG (for Study Epoch 1 and 2): Descriptive statistics will be provided for the trough level of IgG for study Epoch 1 and 2.



#### 13.4.2.2 Safety

The following secondary safety endpoints will be analyzed:

- Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
- Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
- Number and rate per infusion (excluding infections) of local AEs and ARs
- Number and rate per infusion (excluding infections) of systemic AEs and ARs
- Number and rate per infusion (excluding infections) of all AEs and all ARs
- Number and rate per infusion (excluding infections) of all temporally associated AEs
- Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
- Number and rate per infusion (excluding infections) of all SAEs
- Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

Descriptive methods, mainly frequency tables, will be used for all secondary safety endpoints. In addition, incidence of all secondary safety endpoint will be calculates as rate per infusion and rate per subject-year.

#### 13.4.2.3 Mode of Product Administration (For Study Epoch 1 and 2)

- Number of Infusions
- Number of infusions per month
- Number of infusion sites (needle sticks) per infusion/month
- Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion)Maximum infusion rate/site
- Infusion volume/site
- Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE Number of weeks to reach final dose interval (defined as three or four weeks infusion interval)

Nonparametric descriptive statistics (median, quartiles, and range) will be calculated and reported for the infusion administration variables. Frequency table will show the number/proportion of infusions discontinued, slowed or interrupted due to AE and total observation time in subject-years.



#### 13.4.2.4 HRQoL

- Treatment Preference Questionnaire
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- HRQoL Questionnaire: Peds-QL, EQ-5D

Total and domain scores on each of the HRQoL measures will be calculated for each subject, at each data assessment time point. Descriptive statistics will be shown for each of the scores, at each data assessment time point.

### 13.4.3 Tertiary Outcome Measures

#### 13.4.3.1 Infections

- Number of acute serious bacterial infections
- Number of all infections
- Days on antibiotics

For the endpoint of incidence of acute serious bacterial infection and all infections a point estimate and 95% CI (by the Wilson score method) for the proportion of subjects with one or more infection will be calculated. In addition, incidence of all infection endpoints will be calculates as rate per infusion and rate per subject-year. Descriptive statistics will be performed and reported for the days on antibiotics.

#### 13.4.3.2 Healthcare Resource Utilization Endpoints

- Days not able to go to school/work or to perform normal daily activities
- 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

Healthcare resource utilization endpoints, including hospitalization, acute physician visits and days missed for school/work or normal daily activities, will be summed and annualized for reporting purposes. Descriptive statistics will be performed and reported.



### 13.5 Planned Interim Analysis of the Study

Annual reports will be prepared. Details will be described in the SAP.

## 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. The coordinating investigator will be selected before study start.



## 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 review board (ISRB).

The ISRB 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 ISRB will be composed of appropriate sponsor representatives from the relevant functions (e.g., Global Drug Safety, Clinical Research, Medical Affairs, Clinical Development) with expertise/specialization in PIDD clinical care and research. The ISRB can 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 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

Inter-laboratory standardization methods will be described in the data management plan as needed.

# 16. ETHICS

## 16.1 Subject Privacy

The study protocol, documentation, data and all other information generated will be held in strict confidence and in accordance with applicable laws, regulations, and guidelines. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.

Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

## 16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information will be reviewed and approved/given favorable opinion by the ethics committee (EC) and applicable regulatory authorities. The IB, if applicable, 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 informed consent form before enrollment into the study according to applicable national and local regulatory requirements and ICH GCP. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

An assent form may be provided and should be signed by patients enrolled in the study. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2).

The informed consent form 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 informed consent form, 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 informed consent form 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 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 informed consent forms, 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.

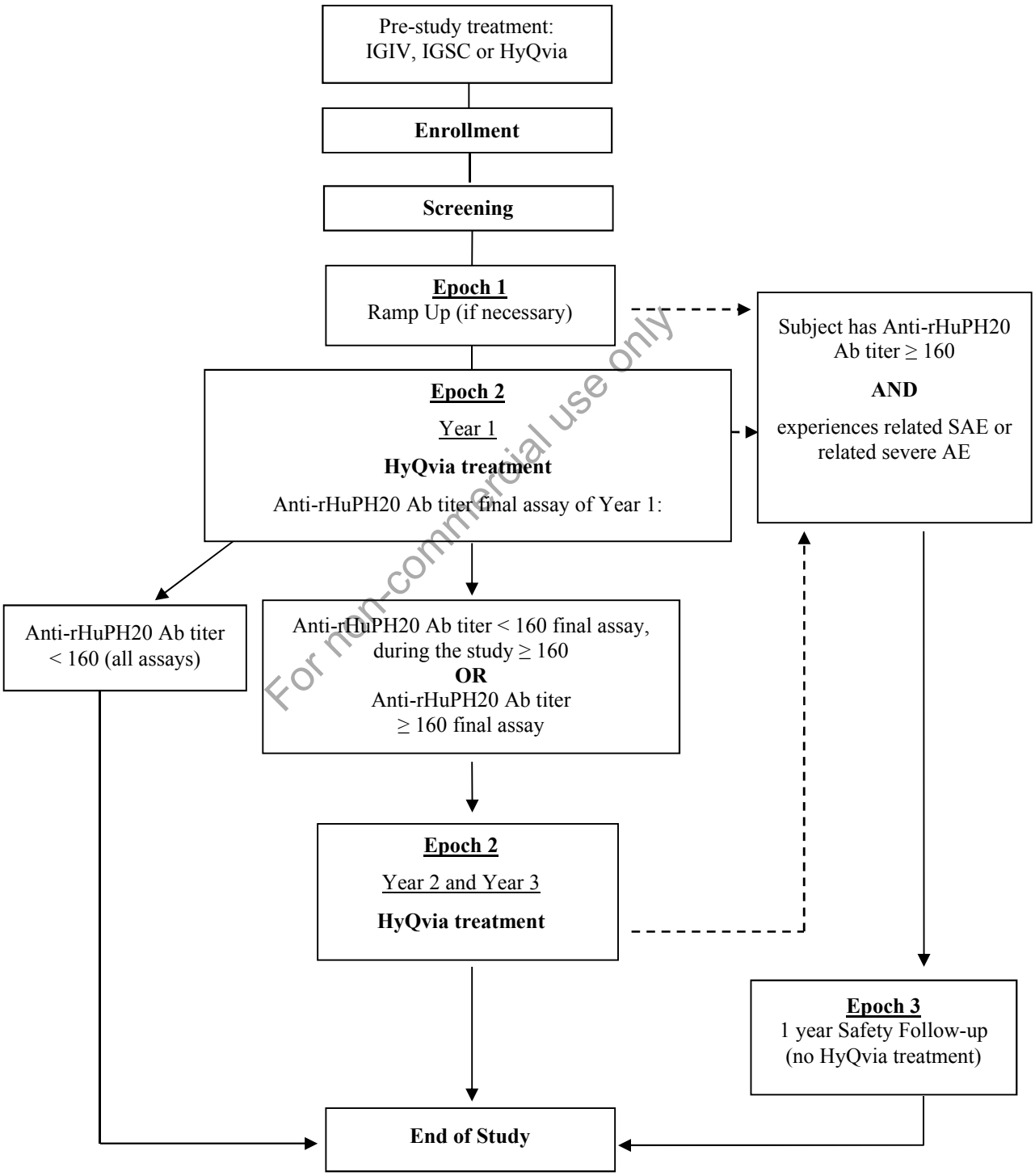
## 19. PUBLICATION POLICY

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 161504**



## 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 | Enrollment / Screening | Treatment Visit in Study Epoch 1 | | |
|---|---|---|---|---|
| | | First Infusion: Baseline | Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals) | Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-Week Treatment Intervals) |
| Location | Site | Site | Site | Site |
| Informed Consent[a] | x | | | |
| Eligibility Criteria | x | | | |
| Infusion | | 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)/ Treatment Preference questionnaire, TSQM-9 Assessment | | x | | |

[a] Occurs prior to any study-specific procedure.
[b] For laboratory assessments, see Supplement 20.3

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

| Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 2 (Visit +/- 2 weeks) | | | | | |
|---|---|---|---|---|---|---|
| | Month 0 | Month 3 | Month 6 | Month 9 | Month 12[a] | Study Completion/ Termination Visit (at Next Infusion), if Applicable |
| Location | Site | Site | Site | Site | Site | Site |
| Informed Consent | | | | | | |
| Infusion[a] | 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 | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x |
| HRQoL (PedsQL, EQ-5D), Treatment Preference questionnaire, TSQM-9 Assessment | | | | | x | x |

[a] Further (additional) infusions may be administered after 12 months if rHuPH20-antibody results not available. AEs, concomitant medications, and non-drug therapies will continue to be recorded until EOS or continuation of Epoch 2 (dependent on antibody assay result).

**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 (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 | 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 | x | x | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x | x | x |
| HRQoL (PedsQL, EQ-5D)/ Rx-Preference, TSQM-9 Assessment | | | | x | | | | x |

[a] In case a subject has an anti-rHuPH20 antibody titer ≥ 160 and experiences a related serious or severe AE, the subject may go to Study Epoch 3 and will have the Study Completion/Termination Visit at the end of this Epoch

**Table 6**
**STUDY EPOCH 3**
**Schedule of Study Procedures and Assessments**

| Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 3 (Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|
| | **Month 0** | **Month 3** | **Month 6** | **Months 9** | **Month 12/ Study Completion/ Termination Visit[a]** |
| Location | Site | Site | Site | Site | Site |
| Infusion | x | x | x | x | |
| Concomitant Medications | x | x | x | x | x |
| Non-drug Therapies | x | x | x | x | x |
| Physical Exam[b] | 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 (PedsQL, EQ-5D Treatment Preference questionnaire, TSQM-9 Assessment | | | | | |

[a] Includes for cases of withdrawal or discontinuation.
[b] Occurs prior to any study-specific procedure.
[c] For laboratory assessments, see Supplement 20.3.

## 20.3 Clinical Laboratory Assessments

**Table 7**
**STUDY EPOCH 1 – Ramp Up**
**Clinical Laboratory Assessments**

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Enrollment / Screening | Treatment Visit in Study Epoch 1 | | |
|---|---|---|---|---|
| | | First Infusion: Baseline | Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals) | Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-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 | | |

**Table 8**
**STUDY EPOCH 2 – Year 1**
**Clinical Laboratory Assessments**

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 2 (Visit +/- 2 Weeks) | | | | | |
|---|---|---|---|---|---|---|
| | Month 0 | 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 | x[a] | | | | | |
| Specific Antibody Tests | | | | | | |
| 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 two 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 in section 12.7.4 within 72 hours in addition to the prescribed tests

**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 (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 Tests[b] | | | | x | | | | |
| Specific Antibody Tests | | | | | | | | 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 has an anti-rHuPH20 antibody titer ≥ 160 and experiences a related serious or severe AE, the subject may go to Study Epoch 3 and will have the Study Completion/Termination Visit at the end of this Epoch.

[b] If there is a reduction in Hgb of two 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 in section 12.7.4 within 72 hours

**Table 10**
**STUDY EPOCH 3**
**Clinical Laboratory Assessments**

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 3 (Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|
| | Month 0 | 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 | | | x | | |
| Specific Antibody Tests | | | | | x |
| IgG Trough Levels and IgG Subclasses | x | | x | | x |
| Antibodies to rHuPH20 | x | x | x | x | x |

## 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 |
| 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: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, 5 (not shown in the table)=death. Grading scale criteria taken from ECOG [41] and WHO [42] guidelines, with the exception of LDH that uses the same thresholds as defined for ALT and AST

## 21. REFERENCES

1. Picard C, Al-Herz W, Bousfiha A et al. Primary immunodeficiency diseases: An update on the classification from the International Union of Immunological Societies Expert Committee for Pri mary Immunodeficiency 2015. J.Clin.Immunol. 2015;35:696-726.

3. Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9:722-728.

4. Rosen FS, Cooper MD, Wedgwood RJ. The primary immunodeficiencies. N.Engl.J.Med. 1995;333:431-440.

5. Wolin MJ, Gale RP. IVIG in bone marrow transplantation. In: Lee ML, Strand V, eds. Intravenous Immunoglobulins in Clinical Practice. New York: Marcel Dekker, Inc.; 1997:113-118.

6. Griffiths H, Chapel H. Prevention of infections in B-cell lymphoproliferative diseeases. In: Lee ML, Strand V, eds. Intravenous Immunoglobulins in Clinical Practice. New York: Marcel Dekker; 1997:203-223.

7. Rechtman DJ. Use of intravenous immune globulin in adults with HIV disease. In: Lee ML, Strand V, eds. Intravenous Immunoglobulins in Clinical Practice. New York: Marcel Dekker, Inc.; 1997:167-174.

8. Abdel-Mageed A, Graham-Pole J, Del Rosario ML et al. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplant. 1999;23:929-932.

9. George JN, Raskob GE. Idiopathic thrombocytopenic purpura: diagnosis and management. Am.J.Med.Sci. 1998;316:87-93.

10. Imbach P, Akatsuka J, Blanchette V et al. Immunthrombocytopenic purpura as a model for pathogenesis and treatment of autoimmunity. Eur.J.Pediatr. 1995;154:S60-S64.

11. McMillan R. The pathogenesis of chronic immune (idiopathic) thrombocytopenic purpura. Semin.Hematol. 2000;37:5-9.

12. Barron KS, Murphy DJ, Jr., Silverman ED et al. Treatment of Kawasaki syndrome: a comparison of two dosage regimens of intravenously administered immune globulin. J.Pediatr. 1990;117:638-644.

13. Rosenfeld EA, Shulman ST, Corydon KE et al. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. J.Pediatr. 1995;126:1000-1003.

14. Hahn AF, Beydoun SR, Lawson V et al. A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy. J.Peripher.Nerv.Syst. 2013;18:321-330.

15. Rozman C, Montserrat E. Chronic lymphocytic leukemia. N.Engl.J.Med. 1995;333:1052-1057.

16. Kyle RA, Rajkumar SV. Multiple myeloma. N.Engl.J.Med. 2004;351:1860-1873.

17. Gardulf A, Nicolay U, Asensio O et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies - A prospective multi-national study. J.Clin.Immunol. 2006;26:177-185.

18. Ochs HD, Gupta S, Kiessling P et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J.Clin.Immunol. 2006;26:265-273.

19. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann.Intern.Med. 1980;93:55-56.

20. Welch MJ, Stiehm ER. Slow subcutaneous immunoglobulin therapy in a patient with reactions to intramuscular immunglobulin. J.Clin.Immunol. 1983;3:285-286.

21. Roord JJ, van der Meer JW, Kuis W et al. Home treatment in patients with antibody deficiency by slow subcutaneous infusion of gammaglobulin. Lancet 1982;1:689-690.

22. Gardulf A, Björvell H, Gustafson R, Hammarström L, Smith CI. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. Immunodeficiency. 1993;4:81-84.

23. Gustafson R, Gardulf A, Hansen S et al. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. Clin.Exp.Immunol. 2008;152:274-279.

24. Gardulf A, Andersen V, Björkander J et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet 1995;345:365-369.

25. Gardulf A, Hammarström L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991;338:162-166.

26. Gardulf A, Hammarström L. Subcutaneous administration of immunoglobulins. What are the advantages? Clin.Immunother. 1996;6:108-116.

27. Schiff RI, Rudd C. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. J.Clin.Immunol. 1986;6:256-264.

28. Smith GN, Griffiths B, Mollison D, Mollison PL. Uptake of IgG after intramuscular and subcutaneous injection. Lancet 1972;1:1208-1212.

29. ZLB Behring. Immune Globulin Subcutaneous (Human), Vivaglobin®. US Label. 8. 2006.
Link to Publisher´s Site:
http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm070360.pdf

30. Wasserman RL, Melamed I, Nelson RP, Jr. et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin.Pharmacokinet. 2011;50:405-414.

31. Supersaxo A, Hein WR, Steffen H. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. Pharm.Res. 1990;7:167-169.

32. Olsson O, Löjgren O. Hyaluronidase as a factor hastening the spread and absorption of water-soluble radiopaque substances deposited intracutaneously, subcutaneously, or intramuscularly. Acta Radiol. 1949;31:250-256.

33. Thomas JR, Yocum RC, Haller MF, von Gunten CF. Assessing the role of human recombinant hyaluronidase in gravity-driven subcutaneous hydration: The INFUSE-LR Study. J.Palliat.Med. 2007;10:1312-1320.

34. Shpilberg O, Jackisch C. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. Br.J.Cancer 2013;109:1556-1561.

35. Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. J.Infus.Nurs. 2007;30:293-299.

36. Rosengren S, Dychter SS, Printz MA et al. Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. AAPS J. 2015;17:1144-1156.

37. Melamed IR, Stein MR, Wasserman RL et al. Recombinant human hyaluronidase facilitates dispersion of subcutaneously administered Gammagard Liquid and enables administration of a full monthly dose in a single site to patients with immunodeficiency diseases [abstract]. J.Allergy Clin.Immunol. 2008;121:S83.

38. Wasserman RL, Melamed I, Stein MR et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J.Allergy Clin.Immunol. 2012;130:951-957.e11.

39. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med.Care 1999;37:126-139.

40. Rabin R, de Charro F. EQ-5D: A measure of health status from the EuroQol Group. Ann.Med. 2001;33:337-343.

41. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am.J.Clin.Oncol. 1982;5:649-655.

42. World Health Organization. Toxicity grading scale for determining the severity of adverse events. 96. 2-20-2003. World Health Organization (WHO).
Link to Publisher´s Site:
http://www.icssc.org/Documents/Resources/AEManual2003AppendicesFebruary_06_2003%20final.pdf

43. U.S.Department of Health and Human Services, Food and Drug Administration, and Center for Biologics Evaluation and Research. Guidance for industry: Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. 17. 2008. U.S. Department of Health and Human Services, Food and Drug Administration (FDA).

44. Committee for Medicinal Products for Human Use. Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg). EMA/CHMP/BPWP/410415/2011 rev 1, 10. 7-23-2015. European Medicines Agency (EMEA).
Link to Publisher´s Site:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500190211.pdf

45. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr.Crit.Care Med. 2005;6:2-8.

## 22. SUMMARY OF CHANGES

**Protocol 161504 Amendment 1 2016 OCT 07**

**Replaces:** Original: 2016 MAR 16

In this section, changes from the previous version of the Protocol, dated 2016 MAR 16, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Minor grammatical 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 product name of SUBCUVIA was replaced by Cuvitru.
   Purpose for Change: SUBCUVIA may no longer be available in countries with participating sites at a certain stage of the study. To prevent issues with product supply, Cuvitru will be used instead.

3. **Protocol Title Page,**
   **Investigator Acknowledgement Pages**
   Description of Change: The EudraCT Number was provided.
   Purpose for Change: Administrative.

4. **Section 1.1 Protocol Title Page,**
   **Investigator Acknowledgement Page for Coordinating Investigator**
   Description of Change: [redacted] was replaced by [redacted].
   Purpose for Change: Administrative.

5. **Section 2 Serious Adverse Event Reporting**
   Description of Change: Instructions for SUSAR reporting were added, and the text "See SAE Protocol Section for further information and SAER form for contact information. Further details are also available in the study team roster" was replaced by "Drug Safety contact information: See SAE Report form. Refer to SAE Protocol Sections and the study ream roster for further information."
   Purpose for Change: To clarify the reporting requirement for SUSARs and to match the requirements of the latest revision of the Sponsor´s protocol template.

6. **Section 3 Synopsis,**
**Section 8.2.3 Epoch 3**
Description of Change: The sentence "These subjects complete the study termination/completion visit when the AE/SAE resolves and the anti-rHuPH20 titer is < 2560." was changed to "These subjects complete the study termination/completion visit when the AE/SAE resolves *or* the anti-rHuPH20 titer is < 2560."
Purpose for Change: Only one condition must be met to complete the study.

7. **Section 3 Synopsis,**
**Section 6.4.2 KIOVIG,**
Description of Change: References to the Investigator´s Brochure (IB) for KIOVIG were deleted, the term "product information" was replaced by "SmPC".
Purpose for Change: KIOVIG is a registered product. Reference information is provided in the SmPC, no IB will be made available for KIOVIG.

8. **Section 3 Synopsis,**
**Section 8.7.3.3 Cuvitru**
Description of Change: Reference to the SUBCUVIA product information was replaced by a reference to the Cuvitru SmPC.
Purpose for Change: Cuvitru will be used instead of SUBCUVIA.
Description of Change: The dosage frequency of product administration was changed from "Once every week or biweekly" to "daily to once every two weeks, at the investigator´s discretion".
Purpose for Change: To match the dosing frequency suggestions of the SmPC for Cuvitru.

9. **Section 3 Synopsis,**
**Section 9.1 Inclusion Criteria**
Description of Change: "…and by diagnostic criteria according to Conley et al.[2]" was removed.
Purpose for Change: Not applicable.

10. **Section 3 Synopsis,**
**Section 9.2 Exclusion Criteria**
Description of Change: "…in the opinion of the investigator." Was added at the end of the sentence describing it. 9.
Purpose for Change: To clarify assessment criteria for "severe dermatitis".

11. **Section 6.1.2 KIOVIG 100 mg/ml solution for infusion and Cuvitru 200 mg/ml solution for injection;**
**Section 8.7.1.4 Cuvitru**
Description of Change: The description of SUBCUVIA was replaced by the description of Cuvitru.
Purpose for Change: To provide information on Cuvitru. SUBCUVIA may no longer be available in countries with participating sites at a certain stage of the study. To prevent issues with product supply, Cuvitru will be used instead.

12. **Section 6.1.2 KIOVIG 100 mg/ml solution for infusion and Cuvitru 200 mg/ml solution for injection;**
**Section 8.7.1.4 Cuvitru**
Description of Change: The description of SUBCUVIA was replaced by the description of Cuvitru.
Purpose for Change: To provide information on Cuvitru. SUBCUVIA may no longer be available in countries with participating sites at a certain stage of the study. To prevent issues with product supply, Cuvitru will be used instead.

13. **Section 6.4.1 HyQvia**
Description of Change: The reference to the IB for Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20) as well as Prescribing Information for HyQvia was deleted.
Purpose for Change: HyQvia is a registered product. Reference information will be provided in the SmPC. An IB or local prescribing information will not be provided by the Sponsor.

14. **Section 8.2 Overall Study Design**
Description of Change: "Female subjects of childbearing potential should employ birth control measures as advised by the investigator or per the site´s standard recommendations for the duration of the study.
Purpose for Change: Clarify expectations as to which birth control measures are considered adequate.

15. **Section 8.8 Source Data**
Description of Change: "Source data for this study comprise the following" […]" was changed to "Source data for this study comprise, but are not limited to, the following: […]".
Purpose for Change: For clarity.

16. **Section 10.1 Informed Consent**

Description of Change: A reference to Section 16.3. Informed Consent was added. Wording (in italics) was added: "…is considered *enrolled in the study and thus becomes* a subject in the study".
Purpose for Change: To cross-reference the procedure of obtaining informed consent, and to specifically define enrollment.

17. **Section 10.3 Screening and Study Visits**

Description of Change: "The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent." was replaced by "Screening will comprise all procedures to confirm subject eligibility. The investigator is responsible for maintaining a patient identification list that includes all enrolled subjects which includes the following information: subject´s full name, subject number, and site number."
Purpose for Change: To define screening; for clarity.

Description of Change: The following paragraph was added "All screening procedures must be completed up to 31 days prior to the first infusion. If a subject is scheduled to receive a dose of IgG before eligibility is fully confirmed (eg due to the unavailability of lab results), the subject may continue receiving the IgG product used prior to enrolment. Subjects may be re-screened once."
Purpose for Change: To specify timelines for screening, to provide an option to treat the subject in the time period between signing the informed consent and first IP infusion, and to limit the number of re-screenings.



18. **Section 12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)**

Description of Change: Section 12.1.1.2 was added. Former Section 12.1.2.3 Safety Reporting was deleted.
Purpose for Change: To define SUSAR and clarify related reporting requirements.

19. **Section 12.1.2 Assessment of Adverse Events**

Description of Change: Text *in italics* was added: "If an investigator becomes aware of an SAE occurring in a subject *within 30 days* after study completion, …"
Purpose for Change: To limit reportability of SAEs after study completion.

20. **Section 12.7 Clinical Laboratory Parameters**
Description of Change: A sentence "Blood drawing for trough levels will always take place before the infusion is administered." was deleted from Section 12.7.5 IgG Trough Levels and IgG Subclasses and Specific Antibodies, and was added to Section 12.7. instead.
Purpose for Change: To define the time point for blood drawing for all trough level measurements.

21. **Section 12.7.5 IgG Trough Levels and IgG Subclasses and Specific Antibody Tests**
Description of Change: Types of specific antibodies were specified, and the time point for blood drawing was defined.
Purpose for Change: To clarify which types of specific antibodies will be measured, and to further clarify the time point of the blood draws.

22. **Section 15 Quality Control and Quality Assurance;**
**Section 16 Ethics;**
**Investigator Acknowledgement Pages**
Description of Change: "… applicable regulatory requirements…" was changed to "…applicable national and local regulatory requirements…" throughout the sections´ text.
Purpose for Change: To further specify regulatory requirements and to match text to the latest applicable version of the Sponsor´s protocol template.

23. **Section 15.6 Non-Compliance with the Protocol**
Description of Change: "… responsible EC is notified…" was changed to "… responsible EC and relevant competent authority is notified…".
Purpose for Change: To further specify reporting requirements and to match text to the latest applicable version of the Sponsor's protocol template.

24. **Section 16.1 Subject Privacy**
Description of Change: Entire text of Section 16 was replaced.
Purpose for Change: To harmonize language with Shire´s requirements for standard privacy language after Baxalta becoming part of Shire.

25. **Section 16.3 Informed Consent**
Description of Change: Text *in italics* was changed or added: "All patients and/or their legally authorized representative must sign an informed consent form before *enrollment* into the study according to applicable national and local regulatory requirements and ICH GCP. *The case history for each individual shall document that informed consent was obtained prior to participation in the study.*"
Purpose for Change: To clarify expectations regarding the documentation of the IC process.

26. **Section 20.1 Study Flow Chart**
Description of Change: A box "Screening" was added.
Purpose for Change: For clarity.

27. **Section 20.2 Table 6**
Description of Change: HRQoL (PedsQL, EQ-5D Treatment Preference questionnaire, TSQM-9) assessments were removed from the table.
Purpose for Change: Subjects will not receive HyQvia during Epoch 3, therefore, no HRQoL assessments on HyQvia will be done

28. **Section 20.3 Table 6**
Description of Change: Retention samples were deleted from the table.
Purpose for Change: No retention samples will be taken (section 12.7.9).

29. **Section 20.3 Table 8**
Description of Change: The same footnote as in Table 9 was added to Hemolysis Tests.
Purpose for Change: For clarity.

30. **Section 20.3 Table 8**
Description of Change: Text in footnote b. ".. tests described above …" was replaced by "tests described in section 12.7.4 ….".
Purpose for Change: To correct reference.

31. **Section 20.3, Table 8**
Description of Change: Specific antibody testing at visit month 6 was deleted.
Purpose for Change: The trough levels of specific antibodies will be measured only at the baseline and the study completion/termination visits.

## INVESTIGATOR ACKNOWLEDGEMENT

**PRODUCT:** HyQvia

**STUDY TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

**PROTOCOL IDENTIFIER: 161504**

**CLINICAL TRIAL PHASE 4**

**AMENDMENT 1: 2016 OCT 07**

**Replaces: ORIGINAL: 2016 MAR 16**

**ALL VERSIONS:**

**Amendment 1: 2016 OCT 07**
**ORIGINAL: 2016 MAR 16**

**Original: 2016 MAR 16OTHER ID(s)**
**NCT Number:** Not Yet Available
**EudraCT Number**: 2016-003438-26
**IND NUMBER:** Not Applicable



By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

## INVESTIGATOR ACKNOWLEDGEMENT

**PRODUCT:** HyQvia

**STUDY TITLE:** Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases

**PROTOCOL IDENTIFIER: 161504**

**CLINICAL TRIAL PHASE 4**

**AMENDMENT 1: 2016 OCT 07**

**Replaces: ORIGINAL: 2016 MAR 16**

**ALL VERSIONS:**
**Amendment 1: 2016 OCT 07**
**Original: 2016 MAR 16**

**OTHER ID(s)**
**NCT Number:** Not Yet Available
**EudraCT Number**: 2016-003438-26
**IND NUMBER:** Not Applicable



By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD, [redacted]
Global Clinical Development Operations

| | |
|---|---|
| **PROTOCOL:** | **161504** |
| **Title:** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases |
| **Short Title:** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD subjects |
| **Study Phase:** | Phase 4 |
| **Drug:** | HyQvia |
| **IND Number:** | Not Applicable |
| **EUDRACT Number:** | 2016-003438-26 |
| **NCT Number** | NCT03116347 |
| **Sponsor:** | Baxalta US Inc.*<br>300 Shire Way, Lexington, MA 02421<br>UNITED STATES<br><br>AND<br><br>Baxalta Innovations GmbH*,<br>Industriestrasse 67, A-1221 Vienna<br>AUSTRIA<br><br>*Baxalta is now part of Shire |
| **Principal / Coordinating Investigator:** | Multicenter |
| **Protocol History:** | **Amendment 2:** 2019 DEC 04<br><br>Replaces: Amendment 1: 2016 OCT 07 |

# PROTOCOL SIGNATURE PAGE

## Sponsor's (Shire) Approval

| Signature: | Date: |
|---|---|
| [redacted], MD<br>[redacted], Clinical Medicine<br>Plasma-Derived Therapies Business Unit Research & Development | |

## Investigator's Acknowledgement

I have read this protocol for Study 161504.

**Title:** Post-Authorization Safety, Tolerability and Immunogenicity 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], Clinical Medicine
Plasma-Derived Therapies Business Unit Research & Development

## 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 ANDTRANSMITTED 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 PH20 (IGI, 10% with rHuPH20).<br>2. KIOVIG 100 mg/mL solution for infusion<br>3. Cuvitru 200 mg/mL solution for subcutaneous injection<br><br>(For better readability the names HyQvia, KIOVIG and Cuvitru will be used throughout the document.) |
| **Name(s) of Active Ingredient(s)** | Human Normal Immunoglobulin |
| **CLINICAL CONDITION(S)/INDICATION(S)**<br>• Primary Immunodeficiency Diseases (PIDD) | |
| **PROTOCOL ID** | 161504 |
| **PROTOCOL TITLE** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases |
| **Short Title** | Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric PIDD subjects |
| **STUDY PHASE** | Ph4 (post-authorization) |
| **PLANNED STUDY PERIOD** | |
| **Initiation** | 2016 |
| **Primary Completion** | 2023 |
| **Study Completion** | 2023 |
| **Duration** | Approximately seven years |
| **STUDY OBJECTIVES AND PURPOSE** | |
| **Study Purpose**<br>The purpose of the study is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age two to <18 years) subjects with Primary Immunodeficiency Diseases (PIDD). | |
| **Primary Objective**<br>Safety of HyQvia treatment in pediatric subjects with PIDD who have received prior immunoglobulin therapy before enrollment into the study. | |
| **Secondary Objective(s)**<br>Further safety assessments (e.g. immunogenicity), tolerability, characteristics of product administration and efficacy (immunoglobulin G [IgG] trough levels) | |

| STUDY DESIGN | |
|---|---|
| **Study Type/ Classification/ Discipline** | Safety, Immunogenicity |
| **Control Type** | No control |
| **Study Indication Type** | Treatment |
| **Intervention Model** | Single-group |
| **Blinding/Masking** | Open-label |
| **Study Design** | This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate the safety, tolerability, and other parameters of subcutaneous (SC) treatment using HyQvia in 40 pediatric subjects with PIDD who have received immunoglobulin therapy before enrollment into this study. Subjects will have regular anti-recombinant human hyaluronidase PH20 (rHuPH20) antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months).<br><br>**Epoch 1:** Pediatric patients with PIDD who are on non-HyQvia intravenous (IV) or SC treatment with immunoglobulin (IV-pretreated, SC pretreated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks. Subjects already treated with HyQvia (HyQvia pretreated) will be enrolled directly into Epoch 2. Epoch 1 infusions will be administered at the study site.<br><br>**Epoch 2:** The ramp-up (Epoch 1) is followed by Epoch 2 with HyQvia treatment at the following intervals. For IV-pretreated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule. For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and 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 (see Section 20.1 Study Flow Chart). Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study termination/completion visit 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.<br><br>The first two or three infusions during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions be performed at home (or equivalent site) by the subject or 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.<br><br>**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 related Serious Adverse Event (SAE) or a related severe Adverse Event (AE) will be followed accordingly.<br><br>Subjects in Epoch 3 will be treated with KIOVIG intravenously or Cuvitru subcutaneously, at the discretion of the investigator and the subject.<br><br>In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or 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.<br><br>Subjects with antibody titer of ≥ 160 when entering Epoch 3 continue regular anti-rHuPH20 antibody testing (approximately every three months) for approximately one year. These subjects complete the study termination or completion visit when the AE or SAE resolves or the anti-rHuPH20 titer is <2560.<br><br>Infusions in Study Epoch 3 will be administered at home or at the study site.<br><br>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 for HyQvia-naïve subjects<br>Study Epoch 2 (Final dosing): Up to three years<br>Study Epoch 3 (Safety Follow-up): Up to one year<br>The maximum subject participation period is approximately four years. |
| **Primary Outcome Measure**<br>1. Number and rate per infusion (excluding infections) of all severe related AEs<br>2. Number and rate per infusion (excluding infections) of related SAEs | |

**Secondary Outcome Measure(s)**

**Efficacy**

1. Trough levels of IgG (for Study Epochs 1 and 2)

**Safety**

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and Adverse Reactions (ARs)
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs
7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20
10. Additional safety outcome measures include clinical laboratory outcomes: raw (actual) values and change from baseline, and vital signs: raw (actual) values and change from baseline

**Mode of Product Administration** (For Study Epochs 1 and 2)

1. Infusions
    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)
3. Assessment of Treatment Preference Questionnaire
4. Assessment of Treatment Satisfaction Questionnaire for Medication: TSQM-9
5. Assessment of Health-related Quality of Life Questionnaires: Peds-QL, EQ-5D

**Tertiary Outcome Measure(s)**

1. Number of acute serious bacterial infections
2. Number of all infections
3. Days not able to go to school/work or to perform normal daily activities due to infection or other illnesses

4. Days on antibiotics
5. Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized
6. Number of acute physician visits (office and emergency room) due to infection or other illnesses

**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**: injectable

   **Mode of Administration:** subcutaneous

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

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

   Example for IgG dosing:

| Pre-Study | | Epoch 1 (Ramp-Up) | | | Epoch 2 (Final Dose) |
|---|---|---|---|---|---|
| **Admin. Route** | **Dose** | **First Infusion at Baseline: 1-Week Dose** | **Second Infusion at Week 1: 2-Week Dose** | **Third Infusion at Week 3: 3-Week Dose** | |
| IV | 0.6 g/kg every 3 weeks | 0.2 g/kg | 0.4 g/kg | - | 0.6 g/kg every 3 weeks |
| IV | 0.6 g/kg every 4 weeks | 0.15 g/kg | 0.3 g/kg | 0.45 g/kg | 0.6 g/kg every 4 weeks |
| SC | 0.1 g/kg every week | 0.1 g/kg | 0.2 g/kg | - | 0.3 g/kg every 3 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 4 weeks |

**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.

**2. KIOVIG**

Subjects may be treated with KIOVIG in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** intravenous

The infusion rate and infusion volume per site will follow the suggestions of the KIOVIG SmPC.

**Dosage frequency**: Once every three or four weeks

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch

**3. Cuvitru**

Subjects may be treated with Cuvitru in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: Solution for injection

**Mode of Administration:** subcutaneous

The infusion rate and infusion volume per site will follow the suggestions of the Cuvitru SmPC.

**Dosage frequency**: daily to once every two weeks, at the investigator´s discretion

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch.

| SUBJECT SELECTION | |
|---|---|
| **Targeted Accrual** | Sample size: 40 pediatric subjects already on IgG treatment pre-study will be enrolled. The study will enroll approximately six subjects 2 to less than 6 years of age, 12 subjects 6 to <12 years of age, 22 subjects 12 to <18 years of age. The study will be conducted in the European Economic Area.<br><br>Study sites: Approximately 20 |
| **Number of Groups/ Arms/Cohorts** | 1 |

**Inclusion Criteria**

1. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency 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 investigational product (IP) in the study.
2. Subject is at least 2 years and below 18 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.



**Exclusion Criteria**

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 amino transferase (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/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 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 the study is 40 pediatric subjects.

**Planned Statistical Analysis**

Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. All SAEs and non-serious AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. All analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

A single interim analysis is planned to be performed. The purpose of the analysis is to update the scientific community, on the interim safety, tolerability and immunogenicity of HyQvia in pediatric subjects with PIDD. Analysis is planned to be performed when 75% of all subjects (30 subjects if 40 are enrolled [dosed]) have completed 12 months of participation (1-year observation period) in Epoch 2. Data for the interim analysis will include, but are not limited to: safety/tolerability, infusion data, infections, and Healthcare Resource Utilization data. No statistical hypothesis testing will be performed in the interim analysis. No modifications to the study design, study conduct, or final analysis will be made during or after the interim analysis, and the analysis is not planned with the intention of deciding whether or not to terminate the study.

## 4. TABLE OF CONTENTS

***Tables***



***Figures***

## 5. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADR | Adverse drug reaction (i.e., related AE) |
| AE | Adverse event |
| AR | Adverse reaction |
| AIDS | Acquired immune deficiency syndrome |
| ALP | Alkaline phosphatase |
| ALT | Alanine amino transferase (SGPT) |
| ANC | Absolute neutrophil count |
| AST | Aspartate amino transferase (SGOT) |
| AUC | Area under the curve |
| B19V | Parvovirus B19 |
| BUN | Blood urea nitrogen |
| BW | Body weight |
| CHMP | Committee for Medicinal Products for Human Use |
| CLL | Chronic lymphocytic leukemia |
| CI | Confidence interval |
| $C_{max}$ | Maximum concentration |
| $C_{min}$ | Minimum concentration |
| CRF | Case report form |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| CXR | Chest x-ray |
| EC | Ethics committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EDTA | Ethylenediamine tetracetic acid |
| ELISA | Enzyme-linked immunosorbent assay |
| EPR | Electronic Patient Reported |
| EU | European Union |

| Abbreviation | Definition |
|---|---|
| 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 |
| HSCT | Hematopoietic stem cell transplantation |
| ICF | Informed consent form |
| ICH | International Council for Harmonization |
| IgA | Immunoglobulin A |
| IgG | Immunoglobulin G |
| IGI | Immunoglobulin |
| IGIV | Immune globulin intravenous (human) |
| IGSC | Immune globulin subcutaneous (human) |
| IP | Investigational Product |
| ISG | Immune serum globulin |
| ISMC | Internal Safety Monitoring Committee |
| ITP | Idiopathic thrombocytopenic purpura |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | Minute(s) |
| mL | Milliliter(s) |
| MM | Multiple myeloma |

| Abbreviation | Definition |
|---|---|
| MMN | Multi-focal motor neuropathy |
| MRI | Magnetic resonance imaging |
| NMC | Non-medical complaint |
| $PaCO_2$ | Partial pressure (tension) of carbon dioxide |
| PASS | Post-authorization safety study |
| PCR | Polymerase chain reaction |
| PIDD | Primary immunodeficiency disease |
| PK | Pharmacokinetic(s) |
| RBC | Red blood cell (count) |
| rHuPH20 | Recombinant human hyaluronidase PH20 |
| SAP | Statistical analysis plan |
| S/D | Solvent/detergent |
| SAE | Serious adverse event |
| SAER | Serious adverse event report |
| SC | Subcutaneous |
| SCIG | Subcutaneous immunoglobulin G |
| SIC | Subject identification code |
| SmPC | Summary of product characteristics |
| $T_{max}$ | Time to maximum concentration |
| TRALI | Transfusion related acute lung injury |
| ULN | Upper limit of normal |
| VASBI | Validated acute serious bacterial infection |
| WBC | White blood cell (count) |

# 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 (Bruton, 1952, 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 (ITP) (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

HyQvia 100 mg/mL solution for infusion for subcutaneous (SC) use is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase PH20 (rHuPH20).

The IG 10% component provides the therapeutic effect of this medicinal product. The rHuPH20 facilitates the dispersion and absorption of IG 10%.

Human normal immunoglobulin contains mainly IgG with a broad spectrum of opsonizing and neutralizing antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1,000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range.

rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan.

Hyaluronan is a polysaccharide found in the intercellular matrix of connective tissue and of certain specialized tissues. It is degraded by naturally occurring hyaluronidases and has a very fast natural turnover in SC tissue. As a permeation enhancer, rHuPH20 depolymerizes hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates more rapid dispersion and absorption and improved bioavailability of the IG 10%.

HyQvia therapeutic indications include:

Replacement therapy in adults, children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients.
- Hypogammaglobulinaemia in patients pre- and post allogeneic hematopoietic stem cell transplantation (HSCT).



### 6.1.2 KIOVIG 100 mg/mL solution for infusion (Immune Globulin Infusion [IGI] 10%) and Cuvitru 200 mg/mL solution for subcutaneous injection

**KIOVIG** is a liquid unmodified IgG preparation with an osmolality that is similar to physiologic osmolality and contains no added sugars, sodium, or preservatives. The manufacturing process includes three independent, validated viral inactivation or removal steps: solvent/detergent (S/D) treatment, nanofiltration and incubation at a low pH and elevated temperature. The product contains immunoglobulins with intact Fc regions (crystallizable region of the antibody) in isotonic solution including glycine for stabilization. KIOVIG is a ready-to-use 10% liquid preparation.

A detailed description of KIOVIG is provided in the Summary of Product Characteristics (SmPC).

**Cuvitru** 200 mg/mL solution for subcutaneous injection is a ready-for-use sterile, liquid preparation of highly purified, concentrated, functionally intact human IgG.

Therapeutic indications include replacement therapy in adults, and children and adolescents (0-18 years) with

- primary immunodeficiency syndromes with impaired antibody production
- hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated
- hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients
- hypogammaglobulinaemia in patient's pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT).

A detailed description of Cuvitru is provided in the SmPC, which is available in those countries where Cuvitru is registered. In countries where Cuvitru is not registered, an IB will be available.



### 6.1.3 Immunoglobulin Treatment

Defective antibody formation, 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 agammaglobulinemia, selective IgG subclass deficiency, common variable immunodeficiency, 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, 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 US, the overwhelming majority of patients have been treated by the intravenous (IV) route. In the past several years SC administration has gained popularity.

Currently, the majority of immunoglobulin products in the US 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 10-20%. 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, SC IgG 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 IM 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, ZLB Behring, 2006). Accordingly, it is recommended that the dose of SC immunoglobulin be adjusted to 137-153% 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] 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) thus 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 sixty years to 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 the 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 h, leaving no observable histopathologic changes[ii]. Weekly infusions into cynomolgus monkeys for 39 weeks in doses up to two mg/kg (> 1,000-fold higher than the HyQvia dose in humans) did not lead to adverse reactions[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.

---

[i] Halozyme Report Number R1005-0551
[ii] Halozyme Report R08014
[iii] Halozyme Report R09050

rHuPH20 can facilitate absorption of small molecules such as insulin and morphine in humans; in phase 1 trials rHuPH20 improved the bioavailability of proteins such as infliximab[iv] and enabled drug dispensation 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, Clemens PL 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, 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 (ADRs) (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, multi-center, 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 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. 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.



[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.

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 after a delay of approximately three to five days.

Data from the clinical trial of HyQvia show that serum IgG trough levels 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 pharmacokinetic 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 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 01 August of 2012, the FDA requested administration of rHuPH20 drug product in all ongoing HyQvia clinical studies in the US to be suspended and patients were switched to treatment with KIOVIG/GAMMAGARD LIQUID only (Protocol Amendment 5). Subjects were treated with conventional IGIV or 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), seven subjects in the range of 12 to <16 years and four subjects in the range of two to <12 years. The median age was 43.0 years. Of the 66 subjects who met all inclusion/exclusion criteria, 50 (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: 60-729 days) and a mean (± 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: 5-300) and the median maximum rate of infusion achieved was 300 mL/hr (range: 10-350). Across all age groups and infusion intervals, a median number of 1.09 infusions/month (range: 0.3-2.1) was administered. IGSC, 10% with rHuPH20 treatment required a median number of 1.58 infusion sites/month (range 0.3-4.2) 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 (22.7%) subjects and 7/66 (10.6%) subjects most frequently 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), 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, 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 US study was a Phase 2/3, prospective, non-controlled, multicenter study to evaluate tolerability and safety and other parameters of SC treatment using Immune Globulin Infusion (Human), 10% (IGI, 10%. IGI, 10% is the same product as IGIV 10% licensed in the 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-pretreated subjects: every three weeks or four weeks, depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects: every three weeks or four weeks, at the discretion of investigator and subject



The rHuPH20 administration was discontinued as of 01 August 2012 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 04 January 2013.

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, 24 completed Epoch 3. Thus, 25 subjects including the one subject who completed Epoch 2 without ever reaching Epoch 3 completed the study.

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: 8.28-10.25]) were comparable to the levels measured at screening (geometric mean: 10.53 g/L [95% CI: 9.46-11.73]).

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.



Median number of infusions per month: 2.90 in Epoch 1; 1.09 in Epoch 2. Median number of infusion sites (needle sticks) per infusion/month: 2.90 in Epoch 1; 1.12 in Epoch 2. Median duration of infusion: less than two hours. Median maximum infusion rate: 240mL/h in Epoch 1; 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: 0.186-0.522) 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 (Immune Globulin (Human) 10% with rHuPH20**

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 European Union (EU) the therapeutic indications for HyQvia are PIDD, CLL, and myeloma. In the USA, 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 was to inform 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.

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 PASS 161302

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

This is a non-interventional, prospective, uncontrolled, multi-center, open-label, post-authorization safety study (PASS) 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 study is ongoing. Subject enrollment has been completed.

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 are 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, however, 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). .Enrollment started in 2014 and finished in 2016. 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. The study enrolled 111 subjects in total. The participation period is due to end in Q1 2020.



### 6.3.7 HyQvia Study 161406

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

This prospective, uncontrolled, multi-center, 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.

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. Subject enrollment has been completed with a total of 264 subjects enrolled. The study is ongoing.

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.

### 6.3.8 HYQVIA Study 161503

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

Study 161503 is a phase 3, open-label, prospective, non-controlled, multicenter, USA-only study to evaluate efficacy, safety, tolerability, immunogenicity, pharmacokinetics and other parameters of HYQVIA treatment in pediatric subjects with Primary Immunodeficiency Diseases (PIDD). 44 subjects aged 2 to <16 years who have received prior IV or SC immunoglobulin therapy have been enrolled in the USA, and enrollment has ended (planned sample size is 40 subjects). The first subject was enrolled (dosed) in Study 161503 on 17 Oct 2017 and the last subject was enrolled on 02 May 2019. Subjects will undergo regular testing for binding anti-rHuPH20antibodies approximately every three months; neutralizing antibodies and characterization of antibodies may also be done.



In Study Epoch 1, patients pre-treated (IV or SC) with non-HyQvia immunoglobulins are enrolled and treated with HyQvia SC in a dose or interval ramp-up during a period of up to six weeks with HYQVIA infusions administered at the study site.

In Epoch 2 subjects will receive HyQvia at intervals of either three or four weeks, depending on the subject's previous IV dosing schedule, or at the investigator´s and subject´s discretion for SC pre-treated subjects. While the first two or three infusions will be administered at the study site, subsequent infusions should be performed at home. A PK assessment should be performed at the six-month visit. After one year in Epoch 2, subjects with a binding anti-rHuPH20 antibody titer < 160 at all time-points will exit the study. Subjects with a titer ≥ 160 will continue in Epoch 2 for another two years. Epoch 3 is approximately one-year safety follow-up of up, if needed: subjects whose anti-rHuPH20 antibody titer was ≥ 160 during Epoch 1 or 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 testing for anti-rHuPH20 antibodies, for approximately one year. Subjects in Epoch 3 will be treated with GAMMAGARD LIQUID IV or SC at the study site or at home.

Subjects who experience a related SAE or severe AE and have an anti-rHuPH20 antibody titer < 160 in Epoch 1 or 2 may either be terminated from the study, change directly to Epoch 3, or continue in Epoch 1 or 2 with appropriate medical intervention such as decreasing the HyQvia infusion rate and/or premedication.

## 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 SmPC 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 of patients 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. Treatment-emergent antibodies against rHuPH20 (binding and neutralizing antibodies) will be monitored during this clinical study.

#### 6.4.1.1 Pregnancy, Breast Feeding, Fertility

Subcutaneous immunoglobulin G (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 rHuPH20in mice and rabbits. No adverse effects on pregnancy and fetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20were transferred to offspring in utero. The effects of antibodies to the rHuPH20component 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 IG 10% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 with respect to reproductive potential at the doses used for facilitating administration of IG 10%.



See Section 6.4.2 for the known risks associated with IGI, 10%.

### 6.4.2 KIOVIG

IGI, 10% administered via IV treatment (KIOVIG) is efficacious and safe in the particular fields of therapeutic use and approved indications, i.e., PIDD, ITP and MMN, as demonstrated in the clinical development program for KIOVIG. Please see the SmPC for KIOVIG.

Serious ARs (defined as SAEs occurring during or within 72 hours of infusion or any casually related SAE occurring within the study period) which occurred in the clinical trials of KIOVIG were aseptic meningitis, pulmonary embolism, and blurred vision.

The most common ARs observed in ≥ 5% of patients were:

- PIDD, IV administration: 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.

- PIDD, SC administration: infusion site (local) event, 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, IV administration: headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

Rare but serious events may occur with IGI products, including hypersensitivity, thrombosis, renal dysfunction/failure, hyperproteinemia, increased serum viscosity, and hyponatremia hemolysis, hemolysis, transfusion related acute lung injury (TRALI), and aseptic meningitis syndrome.

Thrombosis may occur with immune globulin products, including IGI, 10%. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.



Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients receiving immune globulin intravenous (IGIV) products including IGI, 10%. Renal dysfunction and acute failure occur more commonly with IGIV products containing sucrose. IGI, 10% does not contain sucrose.

IGI, 10% contains blood group antibodies (isoagglutinins) that may cause hemolysis. Delayed hemolytic anemia can develop subsequent to IGI, 10% therapy due to enhanced red blood cell (RBC) sequestration. Acute hemolysis, consistent with intravascular hemolysis, has been reported. The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥ 2 g/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of hemolysis but its role is uncertain.

Contraindications to IGI treatment include anaphylactic or severe systemic hypersensitivity reactions to IG and IgA deficient patients with antibodies against IgA and a history of hypersensitivity.

IGI, 10% has a high margin of safety. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and preparation. Three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation

processes, further increasing the margin of safety. In addition, careful screening and monitoring of subjects in this study will be utilized to minimize the above and other known risks associated with IG therapy (e.g., exclusion criteria, blood group typing at baseline, and laboratory monitoring for hemolysis).

Further information is provided in the SmPC for KIOVIG.

### 6.4.3 Cuvitru

Information about Cuvitru is provided in the SmPC, which is available in those countries where Cuvitru is registered. In countries where Cuvitru is not registered, an IB will be available.

### 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 safety, tolerability and immunogenicity of HyQvia in pediatric (age two to <18 years) subjects with PIDD.

### 7.2 Primary Objective

The primary objective of the study is to assess the safety of HyQvia treatment in pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment.

### 7.3 Secondary Objectives

Secondary objectives of the study are further assessments (e.g. immunogenicity), tolerability, characteristics of product administration and efficacy (IgG trough levels).

### 7.4 Tertiary Objectives

Tertiary objectives are further safety and efficacy assessments. The study objectives are described in more detail in Section 11, Section 12 and Section 20.2.

# 8. STUDY DESIGN

## 8.1 Brief Summary

This study is a Phase 4, post-authorization, prospective, non-controlled, multicenter study to evaluate safety, tolerability, and other parameters of SC treatment using HyQvia in 40 pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment.

The purpose of the study is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric subjects.

## 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 Section 20.2 Schedule of Study Procedures and Assessments and Section 20.3 Clinical Laboratory Assessments. In this study 40 pediatric subjects with PIDD will be enrolled, who have received prior immunoglobulin therapy. The study will enroll approximately six subjects aged 2 to <6 years, 12 subjects 6 to <12 years, and 22 subjects 12 to <18 years of age. The study will be conducted in the European Economic Area.



All subjects will have regular anti-rHuPH20 antibody testing (binding and neutralizing anti-rHuPH20 antibody) throughout the study (approximately every three months).

Female subjects of childbearing potential should employ birth control measures as advised by the investigator or per the site´s standard recommendations for the duration of the study.

### 8.2.1 Epoch 1

Pediatric patients with PIDD who are on non-HyQvia IV or SC treatment with immunoglobulin (IV-pretreated, SC-pretreated) will be enrolled and treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to six weeks. Subjects already treated with HyQvia (HyQvia-pretreated) will be enrolled directly into Epoch 2.

Epoch 1 infusions will be administered at the study site.

### 8.2.2 Epoch 2

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

- For IV-pretreated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.
- For SC-pretreated subjects: every three or four weeks, at the discretion of investigator and subject.
- For HyQvia pre-treated subjects: No change in frequency of administration.

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 Section 20.1 Study Flow Chart):

- Subjects with anti-rHuPH20 antibody titer < 160 at all time-points during the study will complete the study termination/completion visit 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.



The first two to three infusions during Epoch 2 will be administered at the study site. It is preferable that subsequent infusions, 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.

### 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 related SAE or a related severe AE will be followed accordingly.

In the event that a subject in Epoch 1 or in Epoch 2 experiences a related SAE or 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.

Subjects with antibody titer of ≥ 160 when entering 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 or the anti-rHuPH20 titer is < 2,560.

Subjects in Epoch 3 will be treated with KIOVIG (IGI, 10%) intravenously or Cuvitru subcutaneously, at the discretion of the investigator and the subject.

Infusions in Study Epoch 3 will be administered at home or at the study site.

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 seven 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 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

1. Number and rate per infusion (excluding infections) of all severe related AEs
2. Number and rate per infusion (excluding infections) of related SAEs

### 8.4.2 Secondary Outcome Measures

#### 8.4.2.1 Efficacy

1. Trough levels of IgG (for Study Epochs 1 and 2)

#### 8.4.2.2 Safety/Tolerability

1. Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
2. Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
3. Number and rate per infusion (excluding infections) of local AEs and ARs
4. Number and rate per infusion (excluding infections) of systemic AEs and ARs
5. Number and rate per infusion (excluding infections) of all AEs and all ARs
6. Number and rate per infusion (excluding infections) of all temporally associated AEs
7. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
8. Number and rate per infusion (excluding infections) of all SAEs
9. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20
10. Additional safety outcome measures include.
    - Clinical laboratory outcomes: raw (actual) values and change from baseline
    - Vital signs: raw (actual) values and change from baseline

#### 8.4.2.3 Mode of Product Administration

For Study Epochs 1 and 2

1. Infusions
    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 (3 weeks or 4 weeks)
3. Assessment of Treatment Preference Questionnaire
4. Assessment of Treatment Satisfaction Questionnaire for Medication: TSQM-9
5. Assessment of HRQoL Questionnaire: Peds-QL, EQ-5D



### 8.4.3 Tertiary Outcome Measures

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

### 8.4.4 Exploratory Outcomes Measure

Not applicable.

## 8.5 Randomization and Blinding

This is a non-randomized, open-label, active treatment clinical study.

## 8.6 Study Stopping Rules

Stopping rules will not be established for this study as the pediatric subjects will be treated with a licensed human normal immunoglobulin, according to the routine standard at the study site for the duration of the study.

## 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 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 KIOVIG (IGIV 10%)

**Dosage Form:** Injection, solution

**Packaging:** IGIV, 10% will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials of 5 g (50 mL) and 10 g (100 mL).

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

**Storage**: Refrigeration. IGIV, 10% 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. Prior to use, the unopened 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.

#### 8.7.1.4 Cuvitru (IGSC 20%)

**Dosage form:** Solution for injection

**Packaging:**
5, 10, 20 or 40 mL of solution in a vial (Type I glass) with a stopper (bromobutyl).
Pack size: 1 vial. Not all pack sizes may be available.

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

**Storage and Shelf Life**: Do not store above 25°C. Do not freeze the product.
Shelf Life: 2 years. Do not use if expiration date is exceeded. Keep the container in the outer carton in order to protect from light. Once opened, use immediately.

### 8.7.2 Administration

rHuPH20 will be administered at a dose ratio of approximately 80 U/g IgG before the infusion of IGI, 10%. The full vial of rHuPH20 associated with each vial of IGI, 10% should be used.

rHuPH20 should be injected at a rate of approximately1-2 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.

### 8.7.3 Description of Treatment

#### 8.7.3.1 HyQvia

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 in whom treatment is expected to be every four weeks).

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

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

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

**Table 2. Example for IgG dosing**

| Pre-Study | | Epoch 1 (Ramp-Up) | | | Epoch 2 (Final Dose) |
|---|---|---|---|---|---|
| **Admin. Route** | **Dose** | **First Infusion at Baseline: 1-Week Dose** | **Second Infusion at Week 1: 2-Week Dose** | **Third Infusion at Week 3: 3-Week Dose** | |
| IV | 0.6 g/kg every 3 weeks | 0.2 g/kg | 0.4 g/kg | - | 0.6 g/kg every 3 weeks |
| IV | 0.6 g/kg every 4 weeks | 0.15 g/kg | 0.3 g/kg | 0.45 g/kg | 0.6 g/kg every 4 weeks |
| SC | 0.1 g/kg every week | 0.1 g/kg | 0.2 g/kg | - | 0.3 g/kg every 3 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 4 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.

#### 8.7.3.2 KIOVIG (IGI 10%)

Subjects may be treated with KIOVIG in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** intravenous

The infusion rate and infusion volume per site will follow the suggestions of the KIOVIG SmPC.

**Dosage frequency**: Once every three or four weeks

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study Epoch.



#### 8.7.3.3 Cuvitru (IGI 20%)

Subjects may be treated with Cuvitru in **Study Epoch 3** (Safety Follow-up).

**Dosage form**: injectable

**Mode of Administration:** subcutaneous

The infusion rate and infusion volume per site will follow the suggestions of the Cuvitru SmPC, which is available in those countries where Cuvitru is registered. In Countries where Cuvitru is not registered, an IB will be available.

**Dosage frequency**: daily to once every two weeks, at the investigator´s discretion

**Dose:** The weekly dose will be equivalent to 100% (±5%) of the dose in the previous study epoch.

### 8.7.4 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 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 humoral immunodeficiency involving a defect in antibody formation and requiring gammaglobulin replacement, as defined according to the IUIS (International Union of Immunological Societies) 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 18 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/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 amino transferase (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 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.



### 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 Section 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 1 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 and assent form, if applicable. See also Section 16.3) and meets all inclusion and none of the exclusion criteria, 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., 161504) 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 informed consent form at study site 02 will be identified as Subject 161504-002003. 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. 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.

The overall study design is illustrated in the Study Flow Chart (Section 20.1). Details on the procedures to be performed at each study visit, including screening, can be found in Section 20.2 Schedule of Study Procedures and Assessments and Section 20.3 Clinical Laboratory Assessments.

All screening procedures must be completed up to 31 days prior to the first infusion. If a subject is scheduled to receive a dose of IgG before eligibility is fully confirmed (e.g. due to the unavailability of lab results), the subject may continue receiving the IgG product used prior to enrollment. Subjects may be re-screened once.

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, 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.

### 10.4 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 Trimethaprim-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 pretreated 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

An electronic 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 attend school/work or to perform normal daily activities due to infection or other illness
- Non-study-required out-patient visits (including urgent care visits to see healthcare providers) and hospitalizations



Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic 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.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Electronic Patient Reported (EPR) modules will be used to enable deployment of required subject diaries to subjects based on protocol requirements. EPRs can be programmed to allow a certain level of data validation at the time of data entry by the subject; this allows cleaning of subject reported data at the time of data collection. Additionally, EPR compliance reports enable monitoring of patient compliance, and proactive follow up if required. EPRs can be deployed in local languages as needed. Automated reminder e-mails are sent to subjects who do not complete required EPRs. Following a certain number of reminder e-mails, the link to that particular EPR is disabled; this ensures that EPRs are collected in a timely manner during the study.

### 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 withdraw or discontinuation) can be found in Section 20.2 Schedule of Study Procedures and Assessments and Section 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 that the investigator/designee can further assess and document that the subject (and/or caregiver) is capable of continuing to independently perform self-infusion procedures.

# 11. ASSESSMENT OF EFFICACY

## 11.1 IgG Trough Levels

IgG trough levels will be determined at several time points (see Section 20.3 Clinical Laboratory Assessments). Standard assay methods will be used for the determination of IgG and IgG subclasses. The measurement will be performed at the central laboratory.

## 11.2 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 complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

For detailed administration time points, see Section 20.2 Schedule of Study Procedures and Assessments.



## 11.3 Treatment Satisfaction Questionnaire for Medication

The Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a 9-item, validated, self-administered instrument to assess patients' satisfaction with medication. The 3 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 complete the assessment using the same translated version throughout the course of the study. For subjects aged 13 to <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). The same observer should be employed for the duration of subject participation.

For detailed administration time points, see Section 20.2 Schedule of Study Procedures and Assessments.

## 11.4 HRQoL Questionnaire

### 11.4.1 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 (QoL) will be assessed separately for the age groups two to four years, and five to seven years, eight to 12 years (PEDS-QL, observer: parent), and 13 to <18 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 Section 20.2 Schedule of Study Procedures and Assessments.



### 11.4.2 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 states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Subjects are asked to describe their health state that day by choosing 1 of 3 responses that reflect the levels of severity for each of the 5 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 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 <18 years, the subject should complete the questionnaire themselves (observer: subject). For subjects under the age of 13, the parent should complete the questionnaire on behalf of their child (observer: parent). 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 Section 20.2 Schedule of Study Procedures and Assessments.

# 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. An AE can therefore 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

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

- Outcome is fatal/results in death (including fetal death)
- 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.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- 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:
    - 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 HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), 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 or paternal 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, a 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 investigator’s brochure 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 investigator's brochure and/or prescribing information as the Reference Safety Information. 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 signing informed consent 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 Report Form. 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.



#### 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:

- 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.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- 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 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:

- 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).
- Unlikely related (either one or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- 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
- 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(s) (ECs) 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 documented on an NMC form and reported to the sponsor 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 Section 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 Section 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., RBC], 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, and glucose.

Hematology and clinical chemistry assessments will be performed on 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 there is a reduction in Hgb of two 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 IgG Trough Levels and IgG Subclasses and Specific Antibody Tests

IgG total and IgG subclass trough levels and trough levels of specific antibodies against Clostridium tetani toxoid, Haemophilus influenzae, and HBV will be determined on all subjects. Testing will be performed at the central laboratory using standard assay methods.



### 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 Section 20.3). For subjects with an anti-rHuPH20 antibody titer ≥160 neutralizing antibodies will also be measured.

At any time during the course of the 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:

- 50% hemolytic complement activity of serum,
- serum complement component 3;
- serum complement component 4;
- (C1q) binding assay, and
- circulating immune complex Raji cell assay.

### 12.7.7 Viral Pathogen Serology

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

### 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 20.4. 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 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/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured as described in Section 20.3.



### 12.8.1 Screening

- All vital signs

### 12.8.2 Infusion at Study Site

1. Within 30 min prior to infusion:
    - All vital signs. Height and weight can be taken at any time at this visit.
2. 30 (± 5) min 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 min 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 US FDA Guidance for Industry to Support Marketing of Human IGIV as Replacement Therapy for Primary Humoral Immunodeficiency (Food and Drug Administration, 2008) and the EMA 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/min; respiratory rate >20 breaths/min, 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 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[vii]. 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 age 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 >two 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 <ten squamous epithelial cells and >25 polymorphonuclear leukocytes at tenX low power magnification to determine suitability of sputum culture.

[vii] Further evaluation, in particular laboratory evaluation (culture and white blood count with differential to evaluate for the presence of immature neutrophils) and chest x-rays, should be aggressively pursued whenever a bacterial pneumonia is suspected

### 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 alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess
4. Imaging studies: typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan

# 13. STATISTICS

## 13.1 Sample Size and Power Calculations

The sample size selected for the study is primarily determined by the objective to collect safety data on HYQVIA in a sufficient number (about 40) of pediatric (age two to <18 years) subjects with PIDD who have received prior immunoglobulin therapy before enrollment into this study. In addition, the guideline of the CHMP on the clinical investigation of human normal immunoglobulin for SC and/or intramuscular administration (Committee for Medicinal Products for Human Use, 2015) indicates that at least 40 patients should be included to evaluate replacement therapy in primary immunodeficiency syndromes.

## 13.2 Analysis Sets

### 13.2.1 Full Analysis Set

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 full analysis set.

### 13.2.2 Per-Protocol Analysis Set

All patients in the full analysis set who have no major protocol deviations will be included in the per-protocol analysis set.

Protocol deviations will be classified as major or minor in accordance with applicable study sponsor's standard operating procedure(s) and prior to statistical analysis in which the Per-protocol Analysis Set will be used.



### 13.2.3 Safety Analysis Set

The safety analysis set will contain all subjects in the full analysis set who receive at least one dose of HyQvia.

## 13.3 Handling of Missing, Unused, and Spurious Data

The handling of missing, unused or spurious data will be described in the statistical analysis plan (SAP)

## 13.4 Methods of Analysis

In this study no hypothesis will be tested. Detailed statistical analysis methods will be described in the SAP. Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. If groups of sufficient sample size (such as age groups or PIDD types) are available, CIs may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class and preferred term. Tables will be prepared to list for each SAE and non-serious AE the number of events and the number of subjects who experienced one or more event. All analyses will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

### 13.4.1 Primary Outcome Measure

- Number and rate per infusion (excluding infections) of all severe related AEs
- Number and rate per infusion (excluding infections) of related SAEs

For the endpoint of incidence of all severe related AEs and related SAEs, a point estimate and corresponding 95% CI (by the Wilson score method) for the proportion of subjects with one or more related SAEs will be provided. In addition, incidence of all severe related AEs and related SAEs will be calculated as rate per infusion and rate per subject-year, and will be analyzed for changes in frequency and for changes in severity over time. All SAEs will be listed. No statistical hypotheses will be tested.



### 13.4.2 Secondary Outcome Measures

#### 13.4.2.1 Efficacy

Trough levels of IgG for Study Epoch 1 and 2: Descriptive statistics will be provided for the trough level of IgG for study Epoch 1 and 2.

#### 13.4.2.2 Safety

The following secondary safety endpoints/outcome measures will be analyzed:

- Proportion of subjects who achieve a treatment interval of three or four weeks in Epoch 2
- Proportion of subjects who maintain a treatment interval of three or four weeks in Epoch 2 for 12 months
- Number and rate per infusion (excluding infections) of local AEs and ARs
- Number and rate per infusion (excluding infections) of systemic AEs and ARs
- Number and rate per infusion (excluding infections) of all AEs and all ARs

- Number and rate per infusion (excluding infections) of all temporally associated AEs
- Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs
- Number and rate per infusion (excluding infections) of all SAEs
- Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

Additional safety endpoints/outcome measures include:

- Clinical laboratory outcomes: raw (actual) values and change from baseline
- Vital signs: raw (actual) values and change from baseline

Descriptive methods, mainly frequency tables, will be used for all secondary safety endpoints. In addition, adverse events will be summarized in terms of AEs per subject (rate per subject) and AEs per subject-year (rate per subject-year).



**13.4.2.3 Mode of Product Administration (For Study Epochs 1 and 2)**

- Number of Infusions
- Number of infusions per month
- Number of infusion sites (needle sticks) per infusion/month
- Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion)
- Maximum infusion rate/site
- Infusion volume/site
- Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE
- Number of weeks to reach final dose interval (defined as three- or four-weeks infusion interval)

Nonparametric descriptive statistics (median, quartiles, and range) will be calculated and reported for the infusion administration variables. Frequency table will show the number/proportion of infusions discontinued, slowed or interrupted due to AE and total observation time in subject-years.

#### 13.4.2.4 HRQoL

- Treatment Preference Questionnaire
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- HRQoL Questionnaire: Peds-QL, EQ-5D

Total and domain scores on each of the HRQoL measures will be calculated for each subject, at each data assessment time point. Descriptive statistics will be shown for each of the scores, at each data assessment time point.

### 13.4.3 Tertiary Outcome Measures

#### 13.4.3.1 Infections

- Number of acute serious bacterial infections
- Number of all infections
- Days on antibiotics



For the endpoint of incidence of acute serious bacterial infection and all infections a point estimate and 95% CI (by the Wilson score method) for the proportion of subjects with one or more infection will be calculated. In addition, incidence of all infection endpoints will be calculated as rate per infusion and rate per subject-year. Descriptive statistics will be performed and reported for the days on antibiotics.

#### 13.4.3.2 Healthcare Resource Utilization Endpoints

- Days not able to go to school/work or to perform normal daily activities due to infection or other illness
- 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

Healthcare resource utilization endpoints, including hospitalization, acute physician visits and days missed for school/work or normal daily activities, will be summed and annualized for reporting purposes. Descriptive statistics will be performed and reported.

## 13.5 Planned Interim Analysis of the Study

### 13.5.1 Overview of Interim Analysis

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 assess the safety of HyQvia treatment in pediatric subjects with PIDD who received immunoglobulin therapy prior to study enrollment. The *purpose of the study* is to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age 2 to <18 years) subjects with PIDD.

A single IA is planned to be performed. The *purpose of the IA* is to update the scientific community, via publications and presentations, on the interim safety, tolerability and immunogenicity of HyQvia in pediatric subjects with PIDD.

All of the following will apply to the IA, or apply as a result of the IA:

- Analysis will include, but not limited to: safety/tolerability, infusion data, infections, and Healthcare Resource Utilization data, as defined below in Section 13.5.2.
- Analysis is planned to be performed when 75% of all subjects (30 subjects if 40 are enrolled [dosed]) 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.
- No statistical hypothesis testing will be performed.
- No early stopping of study (the interim analysis is not planned with the intention of deciding whether or not to terminate the study).
- No modifications to the study design, study conduct, or final analysis will be made during or after the interim analysis.
- No interim clinical study report is planned.

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.

### 13.5.2 Data for Interim Analysis

Data for interim analysis will include, but are not limed to the following:

**Safety/Tolerability**

- Number and rate per infusion (excluding infections) of all severe related AEs.
  Note: This is 1 of 2 of the study primary outcome measures listed in Section 8.4.
- Number and rate per infusion (excluding infections) of related SAEs.
  Note: This is 2 of 2 of the study primary outcome measures listed in Section 8.4.
- Number and rate per infusion (excluding infections) of local AEs and ARs
- Number and rate per infusion (excluding infections) of systemic AEs and ARs
- Number and rate per infusion (excluding infections) of all AEs and all ARs
- Number and rate per infusion (excluding infections) of all SAEs
- Number and proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20
- Number and proportion of subjects with HyQvia-related AEs (causally related AEs), and HYQVIA-related SAEs, and number of such events. AEs recorded in the study database as "possibly related" or "probably related" to HyQvia will be considered HyQvia-related AEs.
- Number and proportion of subjects with HyQvia-related AEs that were mild, moderate, or severe in severity, and number of events in each category
- Number and proportion of subjects with any AEs, any serious and/or nonserious AEs, and any local and systemic AEs/SAEs, regardless of causality
- Number and proportion of subjects who prematurely discontinued study due to AEs
- Rate of AEs, expressed as number of events per infusion, per subject, and per subject-year

**Infections**

- Number of acute serious bacterial infections
- Number of all infections

**Mode of Product Administration (For Study Epoch 1 and 2)**

- Number of Infusions
- Number of infusions per month
- Number of infusion sites (needle sticks) per infusion/month
- Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion)
- Maximum infusion rate/site
- Infusion volume/site
- Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE
- Number of weeks to reach final dose interval (defined as three- or four-weeks infusion interval)



**Healthcare Resource Utilization**

- Days not able to go to school/work or to perform normal daily activities due to infection or other illness
- Days on antibiotics
- 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

### 13.5.3 Methods of Interim Analysis

Continuous data (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value. Categorical data (e.g., occurrence of adverse events) will be summarized in terms of number and percent of subjects and number of occurrences in each category, as appropriate. No statistical hypothesis testing will be performed. No CIs will be presented.

Baseline is defined as the last non-missing value before the initial dose of HyQvia.

## 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. The coordinating investigator will be selected before study start.



## 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, Clinical Development) with expertise/specialization in PIDD clinical care and research. Safety and safety-supported data will be provided to the ISMC. Details and procedural information will be provided in the ISMC Charter. The ISMC can 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 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

Inter-laboratory standardization methods will be described in the data management plan as needed.

# 16. ETHICS

## 16.1 Subject Privacy

The study protocol, documentation, data and all other information generated will be held in strict confidence and in accordance with applicable laws, regulations, and guidelines. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.

Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

## 16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information will be reviewed and approved/given favorable opinion by the ethics committee (EC) and applicable regulatory authorities. The IB, if applicable, 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 informed consent form before enrollment into the study according to applicable national and local regulatory requirements and ICH GCP. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

An assent form may be provided and should be signed by patients enrolled in the study. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2).

The informed consent form 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 informed consent form, 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 informed consent form 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 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 informed consent forms, 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.

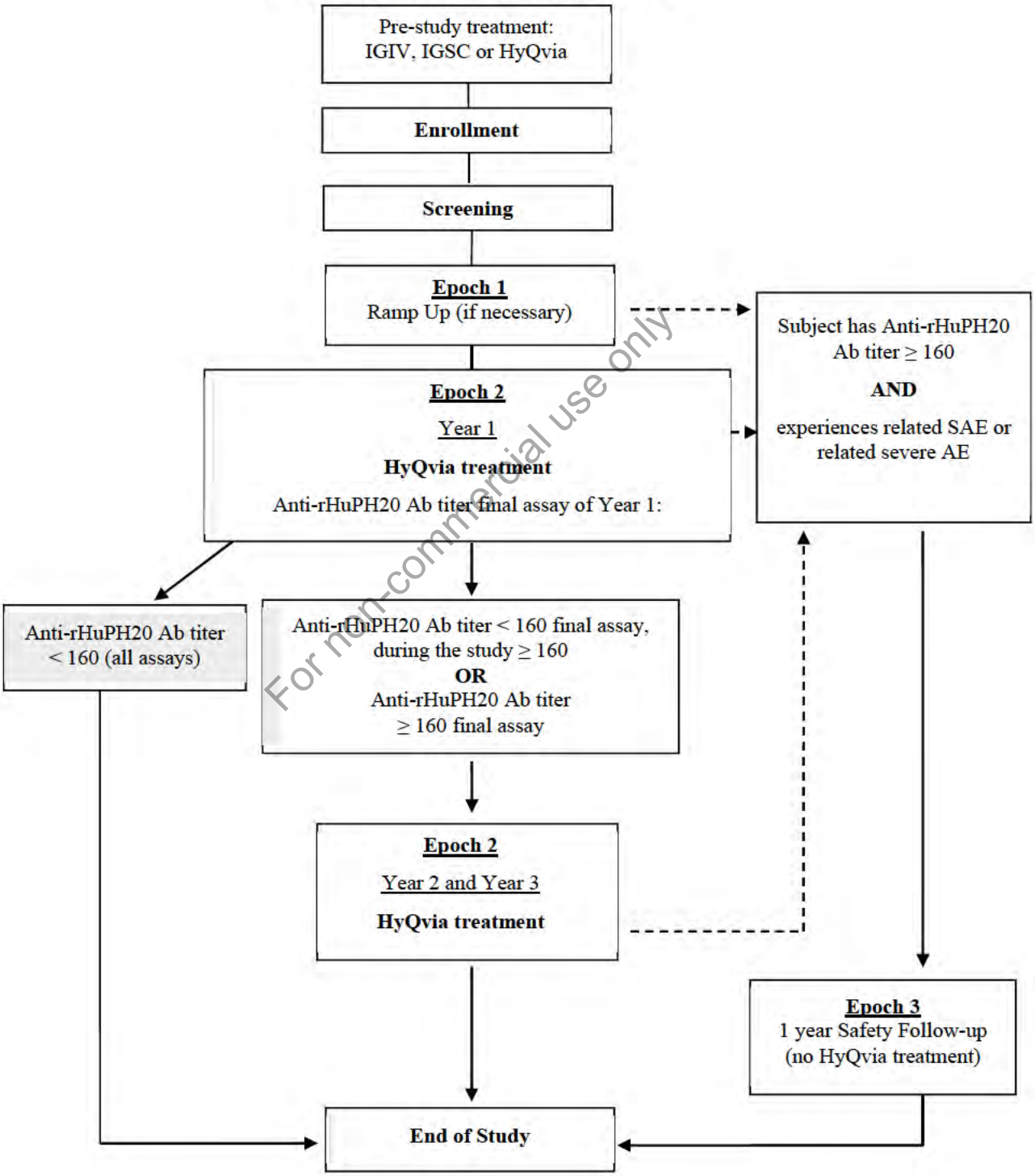
## 19. PUBLICATION POLICY

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 161504**



## 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 | Enrollment / Screening | | Treatment Visit in Study Epoch 1 (Visit +/- 1 Day) | |
|---|---|---|---|---|
| | | First Infusion: Baseline | 2nd Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals) | 3rd Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-Week Treatment Intervals) |
| Location | Site | Site | Site | Site |
| Informed Consent[a] | x | | | |
| Eligibility Criteria | x | | | |
| Infusion | | 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[b] | x | x | | |
| Vital Signs | x | x | x | x |
| HRQoL (PedsQL, EQ-5D)/, TSQM-9 Assessment | | x | | |

[a] Occurs prior to any study-specific procedure.
[b] For laboratory assessments, see Section 20.3

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

| Procedures/ Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | | Visit in Study Epoch 2 (Visit +/- 2 weeks) | | | | |
|---|---|---|---|---|---|---|
| | Month 0 | Month 3 | Month 6 | Month 9 | Month 12[a] | Study Completion/ Termination Visit (at Next Infusion), if Applicable |
| Location | Site | Site | Site | Site | Site | Site |
| Informed Consent | | | | | | |
| Infusion[e] | 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[d] | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x |
| HRQoL (PedsQL, EQ-5D), Treatment Preference Questionnaire, TSQM-9 | (x) [b] | | | | x | (x) [c] |



[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 EOS or continuation of Epoch 2 dependent on antibody assay result.

[b] Only subjects who did not perform Epoch 1 will take these assessments in Epoch 2 at Month 0.

[c] 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.

[d] For laboratory assessments, see Section 20.3

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

## 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 (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[c] | 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[b] | x | x | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x | x | x |
| HRQoL (PedsQL, EQ-5D), Treatment Preference Questionnaire, TSQM-9 | | | | 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] For laboratory assessments, see Section 20.3.
[c] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.

## Table 6. STUDY EPOCH 3
## Schedule of Study Procedures and Assessments

| Procedures/Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 3(Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|
| | Month 0 | Month 3 | Month 6 | Months 9 | Month 12/ Study Completion/ Termination Visit[a] |
| Location | Site | Site | Site | Site | Site |
| Infusion[d] | x | x | x | x | |
| Concomitant Medications | x | x | x | x | x |
| Non-drug Therapies | x | x | x | x | x |
| Physical Exam[b] | 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 (PedsQL, EQ-5D), Treatment Preference questionnaire, TSQM-9 Assessment | x | | | | x |

[a] Includes for cases of withdrawal or discontinuation.
[b] Occurs prior to any study-specific procedure.
[c] For laboratory assessments, see Section 20.3.
[d] Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.

## 20.3 Clinical Laboratory Assessments

**Table 7. STUDY EPOCH 1 – Ramp Up**
**Clinical Laboratory Assessments**

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Enrollment / Screening | | Treatment Visit in Study Epoch 1 (Visit +/- 1 Day) | |
|---|---|---|---|---|
| | | First Infusion: Baseline | Second Infusion: Week 1 (This Treatment is the End of Epoch 1 if Subject is Planning for 3-Week Treatment Intervals) | Third Infusion: Week 3 (Only for Subjects Planning to Ramp Up to 4-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 | | |

## Table 8. STUDY EPOCH 2 – Year 1
## Clinical Laboratory Assessments

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | | Visit in Study Epoch 2 (Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|---|
| | Month 0[c] | 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 | x[a] | | | | | |
| Specific Antibody Tests | (x)[b] | | | | | **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 two 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 in section 12.7.4 within 72 hours in addition to the prescribed tests
[b] Only for subjects who did not perform Epoch 1
[c] Month 0 will be considered to be the "Baseline" visit for subjects who do not participate in Epoch 1

## 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(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 Tests[b] | | | | x | | | | |
| Specific Antibody Tests | | | | | | | | 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 two 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 in section 12.7.4 within 72 hours

## Table 10. STUDY EPOCH 3
## Clinical Laboratory Assessments

| Assessments Routinely Performed Pre-Infusion, Unless Stated Otherwise | Visit in Study Epoch 3 (Visit +/- 2 Weeks) | | | | |
|---|---|---|---|---|---|
| | Month 0 | 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 | | | x | | |
| Specific Antibody Tests | | | | | x |
| IgG Trough Levels and IgG Subclasses | x | | x | | x |
| Antibodies to rHuPH20 | x | x | x | x | x |

## 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 |
| 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: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, 5 (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

## 21. REFERENCES

Abdel-Mageed, A., Graham-Pole, J., Del Rosario, M. L., Longmate, J., Ochoa, S., Amylon, M., Elfenbein, G. J., Janiec, J., Jansen, J. & Lazarus, H. M. 1999. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. *Bone Marrow Transplant,* 23**,** 929-932.

Barron, K. S., Murphy, D. J., Jr., Silverman, E. D., Ruttenberg, H. D., Wright, G. B., Franklin, W., Goldberg, S. J., Higashino, S. M., Cox, D. G. & Lee, M. 1990. Treatment of Kawasaki syndrome: a comparison of two dosage regimens of intravenously administered immune globulin. *J Pediatr,* 117**,** 638-644.

Bass, A., Plotka, A., Mridha, K., Sattler, C., Kim, A. M. & Plowchalk, D. R. 2018. Pharmacokinetics, pharmacodynamics, and safety of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, in healthy subjects when administered in co-mixture with recombinant human hyaluronidase: A phase 1 randomized trial. *Health Sci Rep,* 1**,** e61.

Berger, M., Cupps, T. R. & Fauci, A. S. 1980. Immunoglobulin replacement therapy by slow subcutaneous infusion. *Ann Intern Med,* 93**,** 55-56.

Bruton, O. C. 1952. Agammaglobulinemia. *Pediatrics,* 9**,** 722-728.

Clemens PL, Xu XS, Luo M, Chari A, Usmani SZ, Mateos M-V, van de Donk NWCJ, Kaufman JL, Moreau P, Oriol A, Plesner T, Benboubker L, San-Miguel, J., Sun Y-N, Farnsworth A, Masterson T, Hellemans P, Qi M & Nahi H. Pharmacokinetics (PK) of Subcutaneous Daratumumab in patients with Relapsed or Refractory (RR) Multiple Myeloma (MM): Primary Clinical Pharmacology Analysis of the Open-Label, Multicenter, Phase 1b Study (PAVO). 2018. American Society of Hematology.

Committee for Medicinal Products for Human Use 2015. Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg).EMA/CHMP/BPWP/410415/2011 rev 1.Web Link: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500190211.pdf

Food and Drug Administration 2008. U.S.Department of Health and Human Services, Center for Biologics Evaluation and Research, Guidance for industry: Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency.Web Link: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf

Gardulf, A., Andersen, V., Björkander, J., Ericson, D., Frøland, S. S., Gustafson, R., Hammarström, L., Jacobsen, M. B., Jonsson, E., Möller, G., Nyström, T., Søeberg, B. & Smith, C. I. E. 1995. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet,* 345**,** 365-369.

Gardulf, A., Björvell, H., Gustafson, R., Hammarström, L. & Smith, C. I. 1993. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. *Immunodeficiency,* 4**,** 81-84.

Gardulf, A. & Hammarström, L. 1996. Subcutaneous administration of immunoglobulins. What are the advantages? *Clin Immunother,* 6**,** 108-116.

Gardulf, A., Hammarström, L. & Smith, C. I. 1991. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. *Lancet,* 338**,** 162-166.

Gardulf, A., Nicolay, U., Asensio, O., Bernatowska, E., Böck, A., Costa Carvalho, B., Granert, C., Haag, S., Hernández, D., Kiessling, P., Kus, J., Pons, J., Niehues, T., Schmidt, S., Schulze, I. & Borte, M. 2006. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies - A prospective multi-national study. *J Clin Immunol,* 26**,** 177-185.

George, J. N. & Raskob, G. E. 1998. Idiopathic thrombocytopenic purpura: diagnosis and management. *Am J Med Sci,* 316**,** 87-93.

Goldstein, B., Giroir, B. & Randolph, A. 2005. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med,* 6**,** 2-8.

Griffiths, H. & Chapel, H. 1997. Prevention of infections in B-cell lymphoproliferative diseases. *In:* Lee, M. L. & Strand, V. (eds.) *Intravenous Immunoglobulins in Clinical Practice.* First edition ed. New York: Marcel Dekker.

Gustafson, R., Gardulf, A., Hansen, S., Leibl, H., Engl, W., Linden, M., Muller, A. & Hammarström, L. 2008. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. *Clin Exp Immunol,* 152**,** 274-279.

Hahn, A. F., Beydoun, S. R., Lawson, V., Team, I. i. M. S., Oh, M. S., Empson, V. G., Leibl, H., Ngo, L. Y., Gelmont, D. & Koski, C. L. 2013. A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy. *J Peripher Nerv Syst,* 18**,** 321-330.

Imbach, P., Akatsuka, J., Blanchette, V., Burek-Kozlowska, A., Bussel, J., Gaedicke, G., Gianella-Borradori, A., Gugler, E., Hirt, A., Imholz, B., McMillan, R., Morell, A., Newland, A., Nugent, D., Schoni, M. H. & Wagner, H. P. 1995. Immunthrombocytopenic purpura as a model for pathogenesis and treatment of autoimmunity. *Eur J Pediatr,* 154**,** S60-S64.

Kyle, R. A. & Rajkumar, S. V. 2004. Multiple myeloma. *N. Engl. J. Med,* 351**,** 1860-1873.

McMillan, R. 2000. The pathogenesis of chronic immune (idiopathic) thrombocytopenic purpura. *Semin Hematol,* 37**,** 5-9.

Melamed, I. R., Stein, M. R., Wasserman, R. L., Leibl, H., Engl, W., Yocum, R. C. & Schiff, R. I. 2008. Recombinant human hyaluronidase facilitates dispersion of subcutaneously administered Gammagard Liquid and enables administration of a full monthly dose in a single site to patients with immunodeficiency diseases. *J Allergy Clin Immunol,* 121**,** S83.

Ochs, H. D., Gupta, S., Kiessling, P., Nicolay, U., Berger, M. & Group, S. I. S. 2006. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol,* 26**,** 265-273.

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T. & Carbone, P. P. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol,* 5**,** 649-655.

Olsson, O. & Löjgren, O. 1949. Hyaluronidase as a factor hastening the spread and absorption of water-soluble radiopaque substances deposited intracutaneously, subcutaneously, or intramuscularly. *Acta Radiol,* 31**,** 250-256.

Picard, C., Al-Herz, W., Bousfiha, A., Casanova, J. L., Chatila, T., Conley, M. E., Cunningham-Rundles, C., Etzioni, A., Holland, S. M., Klein, C., Nonoyama, S., Ochs, H. D., Oksenhendler, E., Puck, J. M., Sullivan, K. E., Tang, M. L. K., Franco, J. L. & Gaspar, H. B. 2015. Primary immunodeficiency diseases: An update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. *J Clin Immunol,* 35**,** 696-726.

Rabin, R. & de Charro, F. 2001. EQ-5D: A measure of health status from the EuroQol Group. *Ann. Med,* 33**,** 337-343.

Rechtman, D. J. 1997. Use of intravenous immune globulin in adults with HIV disease. *In:* Lee, M. L. & Strand, V. (eds.) *Intravenous Immunoglobulins in Clinical Practice.* First edition ed. New York: Marcel Dekker, Inc.

Riedl, M. A., Lumry, W. R., Li, H. H., Banerji, A., Bernstein, J. A., Ba, M., Bjrkander, J., Magerl, M., Maurer, M., Rockich, K., Chen, H. & Schranz, J. 2016. Subcutaneous administration of human C1 inhibitor with recombinant human hyaluronidase in patients with hereditary angioedema. *Allergy Asthma Proc,* 37**,** 489-500.

Roord, J. J., van der Meer, J. W., Kuis, W., de Windt, G. E., Zegers, B. J., van Furth, R. & Stoop, J. W. 1982. Home treatment in patients with antibody deficiency by slow subcutaneous infusion of gammaglobulin. *Lancet,* 1**,** 689-690.

Rosen, F. S., Cooper, M. D. & Wedgwood, R. J. 1995. The primary immunodeficiencies. *N Engl J Med,* 333**,** 431-440.

Rosenfeld, E. A., Shulman, S. T., Corydon, K. E., Mason, W., Takahashi, M. & Kuroda, C. 1995. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. *J Pediatr,* 126**,** 1000-1003.

Rosengren, S., Dychter, S. S., Printz, M. A., Huang, L., Schiff, R. I., Schwarz, H. P., Sugarman, B. J. & Muchmore, D. B. 2015. Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. *AAPS J,* 17**,** 1144-1156.

Rosengren, S., Souratha, J., Conway, D., Muchmore, D. & Sugarman, B. 2018. Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects. *BioDrugs,* 32**,** 83-89.

Rozman, C. & Montserrat, E. 1995. Chronic lymphocytic leukemia. *N. Engl. J. Med,* 333**,** 1052-1057.

Schiff, R. I. & Rudd, C. 1986. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. *J Clin Immunol,* 6**,** 256-264.

Shpilberg, O. & Jackisch, C. 2013. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. *Br J Cancer,* 109**,** 1556-1561.

Smith, G. N., Griffiths, B., Mollison, D. & Mollison, P. L. 1972. Uptake of IgG after intramuscular and subcutaneous injection. *Lancet,* 1**,** 1208-1212.

Supersaxo, A., Hein, W. R. & Steffen, H. 1990. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. *Pharm. Res,* 7**,** 167-169.

Thomas, J. R., Yocum, R. C., Haller, M. F. & von Gunten, C. F. 2007. Assessing the role of human recombinant hyaluronidase in gravity-driven subcutaneous hydration: The INFUSE-LR Study. *J Palliat Med,* 10**,** 1312-1320.

Varni, J. W., Seid, M. & Rode, C. A. 1999. The PedsQL: measurement model for the pediatric quality of life inventory. *Med. Care,* 37**,** 126-139.

Wasserman, R. L., Melamed, I., Nelson, R. P., Jr., Knutsen, A. P., Fasano, M. B., Stein, M. R., Rojavin, M. A. & Church, J. A. 2011. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. *Clin Pharmacokinet,* 50**,** 405-414.

Wasserman, R. L., Melamed, I., Stein, M. R., Gupta, S., Puck, J., Engl, W., Leibl, H., McCoy, B., Empson, V. G., Gelmont, D., Schiff, R. I. & IGSC, r. S. G. 2012. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J. Allergy Clin. Immunol,* 130**,** 951-957.e11.

Welch, M. J. & Stiehm, E. R. 1983. Slow subcutaneous immunoglobulin therapy in a patient with reactions to intramuscular immunglobulin. *J Clin Immunol,* 3**,** 285-286.

Wolin, M. J. & Gale, R. P. 1997. IVIG in bone marrow transplantation. *In:* Lee, M. L. & Strand, V. (eds.) *Intravenous Immunoglobulins in Clinical Practice.* First Edition ed. New York: Marcel Dekker, Inc.

World Health Organization 2003. Toxicity grading scale for determining the severity of adverse events.Web Link: http://www.icssc.org/Documents/Resources/AEManual2003AppendicesFebruary_06_2003%20final.pdf

Yocum, R. C., Kennard, D. & Heiner, L. S. 2007. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. *J Infus Nurs,* 30**,** 293-299.

ZLB Behring 2006. Immune Globulin Subcutaneous (Human), Vivaglobin®. US Label.Web Link: http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm070360.pdf

## 22. SUMMARY OF CHANGES

**Protocol 161504: Amendment 2 2019 DEC 04**

**Replaces: Amendment 1: 2016 OCT 07**

In this section, changes from the previous version of the Protocol 161504, Amendment 1, dated 2016 OCT 07, 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. **Throughout the document**
   Description of Change: Updated sections with the recent references.
   Rationale for Change: To update the protocol with the recent publications for rHUPH20.

3. **Title Page**
   Description of Change: Updated address of the US Sponsor, added NCT number.
   Rationale for Change: Administrative.

4. **Protocol Signature Page and Section 1.1**
   Description of Change: Updated name of sponsor signatory.
   Rationale for Change: Administrative.

5. **Synopsis and Section 8.3**
   Description of Change: Revised completion and duration to 2023 scenario in case LSI goes until Epoch 2 Year 3 and then 1 year in Epoch 3.
   Rationale for Change: Duration of study periods and subject participation changed according to the current timelines.

6. **Synopsis and Section 8.1, Section 8.2 and Section 13.5.2**
   Description of Change: Removed wording "approximately" 40 subjects and added "if 40 are enrolled (dosed)".
   Rationale for Change: To avoid confusion regarding the number of patients enrolled and obtain accuracy.

7. **Synopsis and Section 8.2.3 Epoch 3**
   Description of Change: Emphasized 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.

8. **Synopsis, Section 8.4.2.2 and Section 13.4.2.2**
   Description of Change: Provided additional information/clarification on safety outcome measures "additional safety outcome measures include clinical laboratory outcomes: raw (actual) values and change from baseline, and vital signs : raw (actual) values and change from baseline".
   Rationale for Change: To clarify that the laboratory values and vital signs collected routinely as safety assessments are among the outcome measures.

9. **Synopsis and Section 13.5, Section 13.4.2**
   Description of Change: Added planned Interim Analysis.
   Rationale for Change: The purpose of the analysis is to update the scientific community, on the interim safety, tolerability and immunogenicity of HyQvia in pediatric subjects with PIDD.

10. **Section 6.1.1 HyQvia**
    Description of Change: Updated the Europe indication for HyQvia.
    Rationale for Change: To update the HyQvia indication; for the current version.

11. **Section 6.1.2, Section 6.4.3, Section 8.7.3.3**
    Description of Change: Added "A detailed description of Cuvitru is provided in the SmPC, which is available in those countries where Cuvitru is registered. In countries where Cuvitru is not registered, an IB will be available."
    Rationale for Change: Needed for countries where sites are open but Cuvitru is not registered; therefore, reference for the Cuvitru Investigator Brochure is added.

12. **Section 6.3.5, Section 6.4.1.1, Section 9.3, Section 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: To provide update on the current study status.

13. **Section 6.3.6 HyQvia PASS 161302**
    Description of Change: Description of the current study status, wording was updated to reflect the most recent study status, the study has closed enrollment.
    Rationale for Change: To provide update on the current study status.

14. **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: To provide update on the current study status.

15. **Section 6.3.8 HYQVIA Study 161503**
    Description of Change: Additional HYQVIA study conducted in US; description of the current study 161503 status, wording was updated to reflect the most recent study status.
    Rationale for Change: To provide update on the current study status.

16. **Section 6.5 Compliance Statement**
    Description of Change: Updated to current version of GCP E6 guideline (Nov 2016) and added Declaration of Helsinki.
    Rationale for Change: To reflect the most current guidelines.

17. **Section 8.2.2: Study Design**
    Description of Change: Added description to allow shorter infusion intervals (2 weeks, instead of 3 or 4 weeks) if preferable due to tolerability, at the discretion of the investigator.
    Rationale for Change: Infusion intervals to allow more flexibility for the needs of pediatric patients.

18. **Section 8.7.3.1 Description of HYQVIA Treatment**
    Description of Change: Provided 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 and added that dose may be increased if clinically indicated.
    Rationale for Change: To clarify when dose adjustments are required.

19. **Section 12.7: Clinical Laboratory Parameters**
    Description of Change: Sentence was changed 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: To provide 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.

20. **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.
    Rationale for Change: To accurately define tests, and to monitor for potential hemolysis.

21. **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.
    Rationale for Change: To provide improved clarity.

22. **Section 15.4 Safety Monitoring**
    Description of Change: Changed Internal Safety Review Board (ISRB) to Internal Safety Monitoring Committee (ISMC) and added procedural details.
    Rationale for Change: Administrative update.

23. **Section 20.2: General comments for Schedule of Study Procedures and Assessments**
    Description of Change: Inserted cells and updated missing footnotes.
    Rationale for Change: To distinguish between baseline and other treatments and to update administrative changes such as missing footnotes.

24. **Section 20.2 Schedule of Study Procedures and Assessments (Table 3 and Table 7)**
    Description of Change: A margin of ±1 day for the scheduling of treatment visits in Epoch 1 was defined.
    Rationale for Change: To allow a limited amount of flexibility in the scheduling of study drug infusions, and to prevent related protocol deviations.

25. **Section 20.2 Table 4, Table 5, Table 6**
    Description of Change: Added a footnote: § Infusions (including home infusions) administered between scheduled site visits/site infusions may deviate up to +/- 3 days from original schedule.
    Rationale for Change: To allow limited flexibility in the scheduling of study site visits.

26. **Section 20.2 Table 3 and Table 4**
    Description of Change: The Treatment Preference Questionnaire will not be completed at Baseline (Epoch 1); and addition of footnotes (b) and (c) to Table 4 (Epoch 2).
    Rationale for Change: To clarify the guidance regarding when the assessments should be performed.

27. **Section 20.2 Table 8**
    Description of Change: **A**dded a footnote: specific antibody tests will be done only for subjects who did not perform Epoch 1, and month 0 will be considered to be "baseline" visit for subject who didn't participate in Epoch 1.
    Rationale for Change: To clarify that for some subjects Month 0 of Epoch 2 will be considered as baseline for those subjects who didn't have to participate in Epoch 2; therefore also specific antibody tests have to be performed.