TITLE PAGE – NON-INTERVENTIONAL STUDY INFORMATION

PROTOCOL TITLE	Non-Interventional Post-Marketing Safety Study on the Long-Term Safety of HYQVIA (Global)
PROTOCOL ID #	161406
ORIGINAL/ AMENDMENT	Amendment 2 2015 SEP 17 Replaces Protocol Amendment 1: 2015 APR 09 Original: 2015 MAR 02
CLINICAL TRIALS.GOV #	NCT Number: Study to be registered IND Number: 013840 ENCePP Number: Study to be registered, if required
MEDICINAL PRODUCT	
Active Ingredient(s)	Immune Globulin Infusion 10% (Human), IGI, 10%
Medicinal Product	HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]
PRODUCT REF. #	USA: BL 125402 EU/1/13/840/001-005
PROCEDURE #	USA: Not Applicable EMEA/H/C/002491
MARKETING AUTHORISATION HOLDER (MAH)	USA: Baxalta US Inc., One Baxter Way, Westlake Village, CA 91362 EU: Baxalta Innovations GmbH, Industriestrasse 67, A-1221 Vienna, Austria
JOINT PASS	No
RESEARCH QUESTION & OBJECTIVES	
Research Question	
The purpose of the proposed 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 product administration in routine clinical practice.	
Primary Objective	
The primary objective is to collect and assess safety data, in particular the occurrence of long-term changes in incidence and severity of related adverse events in patients treated with HYQVIA.	
Secondary Objective(s)	
Secondary objectives are to collect data on 1. anti-rHuPH20 antibodies and other laboratory safety assessments, total IgG, further safety assessments that are obtained during the routine clinical management of the subjects 2. the prescribed treatment regimen and treatment administration 3. health-related quality of life (HRQoL) and health resource use (HRU) assessments	

COUNTRY(-IES) OF STUDY	This study will be conducted in the US and other countries worldwide where HYQVIA is licensed
AUTHOR	[redacted], [redacted], Baxalta Innovations GmbH, Industriestrasse 67, A-1221 Vienna, Austria

MARKETING AUTHORIZATION HOLDER(S)

MAH	USA: Baxalta US Inc., One Baxter Way, Westlake Village, CA 91362 EU: Baxalta Innovations GmbH, Industriestrasse 67, A-1221 Vienna, Austria
MAH CONTACT PERSON	[redacted], MD [redacted], Clinical Development Baxalta US Inc.

SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs), to the ethics committee(s) (ECs)/institutional review boards (IRBs).

ALL SAEs ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (ECRF) WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE ECRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE MAH TO MEET THE 24 HOUR TIMELINE REQUIREMENT.

See SAER form for contact information.
Further details are also available in the study team roster.

Any non-serious adverse events (AEs), all therapies/procedures to treat the AEs, and the outcome of the AEs are to be reported to the MAH on the appropriate case report forms (CRFs) within 5 business days. If the eCRF is not available for more than 5 business days, then the AE must be reported on the Non-Serious Adverse Event Report Form and transmitted to the MAH (see Non-Serious Adverse Event Report Form for contact information).

ADVERSE EVENT DEFINITIONS AND ASSESSMENT

For information on the definitions and assessment of these events refer to: definitions of AE in Section 11.1.1, and assessment of AEs in Section 11.1.2, SAE in Section 11.1.1.1.

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
B19V	parvovirus B19
BW	body weight
CHMP	Committee for Medicinal Products for Human Use
CLL	chronic lymphocytic leukemia
CRF	case report form
CRO	contract research organization
EC	ethics committee
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	EuroQol 5-Dimension Questionnaire
ER	emergency room
FDA	Food and Drug Administration
FSI	First Subject In
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRQoL	Health-related quality of life
HRU	health resource use
HYQVIA	Immune Globulin (Human) 10% with rHuPH20
ICF	informed consent form
IGI 10%	Immune Globulin Infusion 10% (Human)
IgG	immunoglobulin G
IGIV	immune globulin intravenous (human)
IgM	immunoglobulin M
IRB	Institutional Review Board
IV	intravenous(ly)
LSO	Last Subject Out

Abbreviation	Definition
MAH	marketing authorization holder
MM	multiple myeloma
NMC	non-medical complaint
PASS	post-authorization safety study
PID(D)	primary immunodeficiency (disease/s)
QoL	quality of life
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAER	serious adverse event report
SC	subcutaneous(ly)
SF-36v2	Short Form-36, version 2 QoL questionnaire
SIC	subject identification code
SOC	System Organ Class
SPC	Summary of Product Characteristics
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
VASBI	validated acute serious bacterial infection

3. RESPONSIBLE PARTIES

3.1 MAH's Authorized Representative (Signatory)

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

3.2 Investigator(s)

The name and contact information of all investigators will be maintained by the MAH/MAH´s representative(s) in a separate file and provided to the individual investigators (see Annex 14.1).

3.3 Other Individuals Involved in the Study

The name and contact information of other individuals involved with the study (eg, MAH's/MAH´s representative(s) medical expert and study monitor, MAH's representative(s), laboratories, steering committees, and oversight committees (including ethics committees [ECs]/institutional review boards [IRBs]), as applicable) will be maintained by the MAH/MAH´s representative(s) and provided to the investigator (see Annex 14.1).

4. ABSTRACT

Title:

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

Amendment 2: 2015 SEP 17

Replaces Amendment 1: 2015 APR 09
Original Protocol: 02 MAR 2015

Main author:
[redacted], [redacted],
Baxalta Innovations GmbH, Industriestrasse 67, 1220 Vienna, Austria

Rationale and background:

This prospective, uncontrolled, multi-center, open-label, post-HYQVIA marketing authorization surveillance study with assessment of antibodies against rHuPH20 was agreed upon with the Food and Drug Administration (FDA) in the course of the HYQVIA Biologic License review and approval process. It is designed to obtain additional safety and tolerability data on HYQVIA in patients with Primary Immunodeficiency Diseases (PIDD) under clinical routine conditions. Further data shall be collected in subjects with an anti-rHuPH20 antibody titer ≥ 160.

Research question and objectives:

The purpose of the proposed 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 adverse events 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, health-related quality of life (HRQoL) and health resource use (HRU) assessments.

Study design:

This study is a non-interventional, prospective, uncontrolled, multi-center, open-label, post-marketing surveillance study with assessment of antibodies against rHuPH20 designed to obtain additional safety and tolerability data on HYQVIA in a total of 250 adult evaluable subjects with Primary Immunodeficiency Diseases (PIDD) under routine clinical conditions. Further data shall be collected in subjects with an anti-rHuPH20 antibody titer ≥ 160.

It is planned that approximately 50% of the subjects enrolled will have received subcutaneously (SC) administered immunoglobulins prior to enrollment. The remaining subjects will have received immunoglobulins administered via the intravenous (IV) route prior to enrollment, or will be naïve to immunoglobulin treatment.

Screening for potential eligibility will take place prior to enrollment, and may coincide with a regular visit, or a treatment-related visit, for the subject at the treatment center. Screening for potential eligibility should occur after the subject has been selected to receive, or has started treatment with HYQVIA, and should occur prior to enrollment. A termination visit should ideally occur at the conclusion of the observation period at a regular visit at the treatment center; the termination visit will be defined as the last regular visit at the treatment center before the study´s projected LSO date.

Treatment regimens will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care will be performed as is standard for the site and for the subject´s healthcare. In addition, however, the subject will be invited to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but no more often than 4 times a year, for the measurement of antibodies against rHuPH20. For subjects with an anti-rHuPH20 antibody titer ≥10,000, antibody characterization will be performed. Additional blood samples for rHuPH20 antibody testing should be taken if the visit coincides with other routine laboratory assessments. If testing for antibodies against rHuPH20 is not done for any reason, all other laboratory data will be collected as available.

The study will comprise two periods:

Epoch 1

Subjects will be treated for approximately 1 year with HYQVIA.

Subjects who at no time during Epoch 1 test positive for anti-rHuPH20 antibodies at a titer of ≥ 160, including subjects who did not undergo testing for anti-rHuPH20 antibodies at least once during Epoch 1, will undergo an End-of-Study visit and will exit the study at the end of Epoch 1.

Subjects who at any time during Epoch 1 test positive for anti-rHuPH20 antibodies at a titer of ≥ 160 will continue in Study Epoch 2. Subjects in whom anti-rHuPH20 antibodies ≥ 160 were measured and documented at any time prior to enrollment will also continue in Epoch 2 regardless of any test results for anti-rHuPH20 antibodies that may be available from Epoch 1.

Epoch 2

Subjects who at any time during Epoch 1had an anti-rHuPH20 antibody titer ≥ 160, or had an anti-rHuPH20 antibody titer ≥ 160 documented any time prior to enrollment, will remain in the study for additional 2 years from the time of completing Epoch 1. Treatment with HYQVIA, site visits and all other medical care will continue as in Epoch 1.

If a subject who tested positive for anti-rHuPH20 antibodies with a titer ≥ 160 at any time before or during the study discontinues treatment with HYQVIA, the subject will be asked to continue participation in the study, and will continue to be followed up for the occurrence of AEs and anti-rHuPH20 antibody titers through the completion of Epoch 2. For the remaining time in the study, the subject´s treating physician will prescribe an alternative licensed human normal immunoglobulin or any other alternative treatment. If the subject withdraws consent for further testing of anti-rHuPH20 antibodies, data on AEs will continue to be collected.

The overall duration of the study is approximately six years from study initiation (ie, start of data collection) to study completion (ie, end of data collection). The recruitment period will be approximately three years.

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

Population:

Adult patients with PIDD who have been prescribed treatment with HYQVIA will be enrolled in the US and other countries worldwide where HYQVIA is approved for the treatment of PIDD.

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

1. Subject requires immunoglobulin treatment for PIDD
2. Subject age is compatible with local package insert requirements (US ≥ 16, EU ≥ 18 years of age)
3. Subject has been prescribed or has started treatment with HYQVIA
4. Subject is willing and able to comply with the requirements of the protocol.

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

1. Subject has known hypersensitivity to any of the components of the medicinal product
2. Subject has participated in an interventional clinical study involving a medicinal product or device within 30 days prior to enrollment or is scheduled to participate in an interventional clinical study involving a medical product or device during the course of this study.
3. Subject is a family member or employee of the investigator.

Variables:

Variables assessed include: Antibodies against rHuPH20 (rHuPH20 binding and neutralizing antibodies), characterization of antibodies in positive samples of a titer ≥ 10,000 (to include neutralizing antibodies and antibodies cross-reacting with Hyal 1, 2 and 4), laboratory assessments such as hematology, clinical chemistry, urinalysis, total IgG and seroconversion to HBV, HCV and HIV, pregnancy (if applicable), further safety data (e.g., AEs and SAEs), the prescribed treatment regimen, product administration details, and health related quality of life and health resource use. Data will be collected as available.

Data sources:

Source data for this study comprise hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subject diaries, treatment logs 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, medical imaging data (eg, 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 study.

A subject diary will be provided by the MAH/MAH´s representative(s) and offered to each study subject to record AEs, medications, non-drug therapies, and product administration details. The MAH/MAH´s representative(s) will also provide instruments for the assessment of health-related quality of life (HRQoL) and health resource use (HRU). Use of the subject diary and HRQoL and HRU assessments will be optional.

Study size:

The study will enroll 250 adult subjects. All subjects should complete Epoch 1. It is estimated, that up to 50 subjects may test positive for rHuPH20 antibodies at a titer ≥ 160 measured at any time during Epoch 1, and thus become eligible to continue in Epoch 2. Subjects who have documented positive test results for rHuPH20 antibodies ≥ 160 at any time of their history prior to enrolment will also continue in Epoch 2, regardless of test results for rHuPH20 antibodies (if any) that may become available during Epoch 1.

Data analysis:

Statistical analyses and data displays will be mainly descriptive. If groups of sufficient sample size (such as: age groups, PIDD types) are available, confidence intervals may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class (SOC) and preferred term. Concomitant medications and non-drug therapies will be recorded and tabulated. 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 events.

Milestones:

Initiation (FSI):	2015
Enrollment:	Approximately 3 years
Completion (LSO):	2021 June 12
Duration:	Approximately 6 years
Final Report Submission Date:	2021 November 12

5. AMENDMENTS AND UPDATES

Amd. No.	Date	Section of Protocol	Amendment	Reason
1	2015 APR 09	Throughout the document	Refer to Section 14.4 for the Summary of Changes	Administrative
2	2015 SEP 17	Throughout the document	Refer to Section 14.4 for the Summary of Changes	Refer to Section 14.4 for the Summary of Changes

6. MILESTONES

Milestone	Planned Date
Final protocol submission	2015 MAR 12
Start of data collection	2015
End of data collection	2021 JUN 12
Study Progress Reports	Annually
Interim Analysis	The first interim analysis is planned after 50 subjects have been enrolled. Further interim analyses will be performed approximately every two years after the first. The last interim analysis will be performed not later than approx. 6 months before LSO.
Final Report of Study Results	2021 NOV 12

7. RATIONALE AND BACKGROUND

7.1 Medicinal Product Safety Profile

The medicinal product is registered as HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] in the USA, and HyQvia (Immune Globulin (Human) 10% with rHuPH20) in EU. The product name as registered in the USA will be used in this protocol.

HYQVIA is a product dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin Infusion 10% (Human) / IGI 10%) in the USA, or Immune Globulin 10% / IG 10% in EU) and one vial of recombinant human hyaluronidase (rHuPH20)[i]. Immune Globulin Infusion 10% (Human) or IGI 10%, as registered in the USA, will be used to specify the active ingredient in this protocol.

The IGI 10% component provides the therapeutic effect of this medicinal product. The recombinant human hyaluronidase facilitates the dispersion and absorption of IGI 10%.

Human normal immunoglobulin contains mainly immunoglobulin G (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 subcutaneous 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 IGI 10%.

[i] rHuPH20 is a highly purified, neutral pH-active human hyaluronidase that is generated by recombinant DNA technology. rHuPH20 is the active pharmaceutical ingredient in the marketed product Hylenex® recombinant (hyaluronidase human injection), which is a registered trademark of Halozyme Therapeutics, Inc.

HYQVIA therapeutic indications include:

USA: HYQVIA is an immune globulin with recombinant human hyaluronidase for the treatment of primary immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

EU: HYQVIA is approved in the EU for

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

In other countries HYQVIA is currently under assessment for marketing authorization.

The background of immunoglobulin treatment without/with rHuPH20 in this indication is described below.

During this study the medicinal product is HYQVIA. However, if a subject who tested positive for anti-rHuPH20 antibodies (titer ≥ 160) at any time during the study discontinues treatment with HYQVIA (see Section 9.1), the subject´s treating physician will prescribe an alternative licensed human normal immunoglobulin or any other alternative treatment for the remaining time in the study. The safety data for the selected product is described in the package insert/Summary of Product Characteristics (SPC) of the respective product.

A) 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 (eg, X-linked agammaglobulinemia, selective IgG subclass deficiency, common variable immunodeficiency, or X-linked hyperimmunoglobulin M syndrome, but also in the group of combined immunodeficiencies (eg., 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 chronic lymphocytic leukemia (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[2]. MM is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, hypercalcemia but also recurrent infections.[3]

Individuals with PIDD require lifelong replacement therapy with immunoglobulin products to prevent or reduce the 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 subcutaneous (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.[4;5] 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 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.[6;7;8;9;10]

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.

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).[11;12] 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.[13]

Immunoglobulin administered intravenously is immediately available in the blood, and slowly equilibrates to the extra-vascular compartment over 3 to 5 days.[14] 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 modeling and determined that the bioavailability of SC and IM was 100% when compared to IV.[15] More recent studies mandated by the FDA showed that the bioavailability (measured as the AUC of immune globulin concentration over time) of SC immunoglobulin is lower than that of IV immunoglobulin.[5;16] 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.[5;17] Despite the technical difficulties of comparing AUC for 2 different routes and frequencies of administration, studies of intradermally administered immunoglobulin in rats[ii] 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.[18]

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 BW thus would require at least 3 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.

[ii] Halozyme Report Number R1005-0551.

B) 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.[19] Recombinant human hyaluronidase (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[iii]. Weekly infusions for 39 weeks into cynomolgus monkeys in doses up to 2 mg/kg (> 1000 fold higher than the HYQVIA dose in humans) did not lead to adverse reactions[iv].

In a phase 1/2 clinical study of HYQVIA conducted by Baxter (Study 160602) the average bioavailability of the IgG in 7 subjects was 92%, suggesting a significant improvement compared to IGI 10% 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 on first exposure when rHuPH20 was administered to 100 healthy volunteers in a skin allergy clinical trial.[20] In the Baxter 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 peaks of the observed positive titers ranged from 160 up to 81920 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.

[iii] Halozyme Report R08014.
[iv] Halozyme Report R09050.
[v] Halozyme Report Number 10059.

Antibodies reactive to rHuPH20 have also been identified in the normal population with a prevalence of approximately 5%.[21] No signal of associated infertility or autoimmune/inflammatory condition could be identified.

Non-clinical data for recombinant human hyaluronidase or antibodies to recombinant human hyaluronidase 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 with semi-purified extracts of guinea pig testes combined with complete Freunds adjuvants to produce antibodies to hyaluronidase. However, active immunization or passive administration of antibodies reactive with hyaluronidase did not influence reproduction in mouse, rabbit, sheep, or cynomolgus monkey. The effect of antibodies against recombinant hyaluronidase on male or female human fertility is currently unknown.

Specific Populations

Pregnant or breast-feeding women

For subjects in the USA: HYQVIA should be given to a pregnant or nursing woman only if clearly indicated. Refer to the local package insert/prescribing information for further information.

For subjects in the EU: 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 women and breast-feeding mothers.

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 foetus and the neonate are to be expected.

Development and reproductive toxicology studies have been conducted with recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy and foetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to recombinant human hyaluronidase were transferred to offspring in utero. The effects of antibodies to the recombinant human hyaluronidase component of HyQvia on the human embryo or on human fetal development are currently unknown. Animal studies do not indicate direct or indirect harmful effects of recombinant human hyaluronidase with respect to reproductive potential at the doses used for facilitating administration of IG 10%.

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

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.

Refer to the local package insert/prescribing information for further information.

In other countries HYQVIA is currently under assessment for marketing authorization. Directions on the use of HYQVIA in pregnant or lactating women as provided in the local package insert will apply when approved.

This study with regular assessment of antibodies against rHuPH20 was a commitment to the Food and Drug Administration (FDA). A similar study (Baxalta Protocol 161302, refer to Section 7.2.6) was initiated in the EU as a commitment to the Committee for Medicinal Products for Human Use (CHMP).

7.2 Critical Review of Available Data

In this section, safety, efficacy and pharmacokinetic data obtained from clinical studies with HYQVIA will be presented.

7.2.1 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. 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 pharmacokinetic (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 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.

7.2.2 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[22]. 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 (89) subjects were enrolled in the study, of which 87 were treated via both IV and SC routes. Eighty-four (84) subjects completed Study Epoch 1 and 68 subjects completed Study Epoch 2. Sixteen (16) 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 1359 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 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. Adverse events 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.

[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 adverse reactions. Furthermore, SC infusion with rHuPH20 was the subjects' preferred mode of treatment with GAMMAGARD LIQUID/KIOVIG.

Pharmacokinetic properties

With administration of HYQVIA, peak serum IgG levels are achieved in the recipient's circulation after a delay of approximately 3 to 5 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 body weight/4 weeks given at intervals of 3- or 4-weeks.

The pharmacokinetics 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 intravenous 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.

7.2.3 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 IG, 10% facilitated with recombinant human hyaluronidase (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 IG, 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 IG, 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 IG, 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 IG, 10%/rHuPH20 on IgG trough levels", subjects were requested to change their drug administration interval to a 2-week drug interval (receiving a 2-week dose) from a 4 or 3-week drug administration interval, provided both the subject and the investigator agreed that the change was appropriate. This new treatment interval started after 3 infusions on the 4 or 3 week interval and was maintained for a minimum of 4 months. It was intended to allow for evaluation of whether a more frequent administration of IG, 10% leads to improved IgG trough levels. After the 4 month trial period, subjects could revert to their previous dose interval or continue on the 2 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.

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; 3 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, 4 withdrew, 1 subject died, 1 subject had bone marrow transplant, 6 subjects had their clinical site closed out by sponsor, and 3 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 3 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 (8 subjects), 7 subjects in the range of 12 to <16 years and 4 subjects in the range of 2 to <12 years. The median age was 43.0 years. Of the 66 subjects who met all inclusion/exclusion criteria, 50 (75.8%) completed the study.

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 4 week-infusion interval was the most frequently followed infusion interval. The 2 week-infusion interval was the most frequent interval for 15/66 (22.7%) subjects and 7/66 (10.6%) subjects most frequently followed a 3-week infusion interval.

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% 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 (4-week) infusion interval (median steady-state trough level: 10.90 g/L (2-week interval), 12.30 g/L (3-week interval), 9.76 g/L 4-week interval).
Percent change of steady-state trough levels was 105.90% (mean and median) for subjects who switched from a 3-week to a 2-week infusion interval and a mean of 113.23% (median 112.44%) for subjects who switched from a 4-week to a 2-week infusion interval.

The point estimate for the annualized rate of days off school/work was less than 8 days per year. The rate of days on antibiotics was less than 65 days per year. The rate of hospitalizations was less than 1 per year and the rate of days hospitalized, less than 1 day per year. The rate of acute physician visits due to infection or other illness was less than 5 visits per year.

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, 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. The rate of all causally-related local AEs, by infusion, was 0.10 during rHuPH20-facilitated IGSC, 10% treatment. 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 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.

7.2.4 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 subcutaneous 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 3 weeks. The ramp-up period was Epoch 1.

The ramp-up was followed by Epoch 2, a 6 month period of subcutaneous IGI, 10% with rHuPH20 treatment:

- For IV-pretreated subjects: every 3 weeks or 4 weeks, depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects: every 3 weeks or 4 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, 9 subjects withdrew. At the time when rHuPH20 administration was stopped, 1 subject had completed Epoch 2. The remaining 26 were switched to Epoch 3. During Epoch 3, 2 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 (9.21 g/L [95%CI: 8.28-10.25]) were comparable to the levels measured at screening (median 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 1 day/month. The rate of days on antibiotics was less than 3 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 1 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 2h. 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, urinalysis did not raise any safety concerns with respect to the SC administration of IGI, 10% with rHuPH20.

7.2.5 Baxalta 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 a 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 will be assigned to Study Arm 1 (Alternative Product Arm); subjects in countries where HyQvia treatment during pregnancy is not indicated should be enrolled in this arm. Subjects who continue treatment with HyQvia during pregnancy will be 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 Food and Drug Administration (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 2 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 EU the therapeutic indications for HyQvia are Primary Immunodeficiency Diseases (PIDD), Chronic Lymphocytic Leukemia (CLL), and Myeloma; in the USA HyQvia is licensed for the treatment of PIDD. Licensure in other countries will follow. 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 3 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 2 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 6 years from study initiation (Registry ready to enroll) to study completion (ie, end data collection). The enrollment period is expected to be 3 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 2 years to assess the development, unless prematurely discontinued.

7.2.6 Baxalta 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 in the European Economic Area. The Post-Authorization Safety Surveillance (PASS) 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 adverse events 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 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 3 months, but no more often than 4 times a year, for the measurement of antibodies against rHuPH20.

The overall duration of the study is approximately six years from study initiation (ie, first subject enrolled) to study completion (ie, 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 (ie, last study 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.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The purpose of the proposed 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.

8.2 Primary Objective

HYQVIA is a newly registered product, the primary objective therefore is to collect and assess additional safety data, in particular the occurrence of long-term changes in incidence and severity of related adverse events in patients treated with HYQVIA.

8.3 Secondary Objectives

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

9. RESEARCH METHODS

9.1 Study Design

This study is a non-interventional, prospective, uncontrolled, multi-center, open-label, post-marketing surveillance study with assessment of antibodies against rHuPH20 designed to obtain additional safety and tolerability data on HYQVIA in a total of 250 evaluable adult subjects with Primary Immunodeficiency Diseases (PIDD) under routine clinical conditions. Further data shall be collected in subjects with an anti-rHuPH20 antibody titer ≥ 160 measured during study Epoch 1, or documented at any time prior to enrollment. The overall study design is illustrated in Figure 1.

It is planned that approximately 50% of the subjects enrolled will have received subcutaneously (SC) administered immunoglobulins prior to enrollment. The remaining subjects will have received immunoglobulins administered via the intravenous (IV) route prior to enrollment, or will be naïve to immunoglobulin treatment.

Screening for potential eligibility will take place prior to enrollment, and may coincide with a regular visit, or a treatment-related visit, for the subject at the treatment center. Screening for potential eligibility should occur after the subject has been selected to receive, or has started treatment with HYQVIA, and should occur prior to enrollment.

The dosage regimen and treatment schedule will be chosen by the attending physician in accordance with routine clinical practice. Product administration may or may not coincide with site visits.

There will be no required predefined visits, medical tests, laboratory tests and procedures beyond the treatment center´s standard clinical practice during the course of the study, except for the assessment of antibodies to rHuPH20. The subject will be invited to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but no more often than 4 times a year, for the measurement of antibodies against rHuPH20. For subjects with an anti-rHuPH20 antibody titer ≥ 10,000, antibody characterization will be performed. Additional blood samples for rHuPH20 antibody testing will be taken only if the visit coincides with other routine laboratory assessments. If testing for antibodies against rHuPH20 is not done for any reason, all other laboratory data will be collected as available.

The study is comprised of two Epochs:

Epoch 1

Epoch 1 starts with the enrollment of the subject into the study. Subjects will be treated for approximately 1 year with HYQVIA.

Subjects who at no time during Epoch 1 test positive for anti-rHuPH20 antibodies at a titer of ≥ 160, including subjects who did not undergo testing for anti-rHuPH20 antibodies at least once during Epoch 1, will undergo an End-of-Study visit and will exit the study at the end of Epoch 1.

Subjects who at any time during Epoch 1 test positive for anti-rHuPH20 antibodies at a titer of ≥ 160 will continue in Study Epoch 2. Subjects in whom anti-rHuPH20 antibodies at a titer ≥ 160 were measured and documented at any time prior to enrollment will also continue in Epoch 2 regardless of any test results for anti-rHuPH20 antibodies that may be available from Epoch 1.Epoch 2

Subjects who at any time during Epoch 1 had an anti-rHuPH20 antibody titer ≥ 160, or had an anti-rHuPH20 antibody titer ≥ 160 documented any time prior to enrollment, will continue HYQVIA treatment for additional 2 years from the time of completing Epoch 1. Treatment with HYQVIA will continue as in Epoch 1.

If a subject that tested positive for anti-rHuPH20 antibodies with a titer ≥ 160 at any time before or during the study discontinues treatment with HYQVIA, the subject will be asked to continue participation in the study, and will continue to be followed up for the occurrence of AEs and anti-rHuPH20 antibody titers through the completion of Epoch 2. For the remaining time in the study, the subject´s treating physician will prescribe an alternative licensed human normal immunoglobulin or any other alternative treatment. If the subject withdraws consent for further testing of anti-rHuPH20 antibodies, data on AEs will continue to be collected.

A termination visit should ideally occur at the conclusion of the observation period at a regular visit at the treatment center; the termination visit will be defined as the last regular visit at the treatment center before the study´s projected LSO date.

9.1.1 Study Endpoints

9.1.1.1 Safety

1. Incidence of all related SAEs.
2. Incidence of all SAEs
3. Incidence of non-serious adverse events (AEs), related and not related, local and systemic. Infections will be reported as AEs, but will be reported separately.
4. Incidence and titer of binding and neutralizing antibodies to rHuPH20, and, if available, lab tests such as clinical chemistry, total IgG, etc.

9.1.1.2 Treatment

1. Treatment Regimen
    a. Dose (total dose in mg/kg BW/week)
    b. Infusion interval
2. Treatment Administration
    a. Actual volume per infusion
    b. Maximum infusion rate (total)
    c. Mean rate of infusion
    d. Duration of infusion
    e. Number of infusion sites (needle sticks) per infusion

9.1.1.3 Health Related Quality of Life & Health Resource Use

1. Short Form-36, version 2 (SF-36v2): to be collected every 3 months in first year of study, annually for remainder of study.[23]
2. EuroQol 5-Dimension (EQ-5D) Questionnaire: to be collected every 3 months in first year of study, annually for remainder of study.[24]
3. Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9): to be collected every 3 months in first year of study, annually for remainder of study.[25]
4. Treatment Preference Questionnaire: to be collected annually throughout the study.
5. Health resource use (eg, hospitalizations and length of stay, acute care visits, ER visits, and days missed from work/school): to be collected throughout the study as events occur.

9.2 Setting

Adult patients with PIDD who have been prescribed, or have started treatment with HYQVIA will be enrolled in the US and other countries worldwide where HYQVIA is licensed, as needed. Subject age will be compatible with local package insert requirements. Treatment regimens will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Site visits and all other medical care will be performed as is standard for the site and for the subject´s healthcare, with the exception of the assessment of antibodies against rHuPH20. If testing for antibodies against rHuPH20 is not done, all other laboratory data will be collected as available.

Women who are pregnant at the time of enrollment should be encouraged to enrol in the pregnancy registry that is described in Baxalta Protocol 161301: Pregnancy Registry to collect Long-Term Safety Data from Women treated with HYQVIA (Immune Globulin (Human) 10% with rHuPH20) (see also Section 7.2.5), if locally available, or otherwise may participate in this study.

Pregnant or breast feeding women may continue in the study at the investigator´s discretion (see Section 7.1. Refer also to the local package insert/prescribing information). if a woman prematurely withdraws from the study because of being pregnant or planning to become pregnant, she should be encouraged to participate in the pregnancy registry (Baxalta Protocol 161301).

9.2.1 Medicinal Product(s)

HYQVIA is a dual vial unit with one vial of Immune Globulin Infusion 10% (Human) and one vial of Recombinant Human Hyaluronidase.

The Immune Globulin Infusion 10% (Human) of HYQVIA is a ready-for-use sterile, liquid preparation of highly purified and concentrated IgG antibodies. The distribution of the IgG subclasses is similar to that of normal plasma. The Fc and Fab functions are maintained in the primary component. Pre-kallikrein activator activity is not detectable. The Immune Globulin Infusion 10% (Human) of HYQVIA contains 100 mg/mL protein. At least 98% of the protein is IgG, average immunoglobulin A (IgA) concentration is 37µg/mL, and immunoglobulinM (IgM) is present in trace amounts. The Immune Globulin Infusion 10% (Human) of HYQVIA contains a broad spectrum of IgG antibodies against bacterial and viral agents. Glycine (0.25M) serves as a stabilizing and buffering agent. There is no added sugar, sodium, or preservatives. The pH is 4.6 to 5.1. The osmolality is 240 to 300 mOsmol/kg.

The Recombinant Human Hyaluronidase of HYQVIA is produced from genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase PH20. The purified hyaluronidase glycoprotein contains 447 amino acids with an approximate molecular weight of 61,000 Daltons. This component is supplied as a sterile, clear, colorless, ready-for-use solution and has an approximate pH of 7.4 and an osmolality of 290 to 350 mOsm. Each vial contains 160 U/mL of recombinant human hyaluronidase with 8.5 mg/mL sodium chloride, 1.78 mg/mL sodium phosphate dibasic dihydrate, 1.0 mg/mL human albumin, 1.0 mg/mL edentate disodium dihydrate, 0.40 mg/mL calcium chloride dihydrate, and 0.17 mg/mL sodium hydroxide added for pH adjustment. It does not contain preservatives.

Treatment should be commenced and initially monitored under the supervision of an experienced physician. Each vial of IGI 10% is supplied with the appropriate corresponding quantity of recombinant human hyaluronidase as stated in the table below. The full contents of the recombinant human hyaluronidase vial should be administered regardless of whether the full content of the IGI 10% vial is administered.

Table 2
HYQVIA Administration Scheme

Recombinant human hyaluronidase	Human Normal Immunoglobulin 10%	
Volume (ml)	**Protein (grams)**	**Volume (ml)**
1.25	2.5	25
2.5	5	50
5	10	100
10	20	200
15	30	300

Method of administration

The medicinal product is for subcutaneous use only. In case facilitated subcutaneous infusion of HYQVIA is used for home treatment, therapy should be initiated by a physician experienced in the guidance of patients for home treatment. The patient will be instructed in infusion techniques, the use of an infusion pump or syringe driver, if needed, and measures to be taken in case of adverse reactions. A subject diary to record administration details and reactions, if any, after each infusion will be provided by the MAH/MAH´s representative(s) (refer to Section 9.4.2).

The two components of the medicinal product must be administered sequentially through the same needle beginning with the recombinant human hyaluronidase followed by IGI 10%, as described below.

The HYQVIA components may be infused using a variable rate, electromechanical pump with a subcutaneous needle set that is at least 24 gauge and an administration set that is compatible with the pump.

It is recommended that the recombinant human hyaluronidase component be administered at a constant rate and that the rate of administration of the IGI 10% should not be increased above the recommended rates, particularly when the patient has just started with HYQVIA therapy.

The suggested site(s) for the infusion of the medicinal product are the abdomen and thighs. If two sites are used, the two infusion sites should be on contra lateral sides of the body. Avoid bony prominences.

First, the full dose of recombinant human hyaluronidase solution is infused at a rate of 1 to 2 ml/minute per infusion site. Within 10 minutes of completing the infusion of recombinant human hyaluronidase, the infusion of the required dose of IGI 10% has to be initiated at the same needle site. If two infusion sites are used, the total dosages of the recombinant human hyaluronidase and IGI 10% each have to be divided before start of the infusion.

The following infusion rates of the IGI 10% are recommended:

- Patients with a body weight of 40 kg or above: IGI 10% should be infused at an initial rate of 10 ml/hour/infusion site. If well tolerated, the rate of the administration may be increased at intervals of at least 10 minutes to a maximum of 240 ml/hour/site for the initial one or two infusions. For subsequent infusions the rate can be adjusted to a maximum of 300 ml/hour/site.
- Patients with a body weight under 40 kg: IGI 10% should be infused at an initial rate of 5 ml/hour/infusion site. If well tolerated, the rate of the administration may be increased at intervals of at least 10 minutes to a maximum of 80 ml/hour/site for the initial one or two infusions. For subsequent infusions the rate can be adjusted to a maximum of 160 ml/hour/site.

Treatment with HYQVIA should be performed as specified in the product label according to the standard of care.

Further product information including dosage, dosage regimen, administration, packaging, labeling, and storage for the medicinal product is described in the respective local package insert and the SPC.

9.2.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately six years from study initiation (ie, start of data collection) to study completion (ie, end of data collection). The recruitment period will be approximately three years.

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

9.2.3 Subject Selection Criteria

The selection criteria reflect the licensed indication and patient group as well as Baxalta standard criteria.

9.2.3.1 Inclusion Criteria

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

1. Subject requires immunoglobulin treatment for PIDD
2. Subject age is compatible with local package insert requirements (US ≥ 16, EU ≥ 18 years of age)
3. Subject has been prescribed or has started treatment with HYQVIA
4. Subject is willing and able to comply with the requirements of the protocol.

9.2.3.2 Exclusion Criteria

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

1. Subject has known hypersensitivity to any of the components of the medicinal product
2. Subject has participated in an interventional clinical study involving a medicinal product or device within 30 days prior to enrollment or is scheduled to participate in an interventional clinical study involving a medical product or device during the course of this study
3. Subject is a family member or employee of the investigator

9.2.4 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

9.2.5 Subject Identification Code

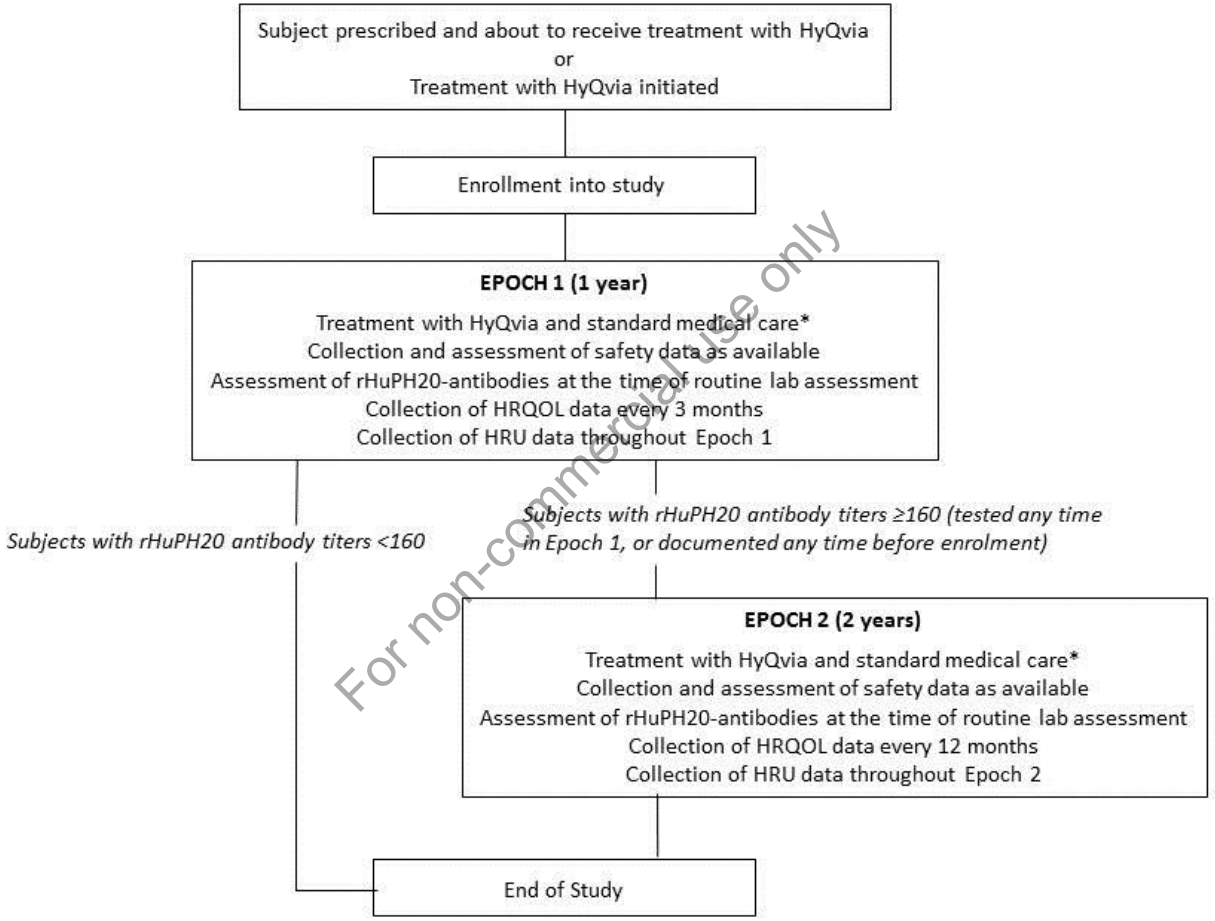
The following series of numbers will comprise the subject identification code (SIC): protocol identifier (eg, 161406) to be provided by the MAH/MAH´s representative(s), 3-digit study site number (eg, 002) to be provided by the MAH/MAH´s representative(s), and 3-digit subject number (eg, 003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 161406-020003. All study documents pertaining to the subject (eg, CRFs, clinical documentation, etc.) will be identified with the SIC. Alternative uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

9.2.6 Screening and Follow-up

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in Figure 1. Details on the assessments/data to be recorded for screening and follow-up, can be found in Table 3 and Table 4.

Figure 1
Study Design for Baxalta Non-Interventional Study 161406



*For subjects who discontinue HyQvia administration at any time during Epoch 1 or Epoch 2, only AEs and assessment of rHuPH20-antibodies at the time of routine lab assessment will be collected

Table 3
Schedule of Study Procedures and Assessments: Epoch 1 and 2

Procedures/Assessments	Screening/ Enrollment Visit	Interval Study Visits	Study Completion/ Termination Visit[h]
		Approximately Every 3 Months or According to the Site's Standard Practice[f]	
Informed Consent[a]	X		
Eligibility Criteria	X		
Medical History	X		
Medications[i]	X	X	X
Non-drug Therapies[i]	X	X	X
Physical Exam[i]	X	X	X
Review Diary/home treatment record[b]		X	X
Adverse Events		X	X
Laboratories[c, i]	X	X	X
Vital Signs[i]	X	X	X
Medicinal Product: Treatment Regimen/Product Administration[d, i]	X	X	X
HRQoL assessments[e, i]	X	X[g]	X
Health resource use[e, i]		X	X

[a] Occurs at enrollment (prior to any study-specific procedure).
[b] If available. Subjects that prematurely discontinue administration of HYQVIA will use the subject diary only to record AEs.
[c] For laboratory assessments, see Table 4.
[d] The subject's treatment regimen will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. If treatment is administered at the site or a subject diary/home treatment record is available then infusion administration details should be collected as outlined in Section 9.3.2. Product administrations may or may not coincide with site visits.
[e] Optional
[f] Site visits and all other procedures and assessments related to the subject's medical management will be performed as is standard for the site and for the subject's healthcare. Additional samples for anti-rHuPH20 antibody assessments should be drawn at the time of routine lab assessments (see Table 4).
[g] Approximately every 3 months in Epoch 1, and every 12 months in Epoch 2, except for the treatment preference assessment. Refer to Section 9.3.3.1
[h] Study duration, and thus the time of the Study Completion Visit, will vary depending on whether subject qualifies for participation in Epoch 1 only, or Epochs 1 and 2.
[i] Subjects who prematurely terminate HYQVIA administration will not continue to collect product administration, medication, non-drug therapies, results of physical exams,vital signs and lab results except for adverse events and results of anti-rHuPH20 antibody assessments, and will not perform HRQoL and health resource use assessments.

Table 4
Clinical Laboratory Assessments: Epoch 1 and 2

Assessments	Screening/ Enrollment Visit	Interval Study Visits	Study Completion/ Termination Visit[f]
		Approximately Every 3 Months, or According to the Site's Standard Practice[d]	
Hematology[a, g]	X[e]	X	X
Clinical Chemistry[a, g]	X[e]	X	X
Urinalysis[a, g]	X[e]	X	X
Serology (HBV, HCV, HIV)[a, g]	X	X	X
Pregnancy Test[b, g]	X	X	X
Anti-rHuPH20 antibodies[c]	X	X	X
Total IgG[a, g]	X[e]	X	X

[a] Test results will be recorded as available from tests performed as part of the site's routine medical management of the subject.
[b] Only females of child-bearing potential and if performed as part of the site's routine medical management of the subject.
[c] Additional blood samples for the testing of anti-rHuPH20 antibodies should be drawn at the time of routine laboratory assessments approximately every 3 months or according to the site´s standard practice, but no more often than 4 times a year. Subjects who test positive for binding anti-rHuPH20 antibodies at a titer of ≥ 160 at any time during Epoch 1 will continue in Epoch 2. For subjects with binding anti-rHuPH20 antibodies of a titer of ≥ 160 assessments for neutralizing antibodies will be done, for subjects with a titer ≥10,000, antibody characterization will be performed in addition (see Section 9.3.1.3.1)
[d] Site visits and all other procedures and assessments related to the subject's medical management will be performed as is standard for the site and for the subject's healthcare (with the exception of anti-rHuPH20 antibodies assessments) and will be documented as available.
[e] If testing is not performed routinely at the date of the screening/enrollment visit, results of the tests that were performed last (but not more than 6 months prior to enrollment) will be recorded as available.
[f] Study duration, and thus the time of the Study Completion Visit, will vary depending on whether subject qualifies for participation in Epoch 1 only, or Epochs 1 and 2.
[g] Will not continue to be recorded for subjects who prematurely terminate HYQVIA administration.

9.2.7 Subject Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, 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 CRF. The data collected on withdrawn subjects will be used in the analysis and included in the non-interventional study report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action).

Subjects will also be discontinued from further study participation for the following reason:

- During Epoch 1, if a subject discontinues HYQVIA administration and has not consented to, or withdraws consent to perform, the assessments for anti-rHuPH20 antibodies, or
- During Epoch 2, if a subject discontinues HYQVIA administration and withdraws consent to perform the assessments for anti-rHuPH20 antibodies

The subject will be discontinued from the study for the following reason:

Collection of data related to the administration of HYQVIA is no longer possible.

9.2.8 Study Stopping Rules

Stopping rules will not be established for this study as subjects will be treated with a licensed medicinal product according to the routine standard at the study site for the duration of the study.

9.3 Variables

9.3.1 Safety Variables

9.3.1.1 Medical History, Medications, and Non-Drug Therapies

At screening/enrollment, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 11.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphocytic; dermatological; and genitourinary.

All medications taken (including treatment with immune globulin)and non-drug therapies received 3 months before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

In addition, the medical history should also include information on the immune globulin treatment given prior to HYQVIA, such as specific product, dosage, and regimen, as well as the date and administration details of last infusion prior to the first HYQVIA administration ever.

The medical history should also include information, if the subject has ever received a medicinal product containing hyaluronidase before the first HYQVIA treatment ever and had an anti-rHuPH20 antibody titer ≥ 160 documented at any time (including HYQVIA treatment prior to study entry, if applicable).

9.3.1.2 Physical Examinations

At screening/enrollment and subsequent study visits (as described in Table 3), a physical examination should be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.

At screening/enrollment, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 11.1.1.4), 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.

9.3.1.3 Clinical Laboratory Parameters

All laboratory data, such as (but not limited to) clinical chemistry, hematology, urinalysis, total IgG, seroconversion results for HIV, HBV, and HCV, pregnancy testing (if applicable), will be collected as available from routine clinical practice, with the exception of the assessment of antibodies against rHuPH20. If testing for antibodies against rHuPH20 is not done for any reason, all other laboratory data will be collected as available.

For the assessment of antibodies to rHuPH20 refer to Section 9.3.1.3.1.

Laboratory data, except for rHuPH20 antibodies, will be transcribed by the investigator into the CRF provided by the MAH/MAH´s representative(s).

Assessment of hematology, clinical chemistry, urinalysis, and any other relevant laboratory tests, will be done at local laboratories, according to standard of care of the study site or at the discretion of the investigator.

9.3.1.3.1 rHuPH20 Antibodies

For the assessment of antibodies to rHuPH20, the subject will be invited to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but no more often than 4 times a year, for the measurement of rHuPH20 binding antibodies. For subjects with an anti- rHuPH20 antibody titer ≥ 160 also neutralizing antibodies will be measured. In addition, characterization of antibodies will be performed in subjects who test positive for antibodies to rHuPH20 at a titer of ≥ 10,000. Characterization will include neutralizing antibodies and antibodies cross reacting to Hyal 1, 2 and 4.

For information regarding sample volumes and processing, refer to the Laboratory Manual for the study. Additional blood samples for rHuPH20 antibody testing should be taken if the visit coincides with other routine laboratory assessments.

Testing will be done in a central laboratory selected by the MAH/MAH´s representative(s). Results for antibodies against rHuPH20 and antibody characterization, if applicable, will be forwarded by the central laboratory to both the investigator and the MAH/MAH´s representative(s) and will not need to be transcribed into the CRF by the investigator.

9.3.1.3.2 Hematology and Clinical Chemistry

Results from the assessment of hematology and clinical chemistry, if routinely performed during clinical practice or indicated based on the clinical judgement of the investigator, will be collected as indicated in Table 4.

Data collected from the hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), and leukocytes (ie, white blood cell count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts, as available. Results from Coombs´ test will also be collected, if available.

Data collected from the clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

9.3.1.3.3 Seroconversion

Results from the assessment of seroconversion will be collected if routinely performed during clinical practice or indicated based on the clinical judgment of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) will be recorded as an SAE.

9.3.1.3.4 Urinalysis

Results from the assessment of urinalysis will be collected if routinely performed during clinical practice or indicated based on the clinical judgment of the investigator.

Data collected from the urinalysis should include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

9.3.1.4 Evaluation of Laboratory Parameters

The investigator's assessment of each laboratory value will be recorded on the appropriate form. For each abnormal laboratory value, the investigator will determine whether the value is clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 11.1, 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 preexisting disease (described in Section 11.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie. because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. However, 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.

During the final analyses following completion of the study, laboratory values will be graded by Baxalta (Grades 0-4) to identify relevant abnormalities.

The Common Toxicity Criteria of the Eastern Cooperative Oncology Group, published by Oken et al.[26], will be used to grade the following laboratory values: Alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), hemoglobin, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and white blood cell (WBC) count. Grading for lactate dehydrogenase will use the same thresholds as defined for ALT and AST.

Sodium and potassium will be graded using the thresholds taken from the WHO toxicity grading system.[27] The laboratory parameters and the corresponding grading scale are provided in Table 5.

Grade refers to severity: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening. Grading for LDH will use the same thresholds as defined for ALT and AST. Parameters not included in Table 5 will not be graded.

Table 5
Grading of Laboratory Parameters[a]

Analyte	Direction	WNL is Grade 0	No Grade 1	Unit Grades	Grade 0 Low	Grade 0 High	Grade 1 Low	Grade 1 High	Grade 2 Low	Grade 2 High	Grade 3 Low	Grade 3 High	Grade 4 Low	Grade 4 High	Source
Alkaline Phosphatase	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
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	.	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	.	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

[a] Grade refers to severity: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening or disabling, 5 (not shown in the table) = death.

9.3.1.5 Retest Results

In case any retention samples will routinely be taken and will be retested to confirm implausible or critical test results, retest results will be documented. Sample storage will follow local standards.

Any samples remaining from anti-rHuPH20 antibody testing will be stored at the Central Laboratory to confirm implausible or critical test results, if required. Samples will be stored in a coded form and according to local requirements for a maximum of 2 years after the final study report has been completed and subsequently will be destroyed.

9.3.1.6 Vital Signs

Results from the assessment of vital signs will be collected if routinely performed during clinical practice or indicated based on the clinical judgment of the investigator.

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 be reported as available.

Vital signs will be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 11.1 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.

9.3.2 Treatment Regimen and Product Administration

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, as available, will be collected.

Details of the treatment regimen and product administration, if performed at the site, should be recorded on the case report form (CRF). Treatment may or may not coincide with site visits. Administration details for home treatment should be recorded by the subject/subject´s legally authorized representative in the subject diary (see Section 9.4.2).

For subjects who discontinue administration of HYQVIA, only the product name and the initial treatment regimen of the alternative licensed immunoglobulin product or alternative treatment prescribed immediately following HYQVIA will be recorded. Further treatment data will not be collected.

9.3.3 Health Related Quality of Life and Health Resource Use

HRQoLand Health Resource Use assessments are a voluntary effort and may be performed optionally.

9.3.3.1 Health Related Quality Of Life

HRQoL assessments may be performed at the following intervals, if coinciding with the subject´s routine site visits.

During Epoch 1, HRQoL assessments (except Treatment Preference Questionnaire) may be performed at the screening/enrollment visit, thereafter approximately every three months, and at the visit that coincides with the end of Epoch 1. The Treatment Preference Questionnaire may be administered at the screening/enrollment visit, and at the visit that coincides with the end of Epoch 1.

For subjects who continue in Epoch 2, additional HRQoL assessments (including the Treatment Preference Questionnaire) may be performed at the time of completing the first year of Epoch 2 (ie. approximately 24 months after enrollment), and at the study termination visit.

Short Form-26, version 2 (SF-36v2)

The SF-36 is a self-administered, validated questionnaire designed to measure generic HRQoL. This 36-item questionnaire measures 8 domains, including: Physical Functioning, Role-physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-emotional, and Mental Health. Two summary scores can be calculated, the Physical Component Score, and the Mental Component Score. Additionally, scores can be calculated for each of the 8 domains. Higher scores indicate better health status.

EuroQoL 5-Dimension (EQ-5D)

The EQ-5D is a validated generic health-related quality of life measure designed by the EuroQol Group. It consists of five questions that assess the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D also includes a standard vertical 20 cm visual analogue scale (VAS) (similar to a thermometer) for recording a rating for current health-related quality of life state (ranging from best imaginable health state [100] to worst imaginable health state [0]).

Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)

The TSQM-9 is a self-administered, validated measure assessing patient satisfaction with their treatment. This questionnaire measures 3 domains: Effectiveness, Convenience and Global Satisfaction. Higher scores indicate greater satisfaction with treatment. In the event that the language is not available, the assessment in the closest language will be used.

Treatment Preference Questionnaire

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

9.3.3.2 Health Resource Use

HRU includes hospitalizations and length of stay, acute care visits, ER visits, and days missed from work/school.

HRU assessments may be performed approximately every three months, if coinciding with the subject´s routine site visits, and at the study termination visit.

9.3.4 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 the study according to the protocol.

Reasons for completion/discontinuation will be reported on the Completion/ Discontinuation CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up, dropout), study terminated by the MAH, or other (reason to be specified by the investigator). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF and will be used in the analysis and included in the study report.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations performed as part of the evaluation of the event will be reported to the MAH/MAH´s representative(s). Details of the outcome may be reported to the appropriate regulatory authorities by the MAH/MAH´s representative(s).

9.4 Data Sources

9.4.1 Source Data

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, subject diaries, treatment logs 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, medical imaging data (eg, 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 study.

For additional information on study documentation and CRFs see Section 9.6.1.

9.4.2 Subject Diary

An electronic subject diary (alternatively, if preferred by the subject, a paper subject diary) will be offered to each subject at enrollment to record the following information:

1. Adverse events
2. Medications and non-drug therapies
3. Product administration details (refer to Section 9.3.2)

Completion of the subject diary is a voluntary effort by the individual subject or subject's legally authorized representative. If used, the diary will remain with the subject for the duration of the study. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

For electronic subject diaries: 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.

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

9.5 Study Size

The study will enroll 250 adult subjects. All subjects should complete Epoch 1. It is estimated, that up to 50 subjects may test positive for rHuPH20 antibodies at a titer ≥ 160 measured at any time during Epoch 1, and thus become eligible to continue in Epoch 2. Subjects who have documented positive test results for rHuPH20 antibodies ≥ 160 at any time of their history prior to enrolment will also continue in Epoch 2, regardless of test results for rHuPH20 antibodies (if any) that may become available during Epoch 1.

9.6 Data Management

9.6.1 Data Collection Methods

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 9.4.1) records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/MAH/MAH´s representative(s), enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), subject diaries (if used), and data clarifications requested by the MAH/MAH´s representative(s).

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 electronic format CRFs are provided by the MAH/MAH´s representative(s), 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.

The handling of data by the MAH/MAH´s representative(s), including data quality assurance, will comply with regulatory guidelines and the standard operating procedures of the MAH/MAH´s representative(s). Data management and control processes specific to the study will be described in the data management plan (see Section 14.1).

9.6.2 Software

The software for data management is to be determined. It is planned to use EDC with the standard data management software of the Contract Research Organization (CRO) selected.

The software for the data analysis is to be determined. It is planned to use the standard data analysis software of the CRO selected.

9.7 Data Analysis

9.7.1 Datasets and Analysis Cohorts

If groups of sufficient sample size (such as: age groups, PIDD types) are available, confidence intervals may accompany the point estimates.

9.7.2 Handling of Missing, Unused, and Spurious Data

The handling of missing data will be described in the statistical analysis plan. Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If any data is considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data points were excluded.

9.7.3 Methods of Analysis

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, PIDD types) are available, confidence intervals may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class (SOC) and preferred term. Concomitant medications and non-drug therapies will be recorded and tabulated. 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 events.

9.7.3.1 Safety Endpoints

For the endpoint of incidence of all related SAEs a point estimate and 95% confidence interval (by the Wilson score method) for the proportion of subjects with one or more related SAEs will be provided. In addition, the SAEs will be listed and the frequency compared to historical data on the SAE frequency during treatment with a subcutaneously administered immunoglobulin not containing rHuPH20.

No statistical hypotheses will be tested.

Descriptive methods, mainly frequency tables, will be used for all other safety endpoints (see Section 9.1.1). The incidence of adverse events will be calculated as the rate per infusion, and rate per subject-year, and will be analyzed for changes in frequency and for changes in severity over time.

9.7.3.2 Treatment – Endpoints

1. Treatment Regimen
    a. Total dose: Dose per kg body mass per week will be summarized descriptively over the set of subjects; if a subject changed the dose, the weighted average will be used with weights proportional to the time the subject was on a particular dose.
    b. Infusion interval: A frequency table will show the number of subjects and the total observation time in subject-years per infusion interval.
2. Treatment Administration

    Nonparametric descriptive statistics (median, quartiles, and range) will be provided for the following:

    a. Actual immunoglobulin and rHuPH20 volume per infusion
    b. Maximum infusion rate (total)
    c. Mean rate of infusion (defined as total volume infused divided by the duration of the infusion)
    d. Duration of infusion (defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion)
    e. Number of infusion sites (needle sticks) per infusion
    f. Number of infusion sites (needle sticks) per month (derived from number of infusion sites per infusion and number of infusions per month)

9.7.3.3 HRQoL & HRU Endpoints

Total and domain scores on each of the HRQoL measures will be calculated for each subject, at each data collection timepoint. Descriptive statistics will be performed on each of the scores, at each data collection timepoint.

HRU endpoints, including hospitalization, ER, acute visit rates and days missed from school/work, will be summed and annualized for reporting purposes. Descriptive statistics will be performed and reported.

9.7.4 Planned Interim Analysis of the Study

Regular study progress information will be provided with the required Annual Reports in the USA, or other formats required by local legislation in other countries. In addition, interim analyses (also to be provided in Annual Reports for the USA, or other locally required report formats as needed) are planned as follows:

The first interim analysis will be performed after 50 subjects have been enrolled. Further interim analyses will be performed following data snap shots approximately every two years after the first. The last interim analysis will be performed not later than approx. 6 months before LSO. Data from the analyses will be used to update the regulatory authorities as needed, and the scientific community at scientific meetings. No changes to the design, conduct, or final analysis of the study will occur due to the interim analyses.

Interim analyses will include the related serious AEs, occurrence of rHuPH20 binding and neutralizing antibodies, all AEs by severity and classified by MedDRA terms, the correlation of adverse events with presence of anti-rHuPH20 antibodies, treatment regimen/product administration variables, and HRQoL and HRU assessments.

9.8 Quality Control

9.8.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the competent/health authority and/or EC, as applicable), and applicable regulatory requirements as described in the Non-interventional Trial 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 MAH/MAH´s representative(s). 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.

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 Non-interventional Trial Agreement.

9.8.2 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 MAH or its representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Non-interventional Trial Agreement. If contacted by an applicable regulatory authority, the investigator will notify the MAH/MAH´s representative(s) of contact, cooperate with the authority, provide the MAH with copies of all documents received from the authority, and allow the MAH/MAH´s representative(s) to comment on any responses, as described in the Non-interventional Trial Agreement.

9.8.3 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol 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 MAH/MAH´s representative(s).

9.8.4 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, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Non-interventional Trial Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan (see Section 14.1).

9.8.5 Auditing

The MAH and/or MAH's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Non-interventional Trial Agreement. Auditing processes specific to the study will be described in the clinical quality management plan (see Section 14.1).

9.8.6 Non-Compliance with the Protocol

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the MAH may terminate the investigator's participation.

9.9 Limitations of the Research Methods

Due to the non-interventional nature of the study, the amount of data that becomes available is beyond the responsible party´s control.

9.10 Other Aspects

Not applicable. The research method has been covered in the previous sections.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Compliance Statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for good pharmacovigilance practices.

10.2 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Non-interventional Trial Agreement.

10.3 Ethics Committee(s)/Institutional Review Boards and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. 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 MAH's/MAH´s representative(s) receipt of approval/favorable opinion from the EC and, if required, upon the MAH's/MAH´s representative(s) notification of applicable regulatory authority(ies) approval, as described in the Non-interventional Trial 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 relevant regulatory authorities, where applicable. The protocol amendment will only be implemented upon the MAH's/MAH´s representative(s) receipt of approval and, if required, upon the MAH's/MAH´s representative(s) notification of applicable regulatory authority(ies) approval.

10.4 Informed Consent

Investigators will choose patients for enrollment 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. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent form will be reviewed by the MAH/MAH´s representative(s) and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The informed consent form will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by 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 to the use of their data for the study, unless they withdraw voluntarily or are terminated from the study for any reason.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Adverse Events

11.1.1 Definitions

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

11.1.1.1 Serious Adverse Event

A **serious** adverse event (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 (ie, 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 human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack, stroke, etc.)
- Diagnosis of hemolytic anemia, reviewed and confirmed by the study site using standard laboratory assessments

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

11.1.1.2 Non-Serious Adverse Event

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

11.1.1.3 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, package insert). "Unexpected" also refers to the AEs that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.1.4 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 during the study, will not be recorded as AEs/SAEs. 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.

11.1.2 Assessment of Adverse Events

Each AE from enrollment until study completion/discontinuation 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 definitions in Section 11.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.1.1.1
- Severity as defined in Section 11.1.2.1
- Causal relationship to medicinal product exposure as defined in Section 11.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first. Follow-up information is to be documented in the CRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, 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 dosage specified in the package insert (including overdosing or underdosing by >20%, abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the dosing schedule defined in the package insert), 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 the medicinal product, or that occurs after paternal exposure to the medicinal product, will be reported on a Pregnancy Form and followed-up at the estimated date of delivery and 1 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 that is described in Baxalta Protocol 161301: Pregnancy Registry to collect Long-Term Safety Data from Women treated with HYQVIA (Immune Globulin (Human) 10% with rHuPH20), if locally available.

11.1.2.1 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/saquelae.
- 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.

11.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the medicinal product is etiologically related to/associated with the AE. Causality assessment includes, eg, 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 medicinal product 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 medicinal product (ie, does not follow a reasonable temporal relationship to the administration of product or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the medicinal product
  - A more likely alternative etiology exists

- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of medicinal product
  - An alternative etiology is equally or less likely compared to the potential relationship to the medicinal product
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of medicinal product, which may include but is not limited to the following:
    1. Reappearance of a similar reaction upon re-administration (positive rechallenge)
    2. Positive results in a drug sensitivity test (skin test, etc.)
    3. Toxic level of the product as evidenced by measurement of the product 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, the investigator shall provide the alternative etiology.

11.1.2.3 Safety Reporting

Adverse Events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Assessments (see Table 3) and Section 11.1 above.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. 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 study product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). Any Adverse Event which occurs during this study, whether or not related to the study product, is to be entered in the eCRF, within 5 business days. All Adverse Events/SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant electronic Case Report Form (eCRF) page(s) in English. Once the Adverse Event/SAE has been recorded in the EDC system, the Sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24 hour timeline requirement and Adverse Events should be reported using the back-up paper Non-serious Adverse Event

Report Form (contacts and instructions to be provided in separate documentation). Once the EDC becomes available, the site must enter all Adverse Event/SAE data as reported on the back-up paper Adverse Event/SAE report form on the applicable eCRF pages.

The initial Adverse Event/SAE information reported on the applicable eCRF pages (or back-up Adverse Event/SAE Report Form if applicable) must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Study drug exposure
- 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), if applicable
    - Cause of death
    - Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAE Report Forms)

11.2 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety, effectiveness, or performance of the product but **does 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
- Missing components
- Damage to the product or unit carton

- A mislabeled product (potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product that causes 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 MAH/MAH´s representative(s) within 1 business day. If requested, defective product(s) will be returned to the MAH/MAH´s representative(s) for inspection and analysis according to procedures.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The investigator will comply with the publication policy as described in the Non-interventional Trial Agreement.

The coordinating investigator will be selected before study start, if applicable.

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14. ANNEXES

14.1 List of Stand-Alone Documents

No.	Document Reference No.	Date	Title
1	TBD	Not finalized	Study Organization
2	TBD	Not finalized	Clinical Monitoring Plan
3	TBD	Not finalized	Data Management Plan
4	TBD	Not finalized	Clinical Quality Management Plan

14.2 ENCePP Checklist for Study Protocols

Not applicable as currently no European Centers are involved.

14.3 Additional Information

Not applicable.

14.4 Summary of Changes

PROTOCOL 161406
AMENDMENT 2

Version: 2015 SEP 17

In this section, changes from the previous version of the Protocol, dated 2015 MAR 02, 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. **Title Page – Serious Adverse Event Reporting;**
   Section 11.1.2.3 Safety Reporting

   Description of Change: The description of the SAE reporting process was changed.
   Purpose for Change: To accommodate SAE reporting procedures both for electronic SAE reporting as well as SAE reporting in case electronic CRF is not available.

3. **Section 4 Abstract – Epoch 1 and Epoch 2;**
   Section 4 Abstract – Study Size;
   Section 9.1 Study Design;
   Section 9.5 Study Size;
   Section 9.3.1.1 Medical History, Medications, and Non-Drug Therapies

   Description of Change: Subjects in whom anti-rHuPH20 antibodies ≥160 were measured and documented at any time prior to enrollment will also continue in Epoch 2, regardless of any test results for anti-rHuPH20 antibodies that may be available from Epoch 1.
   Purpose for Change: To collect further data from subjects with antibodies to rHuPH20.

4. **Section 4 Abstract – Population;**
   Section 9.2.3.1 Inclusion Criteria

   Description of Change: The requirement that female subjects of child bearing potential agrees to inform the investigator if she becomes pregnant, or plans to become pregnant during the study was removed.
   Purpose for Change: HyQvia use during pregnancy is not contraindicated in any country worldwide; the statement that HYQVIA should not be used by women who are pregnant or are planning to become pregnant was removed from the Summary of Product Characteristics (SPC) and package insert for EU in 2015, and replaced by a statement that HYQVIA shoud be given with caution to pregnant women and breast-feeding mothers following approval of the CHMP. Refer to the SPC/package insert information for EU for further details.

5. **Section 4 Abstract – Population;**
   Section 9.2.3.2 Exclusion Criteria

   Description of Change: The exclusion criterion "Subject is planning to become pregnant, pregnant or breast-feeding at the time of enrollment." was removed.
   Purpose for Change: HyQvia use during pregnancy is not contraindicated in any country worldwide; the statement that HYQVIA should not be used by women who are pregnant or are planning to become pregnant was removed from the Summary of Product Characteristics (SPC) for the EU in 2015 following approval of the CHMP. Refer to the SPC/package insert information for EU for further details.

6. **Section 5 Amendments and Updates**

   Description of Change: Amendment No. 2 was added.
   Purpose for Change: To reflect the changes introduced with Amendment 2.

7. **Section 7.1 Medicinal Product Safety Profile – B) Immunoglobulin and Hyaluronidase Treatment**

   Description of Change: "Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans…." was changed to "Non-clinical data for recombinant human hyaluronidase or antibodies to recombinant human hyaluronidase reveal no special hazard for humans…."
   Purpose for Change: Additional data have become available and are reflected in the updated version of the SPC/EU package insert information.

8. Section 7.1 Medicinal Product Safety Profile – B) Immunoglobulin and Hyaluronidase Treatment – Specific Populations

Description of Change: A reference to the local package insert/prescribing information for further details was added to the paragraph "For subjects in the USA".
Purpose for Change: To provide additional information on the HYQVIA.

Description of Change: The section "For subjects in the EU" was updated.
Purpose for Change: To reflect modifications to the SPC/EU package insert information.

Description of Change: The following text was deleted: "If a woman prematurely withdraws from the study because of being pregnant [……..] the development of the reproductive system."
Purpose for Change: To remove redundancies (refer to Section 9.2).

9. Section 7.2.5 Baxalta HYQVIA Pregnancy Registry 161301;
Section 9.2 Setting;
Section 11.1.2 Assessment of Adverse Events

Description of Change: The title of study 161301 "Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HYQVIA (Immune Globulin (Human) 10% with rHuPH20)" was changed to "Pregnancy Registry to collect Long-Term Safety Data from Women treated with HYQVIA (Immune Globulin (Human) 10% with rHuPH20)"
Purpose for Change: To reflect a change in the protocol title as per Protocol 161301 – Amendment 1.

10. Section 7.2.5 Baxalta HYQVIA Pregnancy Registry 161301

Description of Change: Modifications throughout the section.
Purpose for Change: To reflect changes made to Protocol 161301 as described in Amendments 1, 2 and 3.

11. Section 9.2 Setting

Description of Change: The text "Patient with PIDD who have been prescribed…." was changed to "Adult patients with PIDD who have been prescribed….".
Purpose for Change: To emphasize that HYQVIA is currently licensed only for adult patients.

Description of Change: The text "No clinical information [….] will apply when approved." was deleted.
Purpose for Change: To remove redundant text. For information on pregnant or breast-feeding women refer to Section 7.1 – Specific populations.

Description of Change: The following text was added: "Pregnant or breast-feeding women may continue in the study at the investigator´s discretion (see Section 7.1. Refer also to the local package insert/prescribing information)."
Purpose for Change: To clarify that pregnant or breast-feeding women may continue in the study at the investigator´s discretion in accdrance with the revised language of the EU package insert.

12. Section 9.2.6 Screening and Follow-up – Figure 1

Description of Change: The text "Subjects with rHuPH20 antibody titers ≥ 160" was changed to "Subjects with rHuPH20 antibody titers ≥ 160 (tested any time in Epoch 1, or documented any time before enrollment"
Purpose for Change: To collect further data from subjects with antibodies to rHuPH20.

13. Section 9.3.1.3 Clinical Laboratory Parameters

Description of Change: The last part of the first sentence "…(rHuPH20 binding and neutralizing antibodies, and characterization of antibodies, if applicable)." was deleted.
Purpose for Change: To remove a redundancy. Assessment of antibodies against rHuPH20 is described in Section 9.3.1.3.1.

14. Section 9.3.1.3.1 rHuPH20 Antibodies

Description of Change: The language was modified to the effect that assessment for binding antibodies will be performed in subjects that agree to the assessment of rHuPH20 antibodies. For subjects with an anti-rHuPH20 antibody titer ≥160, also neutralizing antibodies will be measured. In addition, antibody characteriation will be performed in subjects who test positive ≥ 10,000.
Purpose for Change: To specify the type of assessment for anti-rHuPH20 antibodies to be performed in subjects that agree to testing.

15. Section 9.3.3.1 Health Related Quality Of Life

Description of Change: The second and third paragraph were modified to describe the timepoints when the Treatment Preference Questionnaire may be administered.
Purpose for Change: To clarify the timepoints when the Treatment Preference Questionnaire may be administered.

16. Section 11.1.2 Assessment of Adverse Events

Description of Change: The text in *italics* was added: "Any pregnancy that occurs after administration of the medicinal product, or that occurs after paternal exposure to the medicinal product, will be reported on a Pregnancy Form and followed-up at the *estimated date of delivery and* 1 year post-delivery, if feasible."
Purpose for Change: To reflect a change to the Baxter protocol template standard text.

17. Section 11.1.2.3 Safety Reporting

Description of Change: The section describes the recording procedures and reporting requirements for AEs and SAEs in the study.
Purpose for Change: To reflect a change to the Baxter protocol template standard text.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT

HYQVIA

[Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]

STUDY TITLE

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

PROTOCOL IDENTIFIER: 161406

AMENDMENT 2: 2015 SEP 17

Replaces: Amendment 1: 2015 APR 09

ALL VERSIONS:
Amendment 1: 2015 APR 09
Original: 2015 MAR 02

OTHER PROTOCOL ID(s)

NCT Number: Study to be registered

IND NUMBER: 013840

By signing below, the investigator acknowledges that he/she has read and understands this protocol, 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, Non-interventional Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements. If applicable, he/she will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures and for obtaining written initial and ongoing ethics committee(s)/institutional review board(s) protocol review and approval,

Signature of Principal Investigator Date

Print Name of Principal Investigator

Signature of MAH Representative Date

[redacted], MD, [redacted], Clinical Development