TITLE PAGE – REGISTRY INFORMATION

PROTOCOL TITLE	Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia
PROTOCOL ID #	161301
AMENDMENT	Amendment 3: 22 OCT 2015 Replaces Amendment 2: 09 APR 2015 Amendment 1: 03 FEB 2015 Original: 27 JUN 2013
EU PAS / CLINICAL TRIALS.GOV/ OTHER REGISTER #	ENCePP/SDPP/5798 NCT Number: NCT02556775 IND NUMBER: 013840
MEDICINAL PRODUCT	
Active Ingredient(s)	Human normal immunoglobulin/Alternative treatment
Medicinal Product	HyQvia/ HYQVIA [Immune Globulin Infusion 10% (Human) with rHuPH20] or Human normal immunoglobulin for intravenous or subcutaneous infusion/Alternative treatment
PRODUCT REF. #	EU/1/13/840/001-005 USA: BL 125402
PROCEDURE #	EMEA/H/C/002491 USA: Not Applicable
MARKETING AUTHORISATION HOLDER (MAH)	EU: Baxalta Innovations GmbH, Industriestrasse 67, A-1221 Vienna, Austria USA: Baxalta US Inc., One Baxter Way, Westlake Village, CA 91362
JOINT PASS	No
RESEARCH QUESTION & OBJECTIVES	
Research Question	
The purpose of this registry is to acquire safety data (including assessment of anti-rHuPH20 antibodies), regarding the course and outcome of pregnancy in women ever treated with HyQvia. Development of the fetus/infant at birth and for the first 2 years will also be followed.	
Primary Objective	
To collect and assess clinical safety data regarding the possible effects of HyQvia on the course and outcome of pregnancy, and on the growth and development of the fetus/infant.	
Secondary Objective(s)	
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.	
COUNTRY(-IES) OF STUDY	European Economic Area, North America, and other countries, where the product is licensed, as needed
AUTHOR	[redacted]

MARKETING AUTHORIZATION HOLDER(S)

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

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, OR IF THE SITE IS COORDINATED BY THE MAH'S REPRESENTATIVE, THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE MAH/MAH REPRESENTATIVE TO MEET THE 24 HOUR TIMELINE REQUIREMENT.

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

For information on the assessment and definitions of these events refer to: assessment of adverse events (AEs) in Section 11.1, and definitions of AE in Section 11.2, SAE in Section 11.2.2.

NON-SERIOUS ADVERSE EVENT REPORTING

Any non-serious adverse events (including the associated concomitant medications), all therapies/procedures to treat the AEs, and the outcome of the AEs are to be reported to the MAH/MAH's representative(s) on the appropriate case report forms (CRFs) within 5 business days. If the site is coordinated by the MAH's representative, data will be entered on the Non-Serious Adverse Event Report Form and transmitted to the MAH/MAH's representative (see Non-Serious Adverse Event Report Form for contact information).

If the eCRF is not available for more than 14 business days, then the AE must be reported on the Non-Serious Adverse Event Report Form and transmitted to the MAH/MAH' representative (see Non-Serious Adverse Event Report Form for contact information).

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AFP	alpha-fetoprotein
CHMP	Committee for Medicinal Products for Human Use
B19V	parvovirus B19
CLL	chronic lymphocytic leukemia
CVS	chorionic villi biopsy
CRF	case report form
CRO	contract research organization
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HyQvia/HYQVIA	Immune Globulin Infusion 10% (Human) with rHuPH20
ICF	informed consent form
IG 10%	Immune Globulin 10%
IgG	immunoglobulin G
IGI	Immune Globulin Infusion (Human)
IGIV	immune globulin intravenous (human)
IgM	immunoglobulin M
IRB	institutional review board

Abbreviation	Definition
IV	intravenous(ly)
MAH	marketing authorization holder
MM	multiple myeloma
PASS	Post-Authorization Safety Surveillance
PIDD	primary immunodeficiency disease(s)
PSUR	periodic safety update report
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAER	serious adverse event report
SC	subcutaneous(ly)
SIC	subject identification code
SOC	System Organ Class
SPC	summary of product characteristics
VASBIs	validated acute serious bacterial infections

3. RESPONSIBLE PARTIES

3.1 MAH's Authorized Representative (Signatory)

[redacted]

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 .

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]), as applicable) will be maintained by the MAH/MAH's representative(s) and provided to the investigator (see Annex 14.1).

4. ABSTRACT

Title: Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia

Protocol Amendment 3: 22 OCT 2015

Replaces Protocol Amendment 2: 09 APR 2015
Protocol Amendment 1: 03 FEB 2015
Original Protocol: 27 JUN 2013

Main Author: [redacted], Baxalta.

Rationale and background: This pregnancy registry with regular assessment of anti-rHuPH20 antibodies 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.

Research question and objectives: The purpose of this registry is to acquire safety data (including assessment of anti-rHuPH20 antibodies) regarding the course and outcome of pregnancy in women ever treated with HyQvia. Development of the fetus/infant at birth and for the first 2 years will also be followed.

The primary objective is to collect, and assess, clinical safety data regarding the possible effects of HyQvia on the course and outcome of pregnancy, and on 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.

Study design: 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).

Population: In this registry 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.

Product:

In Europe the product is licensed under the trade name HyQvia, in the USA the trade name is HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase].

Subjects who stop HyQvia treatment will be followed in Study Arm 1 (Alternative Product Arm). The treating physician of the pregnant woman will prescribe a licensed human normal immunoglobulin other than HyQvia or an alternative treatment.

Subjects who continue treatment with HyQvia while pregnant will be assigned to Study Arm 2 (HyQvia arm).

Product information such as dosage and dosage regimen for the medicinal products are described in the respective package insert/Summary of Product Characteristics (SPC).

Duration of Study Period and Subject Participation:

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 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.

Variables: 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 anti-rHuPH20 antibodies, as requested by the CHMP and the FDA. For subjects with an anti-rHuPH20 antibody titer ≥ 10,000, antibody characterization will be performed. Variables assessed include anti-rHuPH20 antibodies (rHuPH20-binding and neutralizing antibodies) of the mother, fetal development characteristics such as fetal organ screening (by ultrasound), data on the pregnancy and delivery/end of pregnancy, neonatal information, infant's growth and development, if available.

Data sources: Source data comprise eg, hospital records, medical records, clinical and office charts, laboratory notes, outcomes reported by subject, recorded data from automated instruments, subject files, records kept at the laboratories and at medico-technical departments involved in the study.

Study size: There is no minimum sample size pre-specified for this registry.

Data analysis: Statistical analyses and data displays will be descriptive. Data from all enrolled subjects will be included in the analyses. Data will be analysed separately according to Study Arm 1 or 2, and in a combined dataset. If the treatment of the pregnant subject is changed in the course of the study, the subject will continue to be followed in the study arm assigned initially, for the remaining observation period.

Milestones:
Registry ready to enroll: EU:2014, USA: 2015
End of data collection: EU: 2021, USA: 2021

5. AMENDMENTS AND UPDATES

Amd. No.	Date	Section of Protocol	Amendment	Reason
1	03 FEB 2015	Throughout the protocol	Refer to Section 14.4 for the Summary of Changes	The original protocol for the European Registry was expanded to a global Registry to fulfill the commitment to the FDA. The FDA required to establish and maintain a pregnancy registry for women ever treated with HyQvia.
2	09 APR 2015	Throughout the protocol	Refer to Section 14.4 for the Summary of Changes	Administrative
3	22 OCT 2015	Throughout the protocol	Refer to Section 14.4 for the Summary of Changes	Language change regarding pregnancy, breast-feeding and fertility in the EU SPC; update of safety reporting; addition of characterization of anti-rHuPH20 antibodies

6. MILESTONES

Milestone	Date/Planned Date
EU: Final protocol submission	05 SEP 2013 (endorsed by PRAC) 19 SEP 2013 (adopted by CHMP)
USA: Final protocol submission	27 FEB 2015
Registration in EU PAS Register	28 FEB 2014
Registration in US Database	21 SEP 2015
Registry ready to enrol	EU: 2014 USA: 2015
End of data collection	EU: 2021 USA: 2021
Study Progress Report	EU: With every PSUR, but at least annually USA: Annual Status Report on Postmarketing studies
Final Report of Study Results	2021

7. RATIONALE AND BACKGROUND

7.1 Medicinal Product Safety Profile

In this registry, women ever treated with HyQvia who become pregnant will be enrolled.

In Europe the product is licensed under the trade name HyQvia, in the USA the trade name is HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase].

HyQvia is a product dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20)[i].

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

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonising 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 IG 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:

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

USA: HYQVIA is an immune globulin with recombinant human hyaluronidase indicated 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.

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

The background of immunoglobulin treatment without/with rHuPH20 in these indications is described below.

During this study the medicinal product is either HyQvia (Study Arm 2) or an alternative product (Study Arm 1), see Section 9.1 Study Design. 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 (e.g.,X-linked agammaglobulinemia, selective IgG subclass deficiency, common variable immunodeficiency, or X-linked hyperimmunoglobulin M syndrome), but also in the group of combined immunodeficiencies (e.g., severe combined immunodeficiency, Wiskott-Aldrich Syndrome) that have defects in both T- and B-cells.[1]

Immunoglobulin treatment to prevent infections is also performed in Secondary Immunodeficiencies, such as 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 in Sweden. The first attempts, in the late 1970s, used intramuscular preparations administered at slow infusion rates, but in later years rapid infusion rates have been used more successfully.[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 body weight 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.

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 hyalunoridase (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 into cynomolgus monkeys in doses up to 2 mg/kg (> 1,000 fold higher than the HyQvia dose in humans) did not lead to adverse reactions during a follow-up of 39 weeks[iv]. Infusion of rHuPH20 improved absorption and bioavailability of intradermally injected IgG in rabbits, pegylated interferon and infliximab in rats, and increased the rate of infusion and comfort of infusions of lactated Ringer's solution in the arms of adult human volunteers 3- to 4-fold.[20] Studies investigating the effects of rHuPH20 on SC infusions of large quantities of IgG

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

in dogs and rabbits have been difficult to interpret due to the rapid absorption of IgG alone in this model. However, at higher doses of rHuPH20, bioavailability seemed to increase. The human SC compartment is much tighter than that of these animals and thus, human studies were required. rHuPH20 can facilitate absorption of small molecules such as insulin and morphine in humans; in phase 1 trials rHuPH20 improved bioavailability of proteins such as infliximab[v] and enabled drug dispension and absorption at the administration site of rituximab and trastuzumab.[21]
In a phase 1/2 clinical study of HyQvia (Study 160602) the average bioavailability of the IgG in 7 subjects was 92%, suggesting a significant improvement compared to SC administration in the absence of rHuPH20.

The immunogenicity of rHuPH20 has been monitored in a number of clinical trials[vi]. No positive skin reactions were observed when rHuPH20 was administered to 100 healthy volunteers in a skin allergy clinical trial.[22] In Study 160603, a total of 13 subjects had at least one plasma sample that tested positive for rHuPH20-binding antibodies (positivity defined as a sample with a titer of $\geq$ 160) following HyQvia treatment. The peak 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.

Antibodies reactive to rHuPH20 have also been identified in the normal population with a prevalence of approximately 5%.[23] 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 to produce antibodies to hyaluronidase. However, antibodies to hyaluronidase did not influence reproduction in mouse, rabbit, sheep, or cynomolgus monkey.

[v] Halozyme Report R05109.

Specific Populations

Pregnancy, Breast Feeding, Fertility

SCIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the 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 foetal development are currently unknown.

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

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 or breastfeeding women.

For subjects in USA: HyQvia should be given to a pregnant or nursing woman only if clearly indicated.

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

This pregnancy registry with regular assessment of anti-rHuPH20 antibodies was a commitment to the Committee for Medicinal Products for Human Use (CHMP) and the Food and Drug Administration (FDA).

7.2 Critical Review of Available Data

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

[vi] Halozyme Report Number 10059.

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) (eg, 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.[24] 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[vii] 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.

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.

[vii] 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.

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 IG 10% obtained in the same study.

Table 1.
Pharmacokinetic Parameters of HyQvia Compared to Intravenous Administration of IG 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 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 (safety follow-up period, Epoch 3).

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, 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 Epoch1; 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 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 request of 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 anti-rHuPH20 antibodies.

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.

7.2.6 HYQVIA Study 161406

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

This planned prospective, uncontrolled, multi-center, open-label, post-HYQVIA marketing authorization surveillance study with assessment of anti-rHuPH20 antibodies was agreed upon with the Food and Drug Administration (FDA) in the course of the HYQVIA Biologic License review and approval process.

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

The primary objective is to collect and assess safety data, in particular the occurrence of long-term changes in incidence and severity of related 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 and health resource use assessments.

It is planned to have FSI in Q4/2015.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The purpose of this registry is to acquire safety data (including assessment of anti-rHuPH20 antibodies), regarding the course and outcome of pregnancy in women ever treated with HyQvia. Development of the fetus/infant at birth and for the first 2 years will also be followed.

8.2 Primary Objective

The primary objective of the study is to collect and assess clinical safety data regarding the possible effects of HyQvia on the course and outcome of pregnancy, and on the growth and development of the fetus/infant.

8.3 Secondary Objectives

8.3.1 Safety

The secondary objective of the study is 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.

9. RESEARCH METHODS

9.1 Study Design

This study is a non-interventional, prospective, uncontrolled, two-arm, open-label, multicenter post-authorization pregnancy registry of women ever treated with HyQvia. The overall study design is illustrated in Figure 1.

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 registry is designed according to the CHMP Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation data [25]; and the U.S. Department of Health and Human Services Guidance for Industry: Establishing Pregnancy Exposure Registries.[26]

Female patients being treated with HyQvia will notify their treating physician (for example their immunologist) immediately of the pregnancy.

Once Baxalta is notified, details will be provided regarding the registry and how to enroll.

Study Arm 1 (Alternative Product Arm): The subject stops HyQvia treatment (if the subject is still treated) and a licensed human normal immunoglobulin other than HyQvia for IV or SC infusion or an alternative treatment will be administered, as determined by the physician. Subjects in countries, where HyQvia treatment during pregnancy is not indicated, should be enrolled in Study Arm 1. The date and gestational age will be collected for any subject in the Alternative Product Arm who restarts HyQvia. Details about the administration of HyQvia should be recorded on the HyQvia treatment CRF.

Study Arm 2 (HyQvia Arm): Subject continues to receive HyQvia, according to her treatment regimen.

The data for the registry will be derived from several medical specialists (such as immunologist, gynecologist, obstetrician, pediatrician). The specialist responsible for the pregnant woman´s HyQvia treatment and/or the treatment of her underlying disease will be responsible for data collection and CRF completion.

Data will be collected according to the standard of care in the region. After enrollment in the registry by signing the appropriate ICF, the pregnant subject will return to her physicians as she normally would as part of routine medical practice. There will be no required predefined visits, medical tests, laboratory tests and procedures during the course of the registry, except for the assessment of antibodies to rHuPH20. Approximately every 3 months, the pregnant subject will be invited to have a blood sample taken for the measurement of anti-rHuPH20 antibodies. For subjects with an anti-rHuPH20 antibody titer ≥ 10,000, antibody characterization will be performed. Data of the occurrence of AEs, complications of the pregnancy, and fetal growth and development will be recorded on the CRF, if data is available.

After delivery/end of pregnancy data on the outcome of the pregnancy will be collected, if available.

The infant will be followed up for two years to collect safety data. Approximately every 6 ±2 months (as part of routine medical practice) the infant and the legal representative(s) will be invited to return to the pediatrician/lead physician to record assessments according to Table 3 and Table 5.

The pediatrician/lead physician will record data of the development and growth of the infant on the appropriate CRFs, if data is available.

9.1.1 Primary Endpoint

The primary endpoint is the incidence of all SAEs (expectant mother and infant).

9.1.2 Secondary Endpoints

9.1.2.1 Safety

1. Incidence of non-serious AEs, related and not-related to HyQvia/Human normal immunoglobulin or alternative treatment (expectant mother and infant)
2. Incidence of local/immunologic AEs including skin changes (such as: local erythema, local pruritus, induration, nodules) (expectant mother)
3. Development of anti-rHuPH20 antibodies (rHuPH20 binding and neutralizing antibodies) (expectant mother)
4. Complications of pregnancy
5. Fetal growth/development
6. Outcome of pregnancy

7. Neonatal assessment
8. Status of the infant at birth
9. Growth measurement and charts for the infant, if available
10. Development milestones determined by standard test methods, for each region, if available

9.2 Setting

In order to analyse all data which may become available, no exclusion criteria have been defined for this 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 anti-rHuPH20 antibodies, as requested by the CHMP and the FDA.

Should a physician retrospectively (ie, at a more advanced stage of the pregnancy) become aware of a patient who could have been included in this registry, then the physician should include this patient and the patient's data should be entered retrospectively (as available), if the patient provides informed consent.

9.2.1 Medicinal Product(s)

As soon as the patient becomes aware of the pregnancy, she should inform the treating physician. According to her treatment (see Section 9.1), 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.

Product information such as dosage, dosage regimen, administration, packaging, labeling, and storage for the medicinal products are described in the respective package insert/SPC.

9.2.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 6 years from study initiation (Registry ready to enroll) to study completion (ie, end of data collection). The enrollment period is expected to be 3 years.

The participation period for the pregnant woman is from enrollment to 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.

9.2.3 Subject Selection Criteria

9.2.3.1 Inclusion Criteria

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

- For the expectant mother only: Subject became pregnant during or after treatment with HyQvia
- Subject/subject's legally authorized representative is willing to sign ICF

9.2.3.2 Exclusion Criteria

There are no applicable Exclusion Criteria for this registry.

9.2.4 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form and, if applicable, the assent form) 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, 161301) 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 161301-020003. All study documents (eg, CRFs, clinical documentation, sample containers, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy. The expectant mother and the infant will be enrolled individually, each with a unique SIC.

Subject Identification Codes identifying matching mother-infant pairs will be provided in the final Clinical Study Report. The infant's CRF includes a field titled 'Mother's Subject ID'. There will be a manual review of the CRF to match the mother-infant pair.

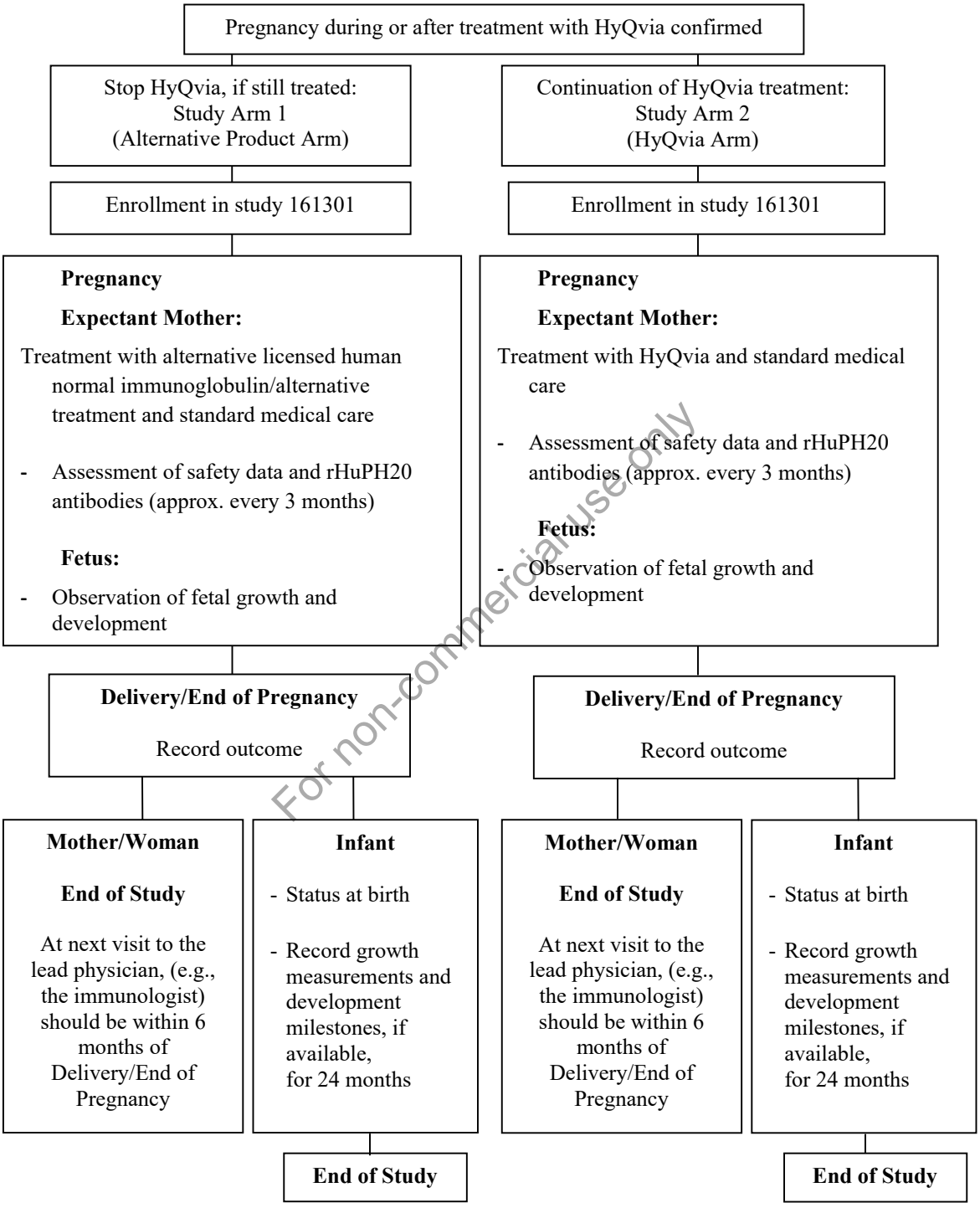
9.2.6 Screening and Study Visits

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.

For subjects in USA: The site should also maintain patient identifier information (such as name of the patient, name of person reporting the pregnancy, date of initial contact with the reporter about the registry and dates of follow-up contacts, telephone number of the reporter), as recommended by the FDA guidance.[26]

The overall study design is illustrated in Figure 1. Details on the procedures and assessments to be performed at each study visit, including screening, can be found in Table 2 to Table 5.

Figure 1.
Study Design for Baxalta Clinical Study 161301



Note: Procedures and assessments are performed according to the routine standard at the site, and are documented as available (with the exception of Informed Consent, Eligibility and anti-rHuPH20 antibodies assessments).

Table 2.
Schedule of Study Procedures and Assessments for the Expectant Mother

Procedures/ Assessments	Screening Visit	Interval Study Visits		Study Completion/ Termination Visit[c]
		Pregnancy Approx. every 3 months	Delivery/ End of Pregnancy	
Informed Consent [a]	X			
Eligibility Criteria	X			
Medical History/ Interval Medical History	X	X	X	X
Medications	X	X	X	X
Non-drug Therapies	X	X	X	X
Physical Exam	X	X	X	X
Vital Signs	X	X	X	X
HyQvia Treatment Regimen/ Administration[d], if applicable	X	X	X	X
Adverse Events		X	X	X
Neonatal/fetal information	X	X	X	
Ultrasound of fetus	X	X		
Laboratories [b]	X	X	X	X

[a] Occurs at enrollment (prior to any study-specific procedure).

[b] Laboratory results, if available, see Table 4.

[c] Study Completion Visit to take place after delivery/end of pregnancy at the next visit to lead physician, (e.g.,the immunologist) (should be within 6 months of delivery/end of Pregnancy). Termination visit applies to cases of withdrawal or discontinuation.

[d] The subject's treatment regimen will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Changes to the treatment regimen, including the reason for the change, will also be collected. If treatment is administered at the site and a home treatment record is available then infusion administration details such as: maximum infusion rate, infusion volume, number and location of infusion sites, date of infusion and infusion start and stop time, and batch number should be collected. Product administrations may or may not coincide with site visits.

Note: Procedures and assessments are performed according to the routine standard at the site, and are documented as available (with the exception of Informed Consent)

Table 3.
Schedule of Study Procedures and Assessments for the Infant

Procedures/ Assessments	Interval Study Visits		Study Completion/ Termination Visit[c]
	Birth	Approx. Month 6, 12, 18 (each visit ± 2 months)	
Informed Consent [a]	X		
Status at Birth	X		
Interval Medical History		X	X
Medications	X	X	X
Non-drug Therapies	X	X	X
Physical Exam	X	X	X
Vital Signs	X	X	X
Adverse Events	X	X	X
Laboratories [b]	X	X	X
Assessment of growth and Development		X	X

[a] Occurs at enrollment (prior to any study-specific procedure).
[b] Laboratory results, if available, see Table 5
[c] Termination visit applies to cases of withdrawal or discontinuation.

Table 4.
Clinical Laboratory Assessments for the Expectant Mother, if available

Assessments	Screening Visit	Interval Study Visits		Study Completion/ Termination Visit [b]
		Pregnancy Approx. every 3 months	Delivery/ End of Pregnancy	
Hematology	X	X	X	X
Clinical Chemistry	X	X	X	X
Urinalysis	X	X	X	X
Anti-rHuPH20 antibodies [c]	X	X		X
Antenatal diagnostic procedure [a]	X	X		

[a] Procedures such as serology tests (eg, rubella, toxoplasmosis), serum markers (AFP, other), CVS, Amniocentesis
[b] Study Completion Visit to take place after delivery/end of pregnancy at the next visit to the lead physician, (e.g., the immunologist) (should be within 6 months of delivery/end of Pregnancy). Termination visit applies to cases of withdrawal or discontinuation.
[C] For subjects with binding anti-rHuPH20 antibodies of a titer of ≥ 160, assessments for neutralizing antibodies will also be done. For subjects with an anti-rHuPH20 antibody titer ≥10,000, antibody characterization will be performed in addition (see Section 9.3.4.1).

Table 5. Clinical Laboratory Assessments for the Infant, if available			
Assessments	**Interval Study Visits**		**Study Completion/ Termination Visit[a]**
	Birth	**Approx Month 6, 12, 18** (each visit ±2 months)	
Hematology	X	X	X
Clinical Chemistry	X	X	X
Urinalysis	X	X	X

[a] Termination visit applies to cases of withdrawal or discontinuation.

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).

9.2.8 Study Stopping Rules

Stopping rules will not be established for this study as the pregnant subjects will be treated with a licensed human normal immunoglobulin or an alternative treatment, according to the routine standard at the study site, for the duration of the study. The study will be terminated by the sponsor if no subjects are enrolled during the predefined enrollment period.

9.3 Variables

9.3.1 Safety Variables

9.3.1.1 Variables for Pregnancy, Pregnancy Outcome, and Infant Follow-up

All data with the exception of anti-rHuPH20 antibodies, will be collected as available from routine clinical practice.

For subjects in USA: The source of the data (such as: obstetrician, pediatrician, pregnant woman/mother) should be captured, and the date when the data are received for the registry, if available, as recommended by the FDA guidance.[26]

1. During pregnancy the outcome of the ultrasound examination (ultrasound reports) of the fetus should be recorded to assess the fetal growth and development. The result should be assessed (for example normal or abnormal) and a short description of the status should be added.
2. Pregnancy outcome. After delivery/end of pregnancy the following neonatal/fetal information should be recorded initially:
    - Data on delivery including mode of delivery, labour/delivery complications (eg, fetal distress, amniotic fluid abnormal) and abnormal placenta
    - Outcome of pregnancy and date [induced or spontaneous termination, fetal death (ectopic, miscarriage, molar pregnancy), live birth normal/abnormal, other]
    - Date of birth
    - Gestational age at birth, Maturity assessment/Dysmaturity
    - Gender of neonate
    - Results of neonatal assessment including:
        - Weight, length and head circumference at birth
        - Conditions at birth including Apgar scores at 1 and 5 minutes, need for resuscitation, admission in intensive care unit
        - Malformation/anomalies diagnosed at birth
    - Neonatal illness, hospitalization, drug therapies
3. Infant follow-up. At interval study visits, infant follow-up information should be collected for the following points:
    - Malformation/anomalies diagnosed since initial report
    - Growth measurement and charts
    - Developmental assessment such as developmental milestones
    - Infant illnesses, hospitalizations, drug therapies, breastfeeding
4. In case of elective termination, spontaneous abortion and late fetal death the following fetal data should be collected:
    - Reason for termination
    - Gestational age at termination
    - Results of physical examination (gender, external anomalies) and pathology

9.3.2 Medical History, Interval Medical History, Medications, and Non-Drug Therapies

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 11.2.4) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological/psychiatric; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary/obstetrical. Furthermore, data on the obstetrical history of the mother should be recorded, including number of previous pregnancies and outcome, previous maternal pregnancy complications, previous fetal/neonatal abnormalities, and, type and history of subfertility.

For the maternal medical history, risk factors for adverse pregnancy outcomes (e.g. hypertension, diabetes, seizure disorder, thyroid disorder) should be evaluated. Also the exposure to other teratogens (e.g. infections, medications, environmental factors) should be recorded, if available.

Data collected on the family history of the mother should include the history of congenital abnormality, psychomotor retardation in the family and the consanguinity between parents. For the current pregnancy, the following data should be collected:

- Date of last menstrual period (LMP)
- Estimated date of delivery
- Weight gain during pregnancy
- Number of fetuses
- Treatment for infertility (specify)
- Recreational drug use, eg, tobacco, alcohol, illicit drugs (specify amount and if and when stopped during pregnancy)
- Complications during pregnancy and date (including any adverse drug reactions)
- Disease course(s) during pregnancy and any complications

The following data for the treatment with HyQvia should be collected on the HyQvia CRF: Indication for which HyQvia was administered, start date of treatment, regimen, treatment interval, date and dose of the last infusion for Study Arm 1 and for ongoing infusions in Study Arm 2.

All medications taken and non-drug therapies received from 6 months before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs. Furthermore, for subjects in Study Arm 1 (Alternative Product Arm) the data of the licensed human normal immunoglobulin/alternative treatment prescribed after stop of HyQvia will be collected on these CRFs.

9.3.3 Physical Examinations

At screening and subsequent study visits (as described in Table 2 and 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, 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 11.2.7), 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.

9.3.4 Clinical Laboratory Parameters

The protocol does not mandate any laboratory testing. However the pregnant subject will be invited to provide blood samples for the assessment of anti-rHuPH20 antibodies , (see Section 9.3.4.1 and Table 4), based on the request of the CHMP and the FDA.

Assessment of hematology, clinical chemistry, urinalysis and antenatal parameters will be done at local laboratories, according to standard of care of the study site or at the discretion of the investigator.

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 of, or related to, a previously recorded AE; is due to a preexisting disease (described in Section 11.2.7); or was 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.

9.3.4.1 rHuPH20 antibodies

Anti-rHuPH20 antibodies should be collected as indicated in Table 4. 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 anti-rHuPH20 antibodies at a titer of ≥ 10,000. Characterization will include neutralizing antibodies and antibodies cross reacting to Hyal 1, 2 and 4.

Testing will be done in a central laboratory selected by the MAH/MAH´s representative(s). Results for anti-rHuPH20 antibodies 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.

9.3.4.2 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 treating physician, will be collected as indicated in Table 4 and Table 5.

Data collected from the hematology panel (if available) 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.

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

9.3.4.3 Urinalysis

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

9.3.4.4 Antenatal Diagnostics

For antenatal diagnostic, data on the following tests and procedures should be collected (if available): Results of serology tests (eg, rubella, toxoplasmosis), serum markers (AFP, other), Chorionic villi biopsy (CVS) and Amniocentesis, fetal ultrasound or other imaging (see also Section 9.3.1.1).

9.3.4.5 Biobanking

Blood samples for anti-rHuPH20 antibodies that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test or an AE). Samples will be stored in a coded form for a maximum of 2 years after the final study report has been completed and, subsequently, will be destroyed.

9.3.5 Vital Signs

Vital signs of the subject (expectant mother and infant) will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), sitting (for the expectant mother) systolic and diastolic blood pressure (mmHg), height/length (in or cm) and weight (lb or kg). The values 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.

9.3.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when she/he 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, adverse event (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, progressive disease, non-compliance with protocol violation(s), recovery), study terminated by MAH, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

The reason for discontinuation will be recorded on the CRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical 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 take place under the direction of the investigator and will be reported to the MAH/MAH's representative(s). Details of the outcome may be reported to the appropriate regulatory authorities by the responsible party.

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, evaluation checklists, outcomes reported by subjects, recorded data from automated instruments, subject files, and records kept at the laboratories, and at medico-technical departments involved in the study.

For additional information on study documentation and CRFs refer to Section 9.6.1.

9.5 Study Size

There is no pre-specified minimum sample size for this registry. All women ever treated with HyQvia who become pregnant will be requested to participate in the registry by the MAH. Every effort will be made to identify and include subjects in this registry. Furthermore physicians treating patients with HyQvia will be informed of the possible enrollment in this registry. The purpose of the registry and the possibility of participation is included in the package insert/Summary of Product Characteristics of the respective country.

9.6 Data Management

9.6.1 Data Collection Methods

The investigator will maintain complete and accurate 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), 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.

Only authorized study site personnel will record or change data on the CRFs. All data with the exception of adverse events (see Serious and Non-serious Adverse Event Reporting, Page 2) should preferably be entered on the CRFs during the study visit or within 10 business days. Changes to a CRF will require documentation of the reason for each change. 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

Electronic Data Capture/Collection (EDC) with the standard data management software of the Contract Research Organization (CRO) selected is used.

The software for the data analysis is the standard data analysis software of the CRO selected.

9.7 Data Analysis

9.7.1 Datasets and Analysis Cohorts

Due to the small number of subjects expected in this study, all subjects will be analyzed according to the Study Arm 1 and 2, and together. If the treatment of the subject is changed in the course of the study, the subject will continue to be followed in the study arm assigned initially, for the remaining observation period.

9.7.2 Handling of Missing, Unused, and Spurious Data

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If any data is considered spurious, eg, 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 descriptive. Data from all enrolled subjects will be included in the analyses. Retrospective reports and prospective reports are clearly labeled. It will be considered to analyze them separately. Retrospective data should be recorded on the Medical History CRF. Details about the analysis of retrospective data will be provided in the Statistical Analysis Plan.

All SAEs, non-serious AEs and other types of safety data will be categorized according to MedDRA system organ class (SOC) and preferred term, as far as possible. Concomitant medications and non-drug therapies will be recorded and tabulated. Tables will be prepared to list for each SAE, non-serious AE and other type of safety data, the number of events/data, and the number of subjects who experienced one or more events. Outcome measures regarding pregnancy loss, stillbirth, and congenital abnormalities, will be compared to published data for the region and, if known, for the specific patient population. Growth and development of the infant will be compared to growth parameters for the specific region as appropriate, if available, or else to standard published charts.

9.7.3.1 Primary Endpoint

For the primary endpoint (incidence of all SAEs, expectant mother and infant) a point estimate and 95% confidence interval (by the Wilson score method) for the proportion of subjects with one or more SAE will be provided. In addition, the SAEs will be listed.

No statistical hypotheses will be tested.

9.7.3.2 Secondary Endpoints

Descriptive methods, mainly frequency tables, will be used for the secondary safety endpoints (see Section 9.1.2).

9.7.4 Planned Interim Analysis of the Study

Regular study progress information will be provided in Europe with each Periodic Safety Update Report (PSUR), but at least annually. In the USA, this information will be made available with the annual status report.

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 Registry/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 Registry/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 and/or its representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Registry/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/MAH's representative(s) 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 Registry/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 Registry/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 Registry/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

In the EU, HyQvia should only be given with caution to pregnant women. In the USA, HyQvia should be given to a pregnant woman only if clearly indicated. The number of pregnancies occurring is expected to be low. Therefore the registry could be terminated with a small sample size and limited data. Also, as an observational study, there is no means to control the amount of data that are entered by the lead physician or other physicians.

9.10 Other Aspects

This paragraph is not applicable, as all aspects of the research method are covered by 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.[27]

10.2 Subject Privacy

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

10.3 Institutional Review Board/Ethics Committee(s) 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 Institutional Review Board (IRB)/EC and applicable regulatory authorities. The IRB/EC's composition, or a statement that the IRB/EC's composition meets applicable regulatory criteria, will be documented. The study will commence only upon the MAH's/MAH's representative(s)'s receipt of approval/favorable opinion from the IRB/EC and, if required, upon the MAH's/MAH's representative(s)'s notification of applicable regulatory authority(ies) approval, as described in the Registry/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 IRB/EC and relevant regulatory authorities, where applicable. The protocol amendment will only be implemented upon the MAH's/MAH's representative(s)'s receipt of approval and, if required, upon the MAH's/MAH's representative(s)'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 IRB/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 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 11.2).

If a pregnant woman experiences an AE between confirmation of pregnancy and enrollment, or an infant experiences an AE between birth and enrollment, the investigator will enter the data on the AE/SAE form in the eCRF. These AEs will be treated as study-solicited events.

Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 11.2.2,
- Severity as defined in Section 11.2.4
- Causal relationship to medicinal product exposure as defined in Section 11.2.5

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. 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/SPC (including overdosing (by >20%), underdosing, 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/SPC), 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.

If an informed consent has also been signed for the child, then AEs for the child will also be assessed and captured as described in Section 11, from birth until study completion/discontinuation for the child.

11.2 Definitions

11.2.1 Adverse Events

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.

11.2.2 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 (eg, 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

- Any pregnancy complication or pregnancy termination by therapeutic, elective or spontaneous abortion shall be considered an SAE.

11.2.3 Non-Serious Adverse Event

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

11.2.4 Severity

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

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

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

11.2.5 Causality

Causality is a determination of whether there is a reasonable possibility that the medicinal product (HyQvia or Human normal immunoglobulin or alternative treatment) 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 medicinal 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:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the medicinal product as evidenced by measurement of the medicinal 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.

11.2.6 Safety Reporting

Adverse Events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Assessments (see Table 2) 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.

If the site is coordinated by the MAH's representative, SAEs must be reported on the paper SAE report form and transmitted to the MAH/MAH's representative immediately (see SAE report form for contact information). Any AE will be reported on the Non-Serious AE report form and transmitted to the MAH's representative for entry in the EDC system within 5 business days (see Non-Serious Adverse Event Report Form for contact information).

All Adverse Events/SAEs must be reported via the EDC system by completing the relevant 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. If the eCRF is not available for more than 14 business days, then AEs 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/MAH's representative 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)

11.2.7 Preexisting Diseases

Preexisting diseases that are present before entry into the study are described in the medical history (except study-solicited events, which should be recorded as AEs/SAEs, see Section 11.1).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.

11.2.8 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/SPC). “Unexpected” also refers to the AEs that are mentioned in the package insert/SPC as occurring with a class of drug or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular medicinal product under investigation.

11.3 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 CHMP requested a preliminary study report to be performed with each PSUR. The FDA requires an annual status report. The final report is estimated for 2021.

The final data will be in the publicly available database of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), details see page 1. The final data will also be communicated directly to the subjects by mail where required as per local regulations.

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

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14. ANNEXES

14.1 List of Stand-Alone Documents

No.	Document Reference No.	Date	Title
1	Version 1	27 JAN 2015	Data Management Plan
2	Version 1	29 JAN 2015	Recruitment Strategy Plan
3	Version 1	04 MAR 2015	Clinical Monitoring Plan
4	Version 1	22 MAR 2015	Communication Plan
5	Version 1	23 MAR 2015	Clinical Quality Management Plan
6	Version 1	12 AUG 2015	Safety Management Plan
7	Version 2	24 SEP 2015	Laboratory Specifications Document
8	NA	28 SEP 2015	Study Organization
9	NA	Not yet finalized	Statistical Analysis Plan

14.2 ENCePP Checklist for Study Protocols

Refer to the completed ENCePP Checklist.

14.3 Additional Information

Not applicable.

14.4 Summary of Changes

PROTOCOL 161301

AMENDMENT 3 - 22 OCT 2015

Replaces: Amendment 2 version 09 APR 2015

In this section, changes from the previous version of the Protocol, dated 09 APR 2015, 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, SAE and AE reporting, Section 11.2.6 Safety Reporting**
   Description of Change: The description of the SAE reporting process was changed. AE reporting in case eCRF is not available is described.
   Purpose for Change: To accommodate SAE/AE reporting procedures both for electronic SAE/AE reporting as well as SAE/AE reporting in case eCRF is not available.

3. **Section 4 Abstract, Section 7.1 Medicinal Product Safety Profile, Section 9.1 Study Design, 9.2 Setting, 9.9 Limitations of the Research Method**
   Description of Change: Text adapted according the revised EU SPC
   Purpose for Change: Additional data have become available and are reflected in the updated version of the SPC/EU package insert information. Language regarding pregnancy, breast-feeding and fertility was changed.

4. **Section 4, Section 9.1 Study Design, Section 9.3.4 Clinical Laboratory Parameters**
   Description of Change: The language was modified regarding measurement of binding and neutralizing rHuPH20 antibodies: For subjects with an anti-rHuPH20 antibody titer ≥ 160, also neutralizing antibodies will be measured. In addition, antibody characterization 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.

INVESTIGATOR ACKNOWLEDGEMENT

Human Normal Immunoglobulin

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

PROTOCOL IDENTIFIER: 161301

AMENDMENT 3: 22 OCT 2015

Replaces
AMENDMENT 2: 09 APR 2015
AMENDMENT 1: 03 FEB 2015
Original: 2013 JUN 27

OTHER PROTOCOL ID(s)

NCT Number: NCT02556775
EU PAS: ENCePP/SDPP/5798
IND/IDE NUMBER: 013840

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

Signature of Principal Investigator Date

Print Name of Principal Investigator

Signature of MAH Representative Date
Barbara Valenta-Singer, MD
Vice President, Clinical Development