TITLE PAGE - PASS INFORMATION

PROTOCOL TITLE	Non-Interventional Post-Authorization Safety Study on the Long-Term Safety of HyQvia in Subjects treated with HyQvia
PROTOCOL ID #	161302
ORIGINAL	26 July 2013
EU PAS REGISTER #	Study to be registered
MEDICINAL PRODUCT	
Active Ingredient(s)	Human normal immunoglobulin
Medicinal Product	Immune Globulin Infusion (Human), 10% with rHuPH20 (HyQvia)
PRODUCT REF. #	EU/1/13/840/001-005
PROCEDURE #	EMEA/H/C/002491
MARKETING AUTHORISATION HOLDER (MAH)	Baxter Innovations GmbH, Industriestrasse 67, A-1221 Vienna, Austria
JOINT PASS	No
RESEARCH QUESTION & OBJECTIVES	
Research Question	
The purpose of the proposed study is to acquire additional long-term data (including assessment of anti-rHuPH20 antibodies) on safety of HyQvia and to assess the prescribed treatment regimens and product administration of HyQvia in routine clinical practice.	
Primary Objective	
Long-term safety of HyQvia treatment in subjects receiving treatment with HyQvia	
Secondary Objective(s)	
Treatment regimen, anti-rHuPH20 antibodies and, as available, other laboratory safety assessments, total IgG, further safety assessments, product administration, and health-related quality of life and health resource use assessments.	
COUNTRY(-IES) OF STUDY	European Economic Area (EEA)
AUTHOR	[redacted], [redacted]

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MARKETING AUTHORIZATION HOLDER(S)

MAH	Baxter Innovations GmbH, Industriestrasse 67, A-1221 Vienna, Austria
MAH CONTACT PERSON	[redacted], MD [redacted] Global Clinical Development Baxter Healthcare Corporation

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 SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE RESPONSIBLE PARTY WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

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 AEs in Section 11.1, and definitions of AE in Section 11.2, SAE in Section 11.2.2.

NON-SERIOUS ADVERSE EVENT REPORTING

Non-serious AEs should be entered into the CRF within 5 days (see Section 9.6.1).

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1. TABLE OF CONTENTS

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Tables

Figures

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BW	body weight
CHMP	Committee for Medicinal Products for Human Use
CLL	chronic lymphocytic leukemia
CRF	case report form
EEA	European Economic Area
EC	ethics committee
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EM(E)A	European Medicines Agency
FSI	First Subject In
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	Health-related quality of life
HRU	Health resource use
HyQvia	Immune Globulin (Human) 10% with rHuPH20
IG 10%	Immune Globulin 10%
IgG	immunoglobulin G
IGIV	immune globulin intravenous (human)
IgM	immunoglobulin M
IUIS	International Union of Immunological Societies
IV	intravenous(ly)
LSO	Last Subject Out
MAH	Marketing authorization holder
MM	multiple myeloma
PASS	Post-authorization safety study
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

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3. RESPONSIBLE PARTIES

3.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted] Global Clinical Development
Baxter Healthcare Corporation

3.2 Investigator(s)

The name and contact information of the Investigators involved with the study will be maintained and provided by the responsible party, see Annex 14.1

4. ABSTRACT

Title: Non-Interventional Post-Authorization Safety Study on the Long-Term Safety of HyQvia in Subjects treated with HyQvia
Original Protocol
Protocol date: 2013JUL26
Main author: [redacted], [redacted]

Rationale and background: This PASS with regular assessment of antibodies against rHuPH20 was a request of the Committee for Medicinal Products for Human Use (CHMP) in the course of the HyQvia Marketing Authorization Procedure. Further data shall be collected to evaluate long-term local and systemic effects of HyQvia in subjects treated with HyQvia

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

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

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

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Study design: This is a non-interventional, prospective, uncontrolled, multi-center, open-label, post-authorization safety study in the European Economic Area (EEA).

Population: Adult patients (≥ 18 years) who have been prescribed treatment with HyQvia will be enrolled in the EEA. Subjects will be treated with HyQvia, a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20). Treatment regimens will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care will be performed as is standard for the site and for the subject´s healthcare. In addition, however, the subject will be requested to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but no more often than 4 times a year, for the measurement of antibodies against rHuPH20, as requested by the CHMP.

Duration of Study Period and Subject Participation: 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. 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.

Subject Selection Criteria:

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

- Subject requires immunoglobulin treatment
- Subject is ≥ 18 years old at the time of screening
- Subject has been prescribed treatment with HyQvia
- Subject agrees to inform the investigator if she becomes pregnant, or plans to become pregnant during the course of the study
- Subject/legal representative has reviewed, signed and dated informed consent

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

- Subject has known hypersensitivity to any of the components of the medicinal product
- Subject has participated in an interventional clinical study involving a medicinal product or device within 30 days prior to enrollment, or is scheduled to participate in an interventional clinical study involving a medicinal product or device during the course of this study.
- Subject is a family member or employee of the investigator.
- Subject is pregnant or breastfeeding at the time of enrollment.

Variables: Antibodies against rHuPH20 (rHuPH20-reactive binding and neutralizing antibodies), laboratory assessments such as hematology, clinical chemistry, urinalysis, seroconversion to HBV, HCV and HIV, total IgG, pregnancy (if applicable), further safety data (e.g., AEs and SAEs), treatment regimen/product administration details, and health related quality of life and health resource use.

Data sources: Source data will comprise hospital records, medical records, clinical and office charts, questionnaires, and home treatment records maintained by the patient (if any).

Study size: It is anticipated that approximately 80 to 120 subjects will be eligible for enrollment in this study.

Data analysis: Statistical analyses and data displays will be mainly descriptive. If groups of sufficient sample size (such as: age groups, PIDD types) are available, confidence intervals may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class (SOC) and preferred term. Concomitant medications and non-drug therapies will be recorded and tabulated. Tables will be prepared to list for each SAE and non-serious AE the number of events and the number of subjects who experienced one or more events.

Milestones:

Initiation (FSI): Q4 2013/ Q1 2014
Enrollment: Approx. 3 years
Completion (LSO): Q4 2019 / Q1 2020
Duration: Approximately 5-7 years

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5. AMENDMENTS AND UPDATES

Amd. No.	Date	Section of Protocol	Amendment	Reason
			None	

6. MILESTONES

Milestone	Planned Date
Start of data collection (first subject in [FSI])	Q4 2013/ Q1 2014
End of data collection (last subject out [LSO])	Q4 2019 / Q1 2020
Study Progress Reports	With every PSUR
Interim Reports	The first interim analysis is planned to be done after 50 subjects have been enrolled. Further interim analyses will be performed approximately every two years after the first. The last interim analysis will be performed not later than approx. 6 months before LSO.
Registration in EU PAS Register	To be registered
Final Report of Study Results	2020

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7. RATIONALE AND BACKGROUND

7.1 Medicinal Product Safety Profile

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 opsonizing and neutralizing antibodies against infectious agents.

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

rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan. Hyaluronan is a polysaccharide found in the intercellular ground substance of connective tissue and of certain specialized tissues. It is degraded by naturally occurring hyaluronidase and has a very fast turnover in subcutaneous tissue. As a permeation enhancer, rHuPH20 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%.

Approved therapeutic indications include:

- Replacement therapy in adults (≥ 18 years) in primary immunodeficiency syndromes such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia
  - common variable immunodeficiency

[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.

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  - severe combined immunodeficiency
  - IgG subclass deficiencies with recurrent infections
- Replacement therapy in adults (≥ 18 years) in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections

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

A) Immunoglobulin Treatment

Defective antibody formation with or without decreased levels of serum immunoglobulins is the most common abnormality in the majority of PIDD and 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 such as X-linked agammaglobulinemia, selective IgG subclass deficiency, common variable immunodeficiency, or X-linked hyperimmunoglobulin M syndrome, but also in the group of combined immunodeficiencies, such as severe combined immunodeficiency or Wiskott Aldrich Syndrome that have defects in both T- and B-cells.[1]

Individuals with these diseases require replacement therapy with immunoglobulin products to prevent or reduce the severity of infections. Initially, immunoglobulin replacement therapy was given by the intramuscular route. But starting in 1981 in the US, the overwhelming majority of patients have been treated by the intravenous (IV) route, though 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; however, in December 2005, the first SC preparation was licensed by ZLB-Behring.[2;3]

Immunoglobulin treatment to prevent infections is also performed in Secondary Immunodeficiencies, such as CLL or multiple myeloma (MM). CLL is the most frequent form of leukemia in Western countries. It is characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen[4]. MM is a plasma-cell neoplasm that is characterized by skeletal destruction, renal failure, anemia, hypercalcemia but also recurrent infections.[5]

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Infections represent a major cause of morbidity and mortality in patients with CLL. The pathogenesis of infection in these patients is multifactorial, including inherent immune defects related to the primary disease process, such as hypogammaglobulinemia [6] but also T cell dysfunction, granulocytopenia, poor phagocytosis and defective complement activity could play a role in the susceptibility to infections[7]. In previous decades, the infections seen in CLL patients were mainly of bacterial origin and similar to that seen in patients with primary immunodeficiency, particularly with common variable immunodeficiency. Less frequently and mainly in the later stages of disease, viral, mycobacterial or fungal infections were observed[7]. An association of recurrent infections and low levels of total immunoglobulins, but also, although weak, of specific anti bacterial antibodies has been observed [7].

Intravenous immunoglobulin (IGIV) has been shown to be useful for the prophylactic therapy in patients who have secondary hypogammaglobulinemia due to an underlying low-grade B-cell tumor [8]. Further, the Cooperative Group for the Study of Immunoglobulin in CLL, performed a randomized, double-blind study for the prevention of infections by the use of IGIV in CLL patients at increased risk of bacterial infection.[9] The study subjects received IGIV (Gammagard, Baxter; 400 mg per kilogram of body weight) or a placebo every three weeks for one year. The patients receiving immunoglobulin had significantly fewer bacterial infections during the study period than those receiving placebo (23 vs. 42; P = 0.01). This reduction was most striking in the patients who completed a full year of treatment (14 vs. 36; P = 0.001). The period from study entry to the first serious bacterial infection was significantly longer in the patients receiving immunoglobulin (P = 0.026). There was no significant difference between the two groups in the incidence of nonbacterial infection. Immunoglobulin therapy was tolerated well. No serious adverse reactions occurred and the incidence of minor reactions was low.

For myeloma and CLL, a systematic review and meta-analysis of randomized-controlled trials comparing prophylaxis with polyvalent IGIV versus control had been performed.[10] The primary outcomes were all-cause mortality and major infections. Nine trials, assessing patients with CLL and MM, were included. No survival benefit could be demonstrated, RR 1.36 (95% CI 0.58-3.19, two trials), but there was a significant decrease in the occurrence of major infections, RR 0.45 (95% CI 0.27-0.75, three trials) and a significant reduction in clinically documented infections, RR 0.49 (95% CI 0.39-0.61, three trials).

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SC administration of immunoglobulin preparations for PIDD patients has been accepted in many countries worldwide and is the predominant mode in the Scandinavian countries, particularly Sweden. The first attempts in the late 1970s used intramuscular preparations administered using slow infusion rates, but in recent years rapid infusion rates have been used more successfully.[11;12;13;14;15]

SC administration of immunoglobulin preparations has become increasingly widespread, with tens of thousands of SC infusions given during the last decade. 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 and therefore 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 at the equivalent total monthly dose, SC IgG leads to higher trough serum IgG concentrations than monthly IV infusions.[16;17] After adequate training by healthcare professionals, SC infusions of immunoglobulin can easily be performed by the patient at home, thus increasing patient comfort and independence and reducing cost.[18]

Immunoglobulin administered intravenously is immediately available in the blood, and slowly equilibrates to the extra-vascular compartment over 3 to 5 days.[19] 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.[20] More recent studies mandated by the FDA have suggested that the bioavailability of SC immunoglobulin is lower than that of IV immunoglobulin.[3;21] 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.[3;22] 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.[23]

[ii] Halozyme Report Number R1005-0551.

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The primary practical disadvantage of SC administration of immunoglobulin is that only small volumes can be infused at each site, necessitating the use of multiple sites on a weekly or biweekly (every-other-week) basis. Generally, using a 16% solution, approximately 20 mL can be infused per site; an adult patient receiving 400 mg/kg BW thus would require at least 3 sites per week or 12 sites per month. Even though weekly or biweekly administration has the benefit of maintaining better IgG trough levels than monthly IV infusions, the requirement for multiple needle insertions may deter many patients.

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 local anesthetics and fluids for re-hydration.[24] However, since these are animal proteins and contain many other proteins beside hyaluronidase, they are immunogenic and are not suitable for chronic use. rHuPH20 is a 63 kd protein genetically engineered from the sequence of the naturally occurring human protein.

rHuPH20 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 did not lead to adverse reactions during a follow-up of 39 weeks[iv]. 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.[25] Studies of the effects of rHuPH20 on SC infusions of large quantities of IgG in dogs and rabbits have been difficult to interpret due to the rapid absorption of IgG alone in this model. However, at higher doses of rHuPH20, there was a suggestion of increased bioavailability. The human SC compartment is much tighter than that of these animals and thus, human studies are required. rHuPH20 can facilitate absorption of small molecules such as insulin and morphine in humans and in phase 1 trials improved bioavailability of proteins such as infliximab.[v]

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

In a phase 1/2 clinical study of HyQvia conducted by Baxter (Study 160602) the average bioavailability of the IgG in 7 subjects was 92%, suggesting a significant improvement compared to IG 10% 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 on first exposure when rHuPH20 was administered to 100 healthy volunteers in a skin allergy clinical trial.[26] In the Baxter Study 160603, a total of 13 subjects had at least one plasma sample that tested positive for rHuPH20-reactive binding antibodies (defined as a sample with a titer of ≥ 160) following HyQvia treatment. The peak of the observed positive titers ranged from 160 up to 81920 and has tended to decline 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. The natural history and association of rHuPH20-reactive antibodies to AEs is being monitored in the still ongoing clinical study 160902.

Non-clinical data for the IG 10% component of HyQvia reveal no special risk for humans based on conventional studies of safety pharmacology and toxicity. Other isoforms of hyaluronidase are found in most tissues of the human body. However, antibodies reactive to rHuPH20 do not cross-react with these other isoforms of hyaluronidase. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and developmental toxicity. Reversible effects on fertility have been reported in male and female guinea pigs immunized with semi-purified extracts of guinea pig testes combined with complete Freunds adjuvants to produce antibodies to hyaluronidase. However, active immunization or passive administration of antibodies reactive with hyaluronidase did not influence reproduction in mouse, rabbit, sheep, or cynomolgus monkey. The effect of antibodies against recombinant hyaluronidase on male or female human fertility is currently unknown.

No clinical studies have been conducted with HyQvia in pregnant women. HyQvia should not be used by women who are pregnant or are planning to become pregnant. It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy when on HyQvia treatment. If a woman becomes pregnant or plans to become pregnant while being treated with HyQvia, treatment with HyQvia should be stopped and an alternative treatment should be considered. She and the treating physician should be made aware of the possibility to participate in the pregnancy registry that is described in

[vi] Halozyme Report Number 10059.

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Baxter Protocol 161301: Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HyQvia (Immune Globulin (Human) 10% with rHuPH20).

There are no safety data available on the use of HyQvia in breast-feeding women. Further, there are also no clinical safety data available on the development of the reproductive system.

This PASS with regular assessment of antibodies against rHuPH20 was a request of the Committee for Medicinal Products for Human Use (CHMP). The CHMP stated in the final assessment report dated 21 March 2013 that further investigations were needed to evaluate long-term local and systemic reactions related to potential antibody development against recombinant human hyaluronidase.

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7.2 Critical Review of Available Data

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

7.2.1 Clinical Study 160602

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

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

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

The only severe and potentially life-threatening AE that occurred in the study was an anaphylactic reaction that was attributed to an antibiotic drug taken immediately prior to onset of the symptoms. This serious adverse event (SAE) occurred more than 24 hours after an infusion and was not considered related to use of the study drugs by the investigator. The subject continued in the study without further reactions. All other AEs, which occurred in four subjects in Study Arm 1 and six of seven subjects in Study Arm 2, were non-serious local AEs, of which the majority were mild and none were severe. Local AEs included infusion site erythema, infusion site pain, infusion site edema, infusion site warmth, injection site pruritus, infusion site swelling, and symptoms categorized as infusion site reactions.

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

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

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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. 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

[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.

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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. 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.

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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.

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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

This is a prospective, open-label, non-controlled, multi-center study in subjects with PIDD and is still ongoing. It is an extension of Study Protocol 160603; therefore, subjects and study sites of study 160603 had the opportunity to participate in Study 160902. The purpose of the study is to assess the long-term safety, tolerability, and practicability of SC treatment with IGSC facilitated with rHuPH20 in subjects with PIDD.

This study is a long-term safety study in which subjects will participate until approximately July 2013. The first study treatment began in Q3/2010; thus, subjects will participate for up to approximately three years. Sixty-six (66) subjects enrolled in the study when they completed Study 160603. Six subjects had to withdraw when their site was closed. Another subject, a [redacted] woman with common variable immune deficiency and many co-morbid conditions, died, in the opinion of the medical examiner, from multiple drug interactions a week after her nineteenth infusion. Multiple endocrinopathy and protein-calorie malnutrition likely contributed, and positional

asphyxia may also have contributed to the subject's death. The subject had not reported any adverse events during or in the week following her infusion. The clinical investigator assessed the death as not associated to the investigational products.

The interim analysis for the Data Summary Set (n=66) covers the period from their first exposure to IGSC + rHuPH20 during the ramp-up phase in Epoch 2 of Study 160603 through the interim analysis cut-off date (06 April 2012) for the study extension, corresponding to an exposure period of 157.7 subject-years.

The nature and rates of AEs reported in the interim analysis data summary are comparable to those reported during Study 160603. The most frequently reported related AEs were infusion site reactions, headache/migraine, myalgia, nausea, and fatigue. There were no SAEs that were related to either of the study drugs. Infusions were well-tolerated; the majority (97.6%) of HyQvia infusions did not require adjustment for tolerability concerns or for AEs. No new safety signals have arisen during the course of Study 160902.

In the study 160603, a total of 13 subjects had at least one plasma sample that tested positive for rHuPH20-reactive binding antibodies (defined as a sample with a titer of $\geq$ 160) following HyQvia treatment. No local or systemic reactions were attributed to the presence of rHuPH20 antibodies. The natural history and association of rHuPH20-reactive antibodies to AEs is being monitored in the clinical study 160902. For the majority of these subjects, antibody titers have declined during the observation period despite ongoing rHuPH20 administration, indicating the absence of an anamnestic response.

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. Subjects are being treated with conventional IGIV or IGSC for 24 or 48 weeks (for those with anti-rHuPH20 antibody titers $\geq$ 160 at the time rHuPH20 was discontinued).

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7.2.4 Clinical Study 161101

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

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

PIDD patients already on IV or SC treatment were enrolled and treated with IGI, 10% and rHuPH20 subcutaneously with a dose/interval ramp-up of 3 weeks. The ramp-up period was Epoch 1.

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

- For IV-pretreated subjects: every 3 weeks or 4 weeks, depending on the subject's previous IV dosing schedule
- For SC-pretreated subjects: every 3 weeks or 4 weeks, at the discretion of investigator and subject

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

A total of 37 subjects started the treatment. All but one of the subjects reached Epoch 2. During Epoch 2, 9 subjects withdrew. At the time when rHuPH20 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.

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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 Epoch2. 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 (Epoch3) 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.

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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.

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8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The study addresses the long-term safety of HyQvia (including the assessment of anti-rHuPH20 antibodies) as well as prescribed treatment regimens and product administration of HyQvia in routine clinical practice.

8.2 Primary Objective

The primary objective of the study 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.

8.3 Secondary Objectives

Secondary objectives of the study are to collect data on the prescribed treatment regimens, anti-rHuPH20 antibodies and, as available, other laboratory safety assessments, total IgG, further safety assessments, product administration and health-related quality of life and health resource use assessments.

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9. RESEARCH METHODS

9.1 Study Design

This study is a non-interventional, prospective, uncontrolled, open-label, multicenter, post-authorization safety study to evaluate the long-term safety of HyQvia under clinical routine conditions. The study is designed according to the Guideline on good pharmacovigilance practices (GPV), Module VIII – Post-authorisation safety studies **(EMA/813938/2011 Rev1).**[27] The overall study design is illustrated in Figure 1.

Screening for potential eligibility will take place prior to enrollment, and should coincide with a regular visit, or a treatment-related visit, for the subject at the treatment centre. Screening for potential eligibility should occur after the subject has been selected to receive, or has started treatment with HyQvia, and should occur within one month prior to enrollment. A termination visit should ideally occur at the conclusion of the observation period at a regular visit at the treatment center. The termination visit will be defined as the last regular visit at the treatment center before the end of Q1 2020.

The HyQvia dosage regimen and treatment schedule will be chosen by the attending physician in accordance with routine clinical practice.

There will be no required predefined visits, medical tests, laboratory tests and procedures beyond the treatment center´s standard clinical practice during the course of the study, except for the assessment of antibodies to rHuPH20 which was a request of the CHMP. The subject will be requested to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but not more often than 4 times a year, for the measurement of antibodies against rHuPH20. Data of additional safety laboratory assessments, total IgG levels, the occurrence of AEs, treatment regimen and product administration details will be recorded on the CRF as available, by the investigator.

If a subject declines to have additional blood drawn for laboratory testing for antibodies against rHuPH20, all other data will be collected as available.

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9.1.1 Study Endpoints

9.1.1.1 Safety

1. Incidence of all related SAEs.
2. Incidence of all SAEs
3. Incidence of non-serious adverse events (AEs), related and not related. Infections will be reported as AEs
4. Incidence of local, suspected to be immunologic AEs including skin changes (such as: local erythema, local pruritus, induration, nodules)
5. Incidence of temporally and/or causally associated systemic allergic AEs such as urticaria, throat swelling, or bronchospasm.
6. Incidence of the new onset of other adverse events that are potentially immunologically mediated, such as arthritis, nephritis, or pneumonitis
7. Incidence of gastrointestinal symptoms (such as: obstipation/constipation, nausea, vomiting, diarrhea, bloating)
8. Incidence and titer of binding and neutralizing antibodies to rHuPH20, and, if available, lab tests such as clinical chemistry, total IgG, etc.

9.1.1.2 Treatment Regimen

1. Dose (total dose in mg/kg BW/week)
2. Infusion interval

9.1.1.3 Health Related Quality of Life & Health Resource Use

1. Short Form-36, version 2 (SF-36v2): to be collected every 3 months in first year of study, annually for remainder of study.[28]
2. EuroQol 5-Dimension (EQ-5D) Questionnaire: to be collected every 3 months in first year of study, annually for remainder of study.[29]
3. Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9): to be collected every 3 months in first year of study, annually for remainder of study.[30]
4. Health resource use (eg., hospitalizations and length of stay, acute care visits, ER visits, and days missed from work/school): to be collected throughout the study as events occur.

HRQoL and HRU assessments are optional. For details see Section 9.3.3

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9.2 Setting

Adult patients (≥ 18 years) who have been prescribed treatment with HyQvia will be enrolled in the EEA. Treatment regimens will be prescribed at the discretion of the attending physician in accordance with routine clinical practice. Site visits and all other medical care will be performed as is standard for the site and for the subject´s healthcare. In addition, however, the subject will be requested to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months but no more often than 4 times a year, for the measurement of antibodies against rHuPH20, as requested by the CHMP.

No clinical studies have been conducted with HyQvia in pregnant women. HyQvia should not be used by women who are pregnant or are planning to become pregnant and an alternative treatment should be considered. It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy during HyQvia treatment. If a woman becomes pregnant, treatment with HyQvia should be stopped. In addition, the treating physician should encourage her to participate in the pregnancy registry that is described in Baxter Protocol 161301: Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HyQvia (Immune Globulin (Human) 10% with rHuPH20).

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9.2.1 Medicinal Product(s)

HyQvia is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20). One ml of human normal immunoglobulin contains 100 mg of human normal immunoglobulin (purity of at least 98% immunoglobulin G (IgG). IG 10% is a clear or slightly opalescent and colourless or pale yellow solution.

Recombinant human hyaluronidase is a purified glycoprotein of 447 amino acids produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Recombinant human hyaluronidase is a clear, colourless solution.

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

Table 2
HyQvia Administration Scheme

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

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Method of administration

The medicinal product is for subcutaneous use only. In case facilitated subcutaneous infusion of HyQvia is used for home treatment, therapy should be initiated by a physician experienced in the guidance of patients for home treatment. The patient will be instructed in infusion techniques, the use of an infusion pump or syringe driver, if needed, and measures to be taken in case of adverse reactions. The keeping of a treatment diary is recommended. No subject diary will be provided by the responsible party.

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

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

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

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

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

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

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

Further details on administration, packaging, labeling, and storage for the medicinal product are described in the product labeling.

The investigator will record the details of the treatment regimen (such as dose, and frequency), and product administration (such as maximum infusion rate, infusion volume, number and location of infusion sites, date of infusion, infusion start and stop time, batch number, as available) in the case report form (CRF).

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9.2.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately six years from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be approximately three years.

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. The termination visit will be defined as the last regular visit at the treatment center before the end of Q1 2020.

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:

- Subject requires immunoglobulin treatment
- Subject is ≥ 18 years old at the time of screening
- Subject has been prescribed treatment with HyQvia
- Subject agrees to inform the investigator if she becomes pregnant, or plans to become pregnant during the course of the study
- Subject/legal representative has reviewed, signed and dated informed consent

9.2.3.2 Exclusion Criteria

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

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

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9.2.4 Informed Consent and Enrollment

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

9.2.5 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 161302) to be provided by the responsible party, 2- or 3-digit study site number (e.g., 02) to be provided by the responsible party, and 3- or 4-digit subject number (e.g., 0003) 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

161302-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

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.

The overall study design is illustrated in Figure 1. Details on the procedures to be performed at each study visit, including screening, can be found in Table 3 and Table 4.

Figure 1
Study Design for Baxter Clinical Study 161302

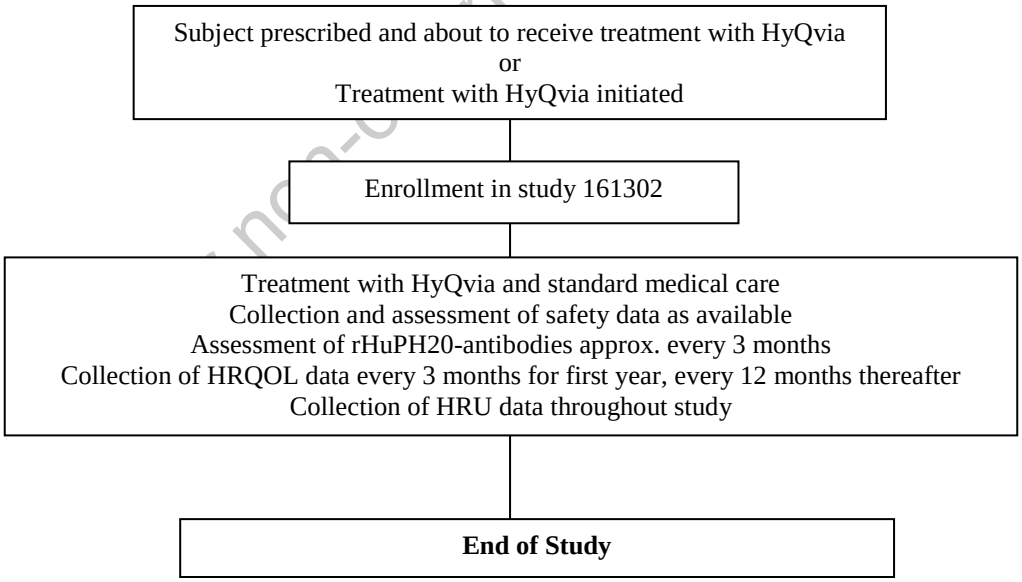

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Table 3
Schedule of Study Procedures and Assessments

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

a. Occurs at enrollment (prior to any study-specific procedure).
b. For laboratory assessments, see Table 4.
c. 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/or 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.
d. Site visits and all other procedures and assessments related to the subject's medical management will be performed as is standard for the site and for the subject's healthcare, with the exception of anti-rHuPH20 antibodies assessments (see Table 4).
e. Approximately every 3 months for the first year and every 12 months thereafter
f. Optional

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Table 4
Clinical Laboratory Assessments

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

a. **All safety laboratory test results except anti-rHuPH20 antibodies will be recorded as available, if tests are performed as part of the site's routine medical management of the subject.**
b. Only females of child-bearing potential, if performed as part of the site's routine medical management of the subject.
c. The subject will be requested to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but no more often than 4 times a year, for the measurement of antibodies against rHuPH20.
d. Site visits and all other procedures and assessments related to the subject's medical management will be performed as is standard for the site and for the subject's healthcare (with the exception of anti-rHuPH20 antibodies assessments) and will be documented as available.
e. If testing is not performed routinely at the date of the screening/enrollment visit, results of the tests that were performed last (but not more than 6 months prior to enrollment) will be recorded as available.
f. Blood samples for rHuPH20 antibody testing to be taken, if the visit coincides with routine lab assessments.

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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 clinical 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). Additionally, the investigator and responsible party have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

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

- The subject becomes pregnant, or subject plans to become pregnant. Medicinal product exposure will be discontinued. Attempts will be made to follow her through completion of the pregnancy, if applicable. To this end, the subject should be invited to participate in the pregnancy registry Baxter Protocol 161301: Registry Study to collect Long-Term Safety Data from Female Subjects who become pregnant during treatment with HyQvia (Immune Globulin (Human) 10% with rHuPH20). Alternatively, the investigator will record a narrative description of the course of the pregnancy and its outcome.

9.2.8 Study Stopping Rules

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

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9.3 Variables

9.3.1 Treatment Regimen/Product Administration

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

If treatment is administered at the site and/or 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.

9.3.2 Safety Variables

9.3.2.1 Medical History, Medications, and Non-Drug Therapies

At screening/enrollment, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 11.2.4) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphocytic; dermatological; and genitourinary.

All medications taken and non-drug therapies received 3 months before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

The medical history should also include information on the previous immune globulin treatment such as start/end date of treatment with a specific product, dosage, regimen, date and administration details of last infusion prior to the first HyQvia administration ever, as available.

9.3.2.2 Physical Examinations

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

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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 11.2.6), 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.

9.3.2.3 Clinical Laboratory Parameters

All laboratory data, such as (but not limited to) clinical chemistry, hematology, urinalysis, seroconversion results for HIV, HBV, and HCV, total IgG, pregnancy testing (if applicable), will be collected as available from routine clinical practice, with the exception of the assessment of antibodies against rHuPH20 (rHuPH20-reactive binding and neutralizing antibodies), based on the request of the CHMP. For subjects that do not agree to testing for antibodies against rHuPH20, all other laboratory data will be collected as available.

For the assessment of antibodies to rHuPH20 refer to Section 9.3.2.3.1.

Laboratory data, except for rHuPH20 antibodies, will be transcribed by the investigator into the CRF provided by the responsible party.

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

The investigator's assessment of each laboratory value will be recorded on the appropriate form. For each abnormal laboratory value, the investigator will determine whether the value is clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 11.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a preexisting disease (described in Section 11.2.6), 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.

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

The Common Toxicity Criteria of the Eastern Cooperative Oncology Group, published by Oken et al.,[31] will be used to grade the following laboratory values: Alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), hemoglobin, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and white blood cell (WBC) count. Grading for lactate dehydrogenase will use the same thresholds as defined for ALT and AST.

Sodium and potassium will be graded using the thresholds taken from the WHO toxicity grading system.[32] The laboratory parameters and the corresponding grading scale are provided in Table 5

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

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Table 5
Grading of Laboratory Parameters[a]

Analyte	Direction	WNL is Grade 0	No Grade 1	Unit Grades	Grade 0 Low	Grade 0 High	Grade 1 Low	Grade 1 High	Grade 2 Low	Grade 2 High	Grade 3 Low	Grade 3 High	Grade 4 Low	Grade 4 High	Source
Alkaline Phosphatase	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
ALT	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
AST	Increase	YES	NO	ULN	.	.	.	2.5	2.6	5.0	5.1	20	20.1	.	ECOG
BUN	Increase	NO	NO	ULN	0.0	1.4	1.5	2.5	2.6	5.0	5.1	10	10.1	.	ECOG
Hemoglobin	Decrease	YES	NO	g/dL	.	.	10.0	.	8.0	9.9	6.5	7.9	0.0	6.4	ECOG
Lymphocytes	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Neutrophils	Decrease	NO	NO	x10^3/uL	2.0	.	1.5	1.9	1.0	1.4	0.5	0.9	0.0	0.4	ECOG
Platelet Count	Decrease	YES	NO	x10^3/uL	.	.	75.0	.	50.0	74.9	25	49.9	0.0	24.9	ECOG
Potassium	Decrease	NO	NO	mmol/L	3.5	.	3.0	3.4	2.5	2.9	2.0	2.4	0.0	1.9	WHO
Potassium	Increase	NO	NO	mmol/L	0.0	5.5	5.6	6.0	6.1	6.5	6.6	7.0	7.1	.	WHO
Serum Creatinine	Increase	YES	NO	ULN	.	.	.	1.4	1.5	3.0	3.1	6.0	6.1	.	ECOG
Sodium	Decrease	NO	NO	mmol/L	136	.	130	135	123	129	116	122	0.0	115	WHO
Sodium	Increase	NO	NO	mmol/L	0.0	145	146	150	151	157	158	165	166	.	WHO
Serum Total Bilirubin	Increase	YES	YES	ULN	.	.	.	.	.	1.4	1.5	3.0	3.1	.	ECOG
WBC	Decrease	NO	NO	x10^3/uL	4.0	.	3.0	3.9	2.0	2.9	1.0	1.9	0.0	0.9	ECOG

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

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9.3.2.3.1 rHuPH20-Reactive Binding and Neutralizing Antibodies

For the assessment of antibodies to rHuPH20, the subject will be requested to have additional blood samples drawn at the time of routine laboratory assessments approximately every 3 months, but not more often than 4 times a year, for the measurement of rHuPH20-reactive binding and neutralizing antibodies. For information regarding sample volumes and processing refer to the Laboratory Manual for the study.

At screening/enrollment and at study termination, additional blood samples for rHuPH20 antibody testing will be taken only if the visit coincides with other routine laboratory assessments.

Testing will be done in a central laboratory selected by the responsible party. Results for antibodies against rHuPH20 will be forwarded by the central laboratory to both the investigator and the responsible party and will not need to be transcribed into the CRF by the investigator.

9.3.2.3.2 Hematology and Clinical Chemistry

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

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

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

9.3.2.3.3 Seroconversion

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

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9.3.2.3.4 Urinalysis

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

9.3.2.4 Biobanking

Blood samples for antibodies against rHuPH20 that remain after study testing is done may be stored and used for additional antibody or antibody-related testing (e.g., 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.

9.3.2.5 Vital Signs

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

Data collected from vital signs assessments will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital sign values are to 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). If the abnormal value not deemed an AE, the investigator will indicate the reason on the source record, ie because it is due to an error, a preexisting disease (described in Section 11.2.6), a symptom of a new/worsened condition already recorded as an AE, or another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

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9.3.3 Health Related Quality of Life and Health Resource Use

9.3.3.1 Health Related Quality Of Life

HRQoL assessments may be performed optionally at the screening/enrollment visit, approximately every three months for the first year, thereafter approximately every 12 months, and at the study termination visit.

SF-36v2

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

EQ-5D

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

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

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

9.3.3.2 Health Resource Use

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

HRU assessments may be performed optionally at each of the subject´s interval and study termination site visits.

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9.3.4 Subject Completion/Discontinuation

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

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, adverse event (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), pregnancy/planning to become pregnant, physician decision (e.g., progressive disease, non-compliance with medicinal product/protocol violation(s), recovery), study terminated by responsible party, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate 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 responsible party. Details of the outcome may be reported to the appropriate regulatory authorities by the responsible party.

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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, home treatment records or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

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

9.5 Study Size

There is no minimum sample size specified for this study. It is expected that a total of approximately 80 – 120 subjects may be enrolled.

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 medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the EC and the study monitor/responsible party, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), home treatment records (if available), and data clarifications requested by the responsible party.

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.

Electronic format CRFs are provided by the responsible party, only authorized study site personnel will record or change data on the CRFs. All data, with the exception of adverse events, should preferably be entered on the CRFs during the study visit or within 10 days of the visit. Changes to a CRF will require documentation of the reason for each change.

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

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9.6.2 Software

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

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

9.7 Data Analysis

9.7.1 Datasets and Analysis Cohorts

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

9.7.2 Handling of Missing, Unused, and Spurious Data

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

9.7.3 Methods of Analysis

Statistical analyses and data displays will be mainly descriptive. Data from all enrolled subjects will be included in the analysis. If groups of sufficient sample size (such as: age groups, PIDD types) are available, confidence intervals may accompany the point estimates. All SAEs and non-serious AEs will be categorized according to MedDRA system organ class (SOC) and preferred term. Concomitant medications and non-drug therapies will be recorded and tabulated. Tables will be prepared to list for each SAE and non-serious AE the number of events and the number of subjects who experienced one or more events.

9.7.3.1 Safety Endpoints

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

No statistical hypotheses will be tested.

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Descriptive methods, mainly frequency tables, will be used for all other safety endpoints (see Section 9.1.1). The incidence of events will be analyzed for changes in frequency and for changes in severity over time.

9.7.3.2 Treatment Regimen – Endpoint

Dose per kg body mass per week will be summarized descriptively over the set of subjects; if a subject changed the dose, the weighted average will be used with weights proportional to the time the subject was on a particular dose.

A frequency table will show the number of subjects and the total observation time in subject-years per infusion interval.

9.7.3.3 HRQoL & HRU Endpoints

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

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

9.7.3.4 Planned Interim Analysis of the Study

Regular study progress information will be provided with the required PSURs. In addition, interim analysis are planned as follows:

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

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

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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), ICH GCP, and applicable regulatory requirements as described in the Noninterventional 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 responsible party. 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.

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 responsible party or its representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Noninterventional Trial Agreement. If contacted by an applicable regulatory authority, the investigator will notify the responsible party of contact, cooperate with the authority, provide the responsible party with copies of all documents received from the authority, and allow the responsible party to comment on any responses, as described in the Noninterventional 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 responsible party.

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.

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The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Noninterventional 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 responsible party and/or responsible party's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Noninterventional Trial Agreement. Auditing processes specific to the study will be described in the auditing plan (see Section 14.1).

9.8.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the responsible party immediately by phone and confirm notification to the responsible party in writing as soon as possible, but within 1 calendar day after the change is implemented. The responsible party (Baxter) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

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

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9.9 Limitations of the Research Methods

Due to the non-interventional nature of the study, the amount of data that becomes available to be entered by the investigator or designee is beyond the responsible party´s control.

9.10 Other Aspects

Not applicable.

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 Noninterventional Trial Agreement.

10.3 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 EC and applicable regulatory authorities. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the responsible party's receipt of approval/favorable opinion from the EC and, if required, upon the responsible party's notification of applicable regulatory authority(ies) approval, as described in the Noninterventional Trial Agreement.

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

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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. Before use, the informed consent form will be reviewed by the responsible party and approved by the EC and regulatory authority(ies), where applicable, (see Section 10.3). The informed consent form will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by

applicable regulatory requirements. Patients and/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 participate in the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The responsible party will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with medicinal product exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form that has been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consent to participate in the study (see Section 10.4).

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Assessment of Adverse Events

Each AE from the first medicinal product exposure until study completion 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). 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 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, whichever comes first.

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

11.2 Definitions

11.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered medicinal product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product. Events that do not necessarily meet the definition of AEs, regardless of causal association with medicinal product, should be treated as AEs because they may be reportable to Regulatory Authorities according to AE reporting regulation; these include the following:

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1. Medicinal product overdose, whether accidental or intentional
2. Medicinal product abuse
3. An event occurring from medicinal product withdrawal
4. Any failure of expected pharmacological action
5. Exposure to medicinal product during pregnancy
6. Unexpected therapeutic or clinical benefit from 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
  - Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack, stroke, etc.)
  - Diagnosis of hemolytic anemia, reviewed and confirmed by the study site using standard laboratory assessments

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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 sequel.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequel, which require (prolonged) therapeutic intervention.

11.2.5 Causality

Causality is a determination of whether there is a reasonable possibility that the medicinal product is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE assessed as not related or unlikely related, the investigator shall provide an alternative etiology. 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

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  - 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

11.2.6 Preexisting Diseases

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

11.2.7 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 (e.g., product labeling). “Unexpected” also refers to the AEs that are mentioned in the product labeling as occurring with a class of medicinal products or as anticipated from the pharmacological properties of the medicinal product, but are not specifically mentioned as occurring with the particular medicinal product under investigation.

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11.2.8 Untoward Medical Occurrences Not Considered Adverse Events

Each **serious** untoward medical occurrence experienced before the first medicinal product exposure (e.g., from the time of signed informed consent up to but not including the first medicinal product exposure) will be described on the SAE Report. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

11.2.9 Non-Medical Complaints

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

- Device malfunctions, which are defined as failure of the device to meet its performance specifications or otherwise to perform as intended
- Reconstitution difficulty
- 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 study device will be documented on an NMC form. If an investigational device fails to perform in the expected manner, the responsible party will be notified. The definition of "expected manner" includes e.g., all the steps of kit opening, assembly, extrusion, and gel formation in a spray pattern. If requested, defective devices will be returned to the responsible party for inspection and analysis according to procedures.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The CHMP requested a study progress report to be submitted with each PSUR. The final clinical study report is estimated for 2020. In addition, interim analyses will be performed as described in Section 9.7.3.4.

The investigator will comply with the publication policy as described in the Noninterventional Trial Agreement.

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14. ANNEXES

14.1 List of Stand-Alone Documents

No.	Document Reference No.	Date	Title
1	Number	not finalized	Study Organization
2	Number	not finalized	Clinical Monitoring Plan
3	Number	not finalized	Data Management Plan
4	Number	not finalized	Auditing Plan
5	Number	not finalized	Investigator List

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

14.2 ENCePP Checklist for Study Protocols

Refer to the completed ENCePP Checklist.

14.3 Additional Information

Not applicable

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INVESTIGATOR ACKNOWLEDGEMENT

Immune Globulin Infusion (Human), 10% with rHuPH20 (HyQvia)

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

PROTOCOL IDENTIFIER: 161302

ORIGINAL: 2013 JUL 26

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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, Noninterventional Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator