8 May 2013
EMA/239112/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

HyQvia

Common name: human normal immunoglobulin

Procedure No. EMEA/H/C/002491/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADA	Anti-drug Activity
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event (experience)
AF	Assessment Factor
ANOVA	Analysis of variance model
AUC	Area under the curve
AUC0-τ	Area under the concentration versus time curve between subsequent infusions
BW	Body weight
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence interval
Cl	Clearance
Cmax	Maximum concentration
Cmin	Minimum concentration
CNS	Central Nervous System
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
FADS	Full analysis data set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HA	Hyaluronan
HED	Human Equivalent Dose
hERG	Ether-a-go-go Related Gene
ICH	International Conference on Harmonisation
ID	Intradermal
IP	Intraperitoneal
IV	Intravenous
MAA	Marketing Authorisation Application
MedDRA	MedDRA Medical Dictionary for Regulatory Activities
NEL	No Effect Level
NOAEL	No Observable Adverse Effect Level
NOEC	No Observable Effect Concentration
PEDS-QL	Pediatric Quality of Life Inventory™
PID	Primary immunodeficiency diseases
PH20	Sperm Surface Hyaluronidase
PK	Pharmacokinetics
PPDS	Per-protocol data set
rHuPH20	Recombinant Human Hyaluronidase
SADS	Safety analysis data set
SAE	Serious adverse event (experience)
SC	Subcutaneous
SCID	Severe combined Immunodeficiency
SD rats	Sprague Dawley rats
SmPC	Summary of Product Characteristics
SNDS	Subcutaneous Immunoglobulin (SCIG) Naïve Subjects Data Set
SF-36	36-item short-form health survey
t1/2	Half-life
TGD	Technical Guidance Document
tmax	Time to achieve the maximum plasma drug concentration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxter Innovations GmbH submitted on 30 September 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for HyQvia, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication.

Replacement therapy in adults (≥ 18 years) in primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections.

Replacement therapy in adults (≥ 18 years) in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

The legal basis for this application refers to:

Article 8(3) of Directive No 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

- Significance of paediatric studies

A paediatric investigation plan (PIP) was agreed with the Paediatric committee (PIP Decision Number: P/306/2010). A PIP compliance verification is available from 17 June 2011: PDCO compliance Opinion Number EMA/359195/2011, which confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed until this date.

The European Medicines Agency has deferred the obligation to submit the results of studies with HyQvia in one or more subsets of the paediatric population in treatment of primary immunodeficiency as model for replacement therapy.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 9 February 2009 (EMEA/H/SA/1170/1/2009/III). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: USA.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers of the active substance

Baxter Healthcare Corporation
4501 Colorado Boulevard
Los Angeles, California
USA
Manufacture of intermediate Precipitate G from human plasma.

Baxter AG
Industriestrasse 131
1221-Vienna
Austria
Manufacture of intermediate Precipitate G from human plasma.

Baxter Manufacturing S.p.A.
Via della Chimica 5
02010 Santa Rufina, Cittaducale, Rieti
Italy
Manufacture of intermediate Precipitate G from human plasma.

Baxter S.A.
Boulevard René Branquart, 80
B-7860 Lessines
Belgium
Manufacture of Ultrafiltrate Centrifugate of Immune Globulin 10% from Precipitate G

Manufacturer of the finished product

Baxter S.A.
Boulevard René Branquart, 80
B-7860 Lessines
Belgium

Manufacturer responsible for batch release

Baxter S.A.
Boulevard René Branquart, 80
B-7860 Lessines
Belgium

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Jan Mueller-Berghaus

Co-Rapporteur: Andrea Laslop

- The application was received by the EMA on 30 September 2011.
- The procedure started on 19 October 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 January 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2012.
- During the meeting on 16 February 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 September 2012.
- During the CHMP meeting on 18 October 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. An extended responses timetable of 90 days was granted by the CHMP to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 January 2013 and requested for an Oral explanation on 18 January 2013. The Rapporteurs circulated the Joint Assessment Report on the responses provided by the applicant on 4 February 2013. The request for an Oral explanation was withdrawn by the applicant on 14 February 2013.
- During the CHMP meeting on 19 February 2013, a 2nd CHMP List of Outstanding Issues adopted by the applicant. The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 27 February 2013. The Rapporteurs circulated the Joint Assessment Report on the responses provided by the applicant on 8 March 2013.

- During the meeting on 21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to HyQvia.

2. Scientific discussion

2.1. Introduction

Problem statement

Primary immunodeficiency diseases (PID) are a class of disorders that result in increased susceptibility to infection including both recurrent pyogenic infections secondary to defects of humoral immunity and opportunistic infections resulting from defects in cell-mediated immunity. Individuals with these disorders require replacement therapy with immunoglobulin products in the range of 0.3 to 0.6 g/kg body weight (BW) every 3 to 4 weeks, which are easily achieved by the intravenous (IV) route. However, adverse drug reactions and the need for experienced medical personnel to administer the infusions are problematic for many patients. Subcutaneous (SC) administrations of immunoglobulin preparations have become increasingly widespread during the last decade. The immunoglobulin preparations currently licensed for SC use in the European Union are formulated at 16% to 20%; the higher concentration relative to IV licensed products (typically formulated at 5 to 12%) allows for a smaller infusion volume. SC administration of immunoglobulin replacement therapy is considered to be effective, safe, and also highly appreciated by patients as it has a relatively low risk of systemic adverse reactions and, when given weekly or every other week, leads to higher trough serum IgG concentrations as compared to monthly IV infusions.

Human normal immunoglobulin 10% (IG 10%) for administration with the excipient recombinant human hyaluronidase (rHuPH20) has been developed to facilitate subcutaneous administration of the IG 10% preparation. The medicinal product is provided as two components in a dual vial unit in an inseparable kit arrangement. The recombinant human hyaluronidase component modifies the permeability of connective tissue through the hydrolysis of hyaluronan.

About the product

HyQvia is a human normal immunoglobulin. It is presented as two separate vials active substance and excipient i.e. combination of human normal immunoglobulin 10% (IGSC, 10%) and recombinant human hyaluronidase (rHuPH20). HyQvia has been developed to enable the SC administration of large volumes of IgG, thus addressing the major disadvantage of present SCIg replacement therapy. HyQvia allows administration of SCIg every 3 or 4 weeks, as an alternative to IVIg administration or more frequent (usually at least once a week) SCIg administration in patients with PID.

The function of rHuPH20 in the new product combination is to promote the dispersion and absorption of IGSC 10% by temporarily increasing the permeability of the subcutaneous tissue.

Administration of the combination product is a 2-step process that comprises injection of the rHuPH20 followed by infusion of IGSC 10% into a single SC site through the same needle/infusion set.

IGSC 10% is identical to Baxter's licensed product for intravenous administration, human normal immunoglobulin for intravenous use 10% (IGIV 10%), a liquid human immunoglobulin G (IgG) preparation. IGIV 10 % is marketed as KIOVIG (EMEA/H/C/000628) in Europe

2.2. Quality aspects

2.2.1. Introduction

HyQvia is presented as two separate vials one with the final formulation of the human normal immunoglobulin, 10% (IGSC, 10%) and the other with the excipient recombinant human hyaluronidase (rHuPH20).

The active substance in HyQvia, human normal immunoglobulin 10% is identical to the active substance in Baxter´s licensed human normal immunoglobulin for intravenous administration IGIV 10%) product KIOVIG (EU product name) / Gammagard Liquid (GGL; US product name) and is manufactured using the same process for both products. Therefore, all information, established tests and performed investigations as described below are also fully applicable for HyQvia.

The recombinant human hyaluronidase (rHuPH20) is a novel excipient and full details of the manufacture, characterisation and controls with cross references to supporting safety data have been provided. The assessment of the rHuPH20 is presented under the chapter 2.2.3 Finished medicinal product.

2.2.2. Active Substance

HyQvia being equivalent to KIOVIG, it is manufactured from human plasma for fractionation compliant to Ph. Eur., and full details are provided in the Baxter Plasma Master File (PMF) dossier annually re-certified by the EMA. Currently, plasma is sourced from Austria, the Czech Republic, Germany, Sweden, Norway, Switzerland, Finland, and the United States of America. Only plasma from centres approved in the PMF is used for the manufacture of products marketed in the European Economic Area (EEA).

Manufacture

Manufacturing process

The IGIV 10% manufacturing process employs a modified Cohn-Oncley cold alcohol fractionation procedure to isolate an intermediate immunoglobulin G (IgG) fraction, referred to as Precipitate G, from frozen human plasma pools. Precipitate G is further purified by a continuous process through the use of cation exchange chromatography and anion exchange chromatography to final formulation. No distinct active substance can be defined which meets the definition of a bulk that is routinely stored and/or tested. For formal reasons, however, the manufacturing description has

been divided into the manufacture of the active substance, ultrafiltrate concentrate. Fractionation of the pooled plasma to obtain the intermediate Precipitate G is performed at the Baxter facilities in Los Angeles/CA/USA, Vienna/Austria, and Rieti/Italy. The Precipitate G is shipped to the Baxter facility in Lessines/Belgium for further manufacture into IG 10% final product.

Purification

Three dedicated virus reduction/inactivation steps are included in the downstream purification of Precipitate G, which are solvent/detergent (S/D) treatment, nanofiltration, and incubation at low pH and elevated temperature in the final formulation. In general, reduction factors obtained by these process steps are lower for non-lipid-enveloped viruses. Therefore viral clearance studies on the fractionation II+III part of the manufacturing process were additionally performed in order to investigate the inactivation/removal capacity of this step. The studies submitted were performed on laboratory scale in line with the guideline CPMP/BWP/268/95. A risk assessment for HIV, HCV, HBV, HAV, WNV and B19V has been provided, including the calculation of the residual risk for one dose of IVIg 10%. No animal-derived auxiliary except for heparin, purified from porcine tissue, is used in the IGIV 10% process. Manufacturing processes of plasma-derived medicinal products have to be investigated for their potential prion removal capacity. Baxter presents a fact sheet which discusses TSE safety for IGIV 10% and Immune Globulin Subcutaneous, 20% (IGSC 20%). This fact sheet is applicable to HyQvia. The residual theoretical risk of plasma for fractionation, steps with proven prion removal capacity as well as steps not investigated for prion removal are summarized. Calculations regarding residual theoretical risk are provided.

The manufacturing process includes 8 different adsorption options (adsorption of coagulation factors, ATIII, and C1-Inhibitor) dependent on the manufacturing site. A detailed comparison of the manufacturing process of precipitate G for IGIV 10% on the different sites is given.

The critical steps for the IGIV 10% manufacturing process have been identified. Immune Globulin Intravenous (Human), 10% Solution (IGIV 10%) conformance lots were manufactured to validate the processes at Baxter Los Angeles (LA), Vienna, Rieti, and Lessines commercial scale facilities. To support the licensure of all possible adsorption options used at a given facility by process validation data, the bracketing approach was used. The Ultrafiltrate Concentrate, which corresponds to the active substance, is immediately further processed and filled into final containers. No storage of the Concentrate prior to the final formulation step is foreseen. All quality control tests are performed for the Drug Product only. Regarding the IVIG 10% manufacturing no major objections have been identified during the assessment. The dossier has now been updated adequately to address any concerns raised during the procedure, mostly in relation to the quality and dossier completeness of the dossier.

2.2.3. Finished Medicinal Product

The finished medicinal product IG 10% is a purified IgG liquid solution formulated with 0.25M glycine (for a stabilising effect) at 10% w/v protein concentration and a pH of 4.6 to 5.1. The preparation is an isotonic solution containing a concentration of approximately 100 mg of protein per ml, of which at least 98% is IgG. Stabilising agents and additional components are present in the following maximum amounts: 18.8 mg/ml glycine, and trace amounts of polysorbate 80,

tri-n-butyl phosphate, and octoxynol 9. The product contains no preservatives. The finished product specifications meet the relevant Ph. Eur. Monographs 0918 and 0338.

Regarding the stability of the IG 10% drug product, the applicant presented 5 stability studies. The stability studies were designed to cover all manufacturing facilities and filling sizes of the product. Baxter proposes a 24 months shelf life for IGIV 10% when stored under refrigerated (+2°C to +8°C) conditions.

HyQvia medicinal product is provided as two components in a dual vial unit in an inseparable kit arrangement i.e. the human normal immunoglobulin (IG 10%) and Recombinant Human Hyaluronidase (rHuPH20) are presented as separate vials.

rHuPH20 has not been previously authorised as an excipient and is considered a novel excipient. Full details of manufacture, characterisation and controls with cross references to supporting safety data have been provided in the dossier. The information on rHuPH20 was presented in separate sections by analogy to the product's dossier structure "active substance" and "finished product". In this document the terms "excipient substance" (the rHuPH20 ingredient) and "excipient product" (the formulated vial with rHuPH20) are used.

rHUPH20 (excipient substance abbreviated as rHUPH20 DS)

The rHuPH20 DS protein is formulated at 1 mg/ml. The solution is filled in Type I glass vials with Type I bromobutyl rubber stoppers.

- Manufacturing process

The manufacturing process of rHuPH20 DS begins with thawing of one vial from the working cell bank (WCB) and expansion of the cells through culture. Description of the generation of the host cell line, the cell banking system and characterization of the host cell line is in accordance with the demands of the ICH guidelines Q5B, Q5D, CHMP 3AB1A, and the Monograph "Products of Recombinant DNA Technology". In addition, the characterisation of the host-vector system, including mechanism of transfer of the vector into the host cells, copy number, physical state and stability of the vector inside the host cell, and measures used to promote and control the expression are described sufficiently. When expanded the culture is transferred to a bioreactor and thereafter harvested. Then the protein is purified through column purification steps and a dedicated viral reduction step (Nanofiltration). The purified protein is concentrated (1 mg/mL), formulated, and filled into vials. The in-process controls performed during manufacture of rHuPH20 Drug Substance are listed. The described acceptance criteria for control parameters of critical steps in the manufacture of rHuPH20 DS are adequate justified and subsequent consequences if Out of Limit events occur are listed.

- Validation

The prospective process validation protocol covered 3 consecutive full scale GMP batches. An inspection of the manufacturing site was conducted in 2012 in order to verify compliance of the manufacturing process of rHUPH20 (recombinant human hyaluronidase) with GMP and the particulars of the Marketing Authorisation Application in accordance with Article 8(2) of Regulation (EC) 726/2004.

The validation of the rHuPH20 DS manufacturing process showed that the cell line exhibits strong and reproducible growth and viability in all vessel sizes. The column purification process

demonstrated reproducibility for both yield and enzyme activity and purity. The virus filtration has operated consistently in all production runs.

- Characterisation

The characterisation of rHuPH20 product includes the determination of physicochemical properties, biological activity, purity, impurities, contaminants, and quantity by appropriate techniques, as described in ICH Q6B. The testing meets the criteria of ICH guidelines Q3A, Q3B, Q5C resp. Q6B and the demands of the CHMP guideline on Control of Impurities of Pharmacopoeial Substances. Furthermore, the characterisation of rHuPH20 is in line with the demands of the Monograph "Products of Recombinant DNA Technology".The Applicant has initiated the validation of an improved RP-HPLC assay to allow separate specifications to be set for the product-related impurities. The Applicant commits to establish these impurity acceptance limits after collecting data from the first 20 commercial lots.

- Container closure system

The rHuPH20 DS is filled in borosilicate glass vials that are closed with bromobutyl stoppers suitable for long-term storage. The vial is manufactured from low extractable borosilicate glass that conforms to ASTM Type I, Class A and USP Type I requirements.

- Stability

Based on the available stability data for commercial scale lots, the proposed shelf life for the rHuPH20 DS production lots has been set at three years when the lots are stored at ≤ -30°C. The stability testing plan is sufficient and complies with ICH guidelines Q1A and Q5C. Based on the presented data, the proposed shelf-life is considered acceptable.

rHuPH20 (excipient finished product)

Recombinant human hyaluronidase (rHuPH20) is a solution for subcutaneous injection that functions as a permeation enhancer. The preparation is supplied at the concentration of 160 U/mL with fill sizes of 1.25 mL, 2.5 mL, 5 mL, 10 mL and 15 mL. rHuPH20 solution is a clear, colourless solution essentially free of particles.

The rHuPH20 is manufactured into the rHuPH20 finished product by contract fill-finish organization. Quality Control testing and release of the rHuPH20 finished product, and the packaging and labeling and release of Immune Globulin, 10% and rHuPH20 is performed by Baxter S.A., B-7860 Lessines, Belgium.

- Manufacturing process

The rHuPH20 DP is manufactured in smaller and larger batch sizes using essentially the same process. The description of the manufacturing process is detailed and considered sufficient. The rHuPH20 DP manufacturing process will be conducted at two batch sizes, smaller ± 10% and larger ± 10%. For the smaller batch size, up to two rHuPH20 DS lots may be blended; for the larger size, one to three rHuPH20 DS lots or parts thereof may be used.

There are no reprocessing steps planned at this time. The critical steps for the rHuPH20 finished product manufacturing process have been identified. They are noted along with appropriate control tests, test methods, acceptance criteria, and actions if acceptance criteria are not met.

- Process validation

The validation exercise for rHuPH20 in both sizes of batches have been completed in accordance with their respective validation protocols. The review and evaluation of the validation batches indicate that rHuPH20, 160 U/mL manufacturing process at BPS is under control and capable of consistently producing product that complies with all established specifications and quality characteristics.

All excipients used for the manufacturing of rHuPH20 are compendial materials and their specifications are in compliance with the current edition of the European Pharmacopoeia. Analytical procedures for the tests on excipients are performed by the vendors according to the requirements of the current Ph. Eur. monographs and have been qualified for use. Therefore, no validation information is provided.

Human albumin is the only excipient (stabiliser) of biological origin used in the manufacture of rHuPH20. For the production of conformance lots of rHuPH20 finished product, Buminate, Albumin (Human), was used as excipient (stabiliser). For future lots of rHuPH20 supplied with IG 10% in the EU, Baxter intends to use Human Albumin Baxter as excipient. This human albumin is licensed in the EU through Mutual recognition procedure (MRP) procedure DE/H/0474/003 and has been on the European market since 2006. Human Albumin Baxter complies with the current Ph. Eur.

- Control of drug product

Validation of the analytical procedures used for release testing of rHuPH20 finished product was performed in compliance with ICH guidelines. Detailed assay validation information for the non-compendial analytical procedures is provided in the referenced validation reports. The non-compendial analytical methods are satisfactorily validated. Eight conformance and six clinical batches of rHuPH20 finished product were analysed according to the defined specifications and procedures. All lots pass the release specifications for rHuPH20 finished product. The analytical batch data demonstrate the robustness and reproducibility of the manufacturing process for rHuPH20 finished product. Product-related impurities that were detected and assessed were either rHuPH20-related impurities or albumin and its related impurities (non-albumin plasma proteins).

The rHuPH20 assay working reference standard currently in use is a rHuPH20 finished product lot. This is the same standard that is used as reference material for the potency assay of the excipient substance.

- Container closure system

The description of Container Closure System is adequate. Sufficient information is provided. The tests methods for container closure are in conformance with Ph. Eur. requirements

- Stability

Stability data for three clinical lots (36 months/2 lots and 30 months/1 lot) as well as for 18 months for six conformance lots were provided. Based on the provided stability data the proposed storage condition of 24 months when stored at 2-8°C is acceptable.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for HyQvia is approvable.

2.2.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Description of post-authorisation measure(s)
REC
Improvement of the RP-HPLC assay to allow separate specifications to be set for the product-related impurities. The Applicant commits to establish these impurity acceptance limits after collecting data from the first 20 commercial lots. (REC)

2.3. Non-clinical aspects

2.3.1. Introduction

HyQvia is a dual vial unit consisting of one vial of human normal immunoglobulin 10% (IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20). HyQvia is intended for subcutaneous use in primary (e.g. congenital agammaglobulinaemia, severe combined immunodeficiency) and secondary immunodeficiency disorders. The two components of the medicinal product must be administered sequentially through the same needle beginning with the Recombinant Hyaluronidase followed by IG, 10%. The recombinant human hyaluronidase component modifies the permeability of connective tissue through the hydrolysis of hyaluronan.

Nonclinical programme

Human immunoglobulins are naturally occurring proteins with well-established safety and tolerability record. It is generally acknowledged that testing of human immunoglobulin preparations in animal models is of limited value and these limitations are also discussed in the ICH S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals CPMP/ICH/302/95, which are applicable to plasma derived products).

Nevertheless, non-clinical testing of IG 10% have been performed and focused on efficacy, safety, pharmacokinetics, toxicity and mutagenicity. Efficacy was assessed by a mouse protection test in vivo. Further evidence for efficacy of the product was provided using in vitro testing. Nonclinical safety was assessed by a series of studies in animal models. Anaphylactoid potential was investigated in spontaneously hypertensive rats (blood-pressure lowering effect) and in guinea pigs (bronchospastic effect); the thrombogenic potential was investigated in a Wessler rabbit model. Influence on vital function (cardiovascular, respiratory and blood coagulation parameters) was tested in dogs. Pharmacokinetics in rats demonstrated no difference between products and lots

tested regarding in vivo recovery and serum halflife. Toxicity testing included single-dose studies using mice and rats and a local tolerability in rabbits. Mutagenicity data – although not necessarily needed for plasmaderived products – was generated in bacteria (Ames test).

Two different manufacturing procedures have been described for the production of rHuPH20. Pharmacodynamic and pharmacokinetic studies demonstrated no significant differences between the functional activities of the enzyme preparations and established that the pharmacological properties of the two preparations of hyaluronidases are essentially equivalent. Nonclinical safety evaluation of rHuPH20 included a single dose IV study in rats, range-finding and pivotal repeat-dose toxicity study in rhesus monkeys, pivotal 6 week repeat-dose toxicity study in cynomolgus monkeys, repeat-dose local tolerance toxicity study in rats. rHuPH20(prepared with a different manufacturing process) in a 7-day repeat-dose range-finding toxicity study in cynomolgus monkeys, pivotal 39-week repeat-dose toxicity study in cynomolgus monkeys, range-finding and pivotal embryo-fetal developmental toxicity studies in mice, and pivotal perinatal and postnatal developmental toxicity study in mice. Both enzyme preparations of rHuPH20 demonstrated favorable safety to support the use of rHuPH20 as a locally acting, transiently active, permeation enhancer in SC formulations of therapeutics.
The nonclinical safety assessment of the rHuPH20 has been based in large part on recommendations provided in an FDA guidance 2005 (Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients May 2005), and is consistent with principles described by an EMA guideline 2010 (Guideline on Repeated Dose Toxicity March 2010). The pivotal non-clinical studies were conducted in accordance with the respective ICH guidance and in accordance with GLP.

The combination of IG 10% and rHuPH20 is not considered to have a different safety profile than that of the single components based on demonstrated favourable safety profiles of both components. In addition, based on the preclinical local safety assessment of the combination of IG 10% and rHuPH20, it is not anticipated that rHuPH20 has an impact on the systemic effects and safety of IG 10%. Therefore, non-clinical evaluation focused on PK and local tolerability of the combination.
The nonclinical testing strategy for IG 10% with rHuPH20 was based in large part on recommendations provided in an United States Food and Drug Administration (FDA) draft guidance (Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route. March 2008).

All pivotal nonclinical toxicity studies were conducted consistent with ICH Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations. In addition, also non-GLP studies were conducted. These non-GLP studies were not considered to compromise the scientific integrity or affect the experimental results.

Scientific advice regarding quality, pre-clinical and clinical development was given by CHMP on 19.02.2009 (EMEA/H/SA/1170/1/2009/III).

2.3.2. Pharmacology

Primary pharmacodynamic studies

IG 10%

In vitro and in vivo nonclinical studies of antibody function of IG 10% demonstrated efficacy and safety profiles for IG 10% that were comparable to two marketed IV immunoglobulin products (Gammagard S/D and Gamimune N, 10%) used as controls. Primary pharmacodynamic studies with IG 10% showed a broad spectrum of antibodies at high titres against bacteria and viruses. Opsonic activity was comparable to the reference Gammagard.

rHuPH20

The ability of rHuPH20 permeation enhancer to act as a spreading factor was tested by subcutaneous injection of the enzymes (from 0.5 to 5 U/mouse) with Trypan blue dye (50 µL) into nude mice. Bovine USP Hyaluronidase reference standard (RS) was used at the same doses as a comparator in these experiments. The USP Hyaluronidase RS and rHuPH20 hyaluronidase enzymes showed equivalent activity in vivo at concentrations of five units. Thus, rHuPH20 demonstrated capability to increase dye diffusion in nude mice temporarily and reversibly in a dose-dependent fashion. Transient action of rHuPH20 was demonstrated in the dermal barrier reconstitution assay in nude mice. The effects of rHuPH20 were reversed within 24 h after injection. These data established that the dermal barrier is reconstituted within 24 h of administration of rHuPH20 in nude mice skin. rHuPH20 does not alter vascular permeability when injected intradermally compared to 100 ng Vascular Endothelial Growth Factor (VEGF) positive control, as determined by Miles Assay (dye extravasation assay). The increase in drug dispersion facilitated by rHuPH20 permeation enhancer is limited by particle size. The results demonstrated significantly increased dispersion with particles up to 200 nm in diameter. An additional Trypan Blue dye dispersion study in nude nice was performed to evaluate the functional local activity of rHuPH20 prepared with a different manufacturing processwhen circulating levels of a rabbit anti-rHuPH20 antibody are present in the animals. It can be concluded that circulating levels of a neutralizing antibody to rHuPH20 do not affect the intradermal dispersive effects of rHuPH20 in NCr nu/nu mice as measured by mean dye dispersion area. The provided data demonstrate satisfactorily the mechanism of action and the reversibility of recombinant hyaluronidase.

IG 10% in combination with rHuPH20

In a porcine model, administration of rHuPH20 increased the dispersion and absorption of IG 10% and mitigated induration and the resulting tissue damage after administration of large volumes of IgG (c.f. section Local tolerance).

Potential effects of hyaluronidase on the biochemical properties of IG 10% could not be identified after incubation of IG with the enzyme at high concentrations. The functionality and integrity of the IgG molecules was not modified by the enzyme.

Secondary pharmacodynamic studies

IG 10%

As clinical pharmacodynamic data on IG 10%, alone are available from long-term use of the licensed Baxter product Kiovig, further non-clinical studies on secondary pharmacodynamics were not conducted.

rHuPH20

For rHuPH20, there were no secondary pharmacodynamic effects observed in safety and toxicology studies in various animal species. In fact, rHuPH20 was shown to act locally and transiently with only minimal and short systemic exposure after subcutaneous administration. Therefore, no secondary pharmacodynamic effects are expected with the application of rHuPH20.

IG 10% in combination with rHuPH20

No dedicated secondary pharmacodynamic studies were conducted with IG 10% in combination with rHuPH20, which is considered acceptable.

Safety pharmacology programme

IG 10%

Safety pharmacology studies comprised investigation of the anaphylactoid potential after intra-arterial injection in spontaneously hypertensive rats and in Guinea pigs (bronchospastic effect). Influence on vital function including cardiovascular, respiratory and blood coagulation parameters was tested in dogs. The comparison was performed between three lots of IG 10% with GAMMAGARD S/D. Anaphylactoid reactions have been observed in both species tested but were consistently comparable to that of the active control Gammagard S/D. The comparability was also consistent with other parameters such as thrombogenic potential, cardiovascular, respiratory and disseminated intravascular coagulation variables.

rHuPH20

No dedicated safety pharmacology studies were conducted with rHuPH20. Clinical observations were included as part of all in vivo nonclinical toxicity and PK studies and revealed no central nervous system-related side effects. In addition, assessment of electrocardiogram (ECG), blood pressure, and respiratory rate in the 39-week toxicity study in cynomolgus monkeys with rHuPH20 prepared with a different manufacturing process found no effects related to rHuPH20 administration. Therefore, the core endpoints of safety pharmacology testing (central nervous system, cardiovascular system, and respiratory system) have been addressed in the toxicology program.

IG 10% in combination with rHuPH20

Based on existing data with the individual constituents no additional core safety pharmacology studies of the combination have been performed. This is considered acceptable as interference of the two drugs is unlikely and the safety margins are sufficient.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with IG 10%, rHuPH20 or IG 10% in combination with rHuPH20.

The effect of high concentrations of rHuPH20 was tested on biochemical properties of IG 10% in order to identify possible effects of high amounts of hyaluronidase on the functionality and integrity of the IgG molecules and the tolerability of the preparation. Results indicate that rHuPH20 did not alter the prekallikrein activator (PKA) and amidolytic activity, molecular size distribution of IG, pH, percentage of functional intact IgG, and IgG subclass distribution

2.3.3. Pharmacokinetics

The analysis and detection of IG as well as the enzyme activity has been performed by using standard methods including nephelometric measurement or ELISAs for IgG and turbidimetric or high sensitivity assays for hyaluronidase.

Only selected aspects of ADME studies have been addressed which is acceptable due to the nature of the product.

The pharmacokinetics of solely IV administered IG 10% is well established. IG 10% pharmacokinetic study after IV administration in rat indicates bioequivalence with GAMMAGARD S/D: in vivo recovery ranged from 69.7 to 80.1 %, the alpha-phase of the half-life from 21.2 to 23.7 hours and the beta-phase from 136.7 to 166.4 hours. Data derived from rodents differ significantly from human kinetics and are therefore not predictive. Human clinical studies revealed that the median half-life of the IG was ~ 36 days after IV administration.

Studies in mice, rats, and cynomolgus monkeys demonstrated rapid clearance of hyaluronidase activity from plasma after IV administration and limited systemic exposure following ID or SC administration. Moreover, rHuPH20 activity was determined to be transient at the injection site. At the dose of rHuPH20 proposed to be administered SC in patients, measurable systemic concentrations rHuPH20 are not expected. These data indicate that the enzyme acts mainly locally, systemic distribution is very unlikely and that rHuPH20 activities were significantly lower compared to IV administration.

SC administration of IG 10% in combination with rHuPH20 did not have any impact on the kinetics of IG in rabbits, which was justified by species-specific small amounts of hyaluronic acid in the rabbit tissues. Clearer effects could be achieved in the dog model where at least the highest dose of enzyme led to significantly increased levels of plasma IgG. In this regard it is noted that data derived from clinical studies (Study 160603) clearly demonstrated that SC rHuPH20 significantly

reduces the number of required infusion sites per month from 21.43 to 1.09.

The metabolism and excretion of IG 10% is deemed to follow the pathway mediated by the neonatal Fc receptor which plays a critical role in the IgG metabolism and elimination. As per guideline ICH S6 the expected consequence of metabolism of biotechnology derived pharmaceuticals is the degradation to small peptides and individual amino acids. As the metabolic pathways are generally understood, further metabolism and excretion studies have not been performed. For the same reasons, no dedicated metabolism and excretion studies were conducted with rHuPH20. This approach is considered acceptable for a biological product.

2.3.4. Toxicology

Single dose toxicity

IG 10%

Acute toxicity studies were performed in mice and rats using IG 10% in comparison with Gammagard S/D.

In single dose toxicity studies major findings in mice included behavioural depression with or without dyspnea. Mortalities were explained by cardiac failure or lung edema as a result of volume overload. Doses at 2000 mg/kg IG 10% in rats revealed no pathological findings other than pulmonary haemorrhage which was assumed to be related to the CO_2 inhalation used for study termination.

rHuPH20

Single dose toxicity explored with a single application of 10500 U/kg to rats, led to slightly dilated renal tubules containing morphous amphophilic material with hyaline casts.

IG 10% in combination with rHuPH20

No single-dose toxicity studies were conducted with IG 10% and rHuPH20. This is acceptable in respect to the fact that the combination of IG 10% and rUhPH20 is not considered to have a different safety profile than that of the single components.

Repeat dose toxicity

IG 10%

Considering the clinical experience already gained with the marketed product and the possible antigenicity in animal studies, the absence of repeat-dose toxicity studies for IG 10% is considered acceptable.

rHuPH20

The first repeat-dose studies for rHuPH20 were performed in rhesus monkey by once weekly

peribulbar injections of the enzyme. This administration schedule was well tolerated with a NOAEL of 0.1 mg/kg BW and primarily intended to facilitate SC administration of drugs, e.g. the peribulbar injection of local anaesthetics. Data derived from PK studies indicate that rHUPH20 acts mainly locally and that systemic distribution is very unlikely. Core safety pharmacology endpoints have been integrated into these studies and did not indicate increased risk for the development of cardiotoxic events. Also a once weekly SC administration of rHuPH20 for 39 consecutive weeks to cynomolgus macaques at doses of 0.02, 0.2, and 2.0 mg/kg was not associated with any overt toxicity. The cellular infiltration at the application site was regarded as minimal. The more important finding in this study was the occurrence of rHuPH20-reactive binding antibodies as well as hyaluronidase neutralizing activity which generally increased over time. This finding was explained by a rHuPH20 sequence similarity between man and cynomolgus macaques of only 89% which might cause immunogenic responses due to foreign epitopes. These titres dropped or were undetectable over the course of the recovery period.

IG 10% in combination with rHuPH20.
No repeat-dose toxicity studies were conducted with IG 10% and rHuPH20.

Genotoxicity

As reported in the ICH S6(R1), the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. Nevertheless the Applicant performed an AMES test for IG 10% with a concentration up to 0.1 mg/plate with negative results.

Carcinogenicity

In accordance with ICH Guideline S6 (R1) standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals and therefore not required.

Reproduction Toxicity

IG 10%
No reproduction studies have been conducted. Immunoglobulin products cross the placenta, increasingly during the third trimester. However, clinical experience with immunoglobulins suggests that no harmful effects are to be expected. In addition, no adverse effects on fertility have been described so far.

rHuPH20

Fertility
Sperm plasma membrane proteins offer the theoretical possibility of immunizing either males or females and achieving a contraceptive effect (Primakoff et al, 1997). In order to clarify this aspect, several unpublished and published investigations have been conducted.

Antibodies were seen in human subjects and although no data suggesting adverse effects on fertility were noted in the applicants' data, fully effective (Primakoff et al 1988), but reversible (Primakoff et al 1997) contraception was described for the Guinea pig model. Pomering et al (2002) demonstrated that immunization of rabbits with rPH-20 did not result in infertility despite the fact that plasma anti-rPH-20 antibodies reduced the numbers of ova fertilized in vitro.

Studies by Deng et al (2001) demonstrated - by using circulating antibodies from immunized cynomolgus macaques - that circulating antibodies specifically recognized PH-20 on Western blots and were shown to bind to the surface of macaque sperm.

Therefore several aspects on reproduction have been integrated into the 39 weeks cynomolgus macaques' chronic toxicity study covering histopathology of the reproductive organs and semen analysis (sperm concentration, motility and morphology). No overt findings have been reported. In addition, an evaluation of retrospective breeding trials from female primates has been provided where no association between fertility and antibody titres was observed.

The effects of rHuPH20 and PH20 directed antibodies on reproduction have also been examined in other animal species such as mouse and sheep and did not indicate potential impact on fertility.

From a preclinical point of view there is no clear evidence that rHuPH20 (directly and/or indirectly via antibodies) has a negative impact on fertility. The available data has been summarised in a statement on non-clinical studies (including reversible effects on fertility in guinea pig) in section 5.3 of the SmPC.

Embryo-toxicity

Embryo-foetal development studies in mice demonstrated that exposure of the embryo at doses ≥ 9 mg/kg/day of the enzyme (also given SC) results in increased resorption rates which is caused by defects of the heart formation via degradation of its hyaluronic acid. A safety window of almost 400 compared to the intended human dose seems sufficient.
The provided mouse toxicokinetic data address the potential effect of circulating anti-rHuPH20 antibodies on peri-postnatal development of the offspring. Antibody exposure was demonstrated from late gestation through to adulthood. No effects on behaviour, learning and memory, or motor activity were observed.

Local Tolerance

Local tolerance studies have been performed with IG 10% in combination with rHuPH20 in different animal species. Studies in rabbits demonstrated that the effect of the IG was not enhanced by co-administration of the enzyme. The pivotal studies have been carried out in pigs.
Pre-administration of rHuPH20 mitigated adverse tissue effects which usually occur by administration of large volumes of IgG. Less local swelling and significantly reduced incidence of induration, and decreased interstitial pressure could be measured.

Other toxicity studies

- Studies on impurities

Recombinant human hyaluronidase (rHuPH20) contains small amounts of HEPES as impurity. An exposure of up to the risk reference dose (RfD) is considered to be associated with only a minimal or no risk of adverse health effects. The clinical exposure in study 160603 of 59.4 µg/m^2 for children and 88.0 µg/m^2 for adults was approximately 1000 times lower than the calculated RfD for children and adults.

2.3.5. Ecotoxicity / environmental risk assessment

According to the "Guideline on the Environmental Risk Assessment for Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 1) "Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment." It is therefore agreed that an ERA for HyQvia is not required.

2.3.6. Discussion on non-clinical aspects

Available pharmacology data for IG 10% characterised adequately the pharmacological profile of the product. Considering the experience already gained with the marketed product, the limited pharmacology studies (including safety pharmacology) are considered sufficient. In vitro and in vivo nonclinical studies of antibody function of IG 10% were performed in support of the original MAA for KIOVIG in 2004. These studies demonstrated efficacy and safety profiles for IG, 10% that were comparable to two marketed IV immunoglobulin products (GAMMAGARD S/D and GAMIMUNE N, 10%) used as controls. The data have been assessed and were finally accepted within the MA procedure in the European Union (EU) under the trade name KIOVIG on 19 January 2006 for the treatment of primary immunodeficiency (PID), secondary immunodeficiencies and certain autoimmune disorders.

Two manufacturing processes have been employed for recombinant hyaluronidase (rHuPH20). Pharmacodynamic studies demonstrated no significant differences between the functional activities of the enzyme preparations using two different manufacturing processes and established that the pharmacological properties of the two preparations of hyaluronidase are essentially equivalent. The pharmacokinetics with the two different manufacturing processes were directly compared after intravenous administration to mice. No significant difference in the PK characteristics of the two preparations was demonstrated.

rHuPH20 is a highly purified, neutral pH-active human hyaluronidase, which is a glycoprotein enzyme generated by recombinant DNA technology. The pivotal non-clinical studies were conducted in accordance with the respective ICH guidance and in accordance with GLP. Nonclinical safety evaluation of rHuPH20 included a single dose IV study in rats, range-finding and pivotal repeat-dose toxicity study in rhesus monkeys, pivotal 6 week repeat-dose toxicity study in cynomolgus monkeys, repeat-dose local tolerance toxicity study in rats. rHuPH20 (prepared with a different manufacturing process) nonclinical assessment was conducted in a 7-day repeat-dose range-finding toxicity study in cynomolgus monkeys, pivotal 39-week repeat-dose toxicity study in cynomolgus monkeys, range-finding and pivotal embryo-foetal developmental toxicity studies in mice, and pivotal perinatal and postnatal developmental toxicity study in mice.

Studies in mice, rats, and cynomolgus monkeys demonstrated rapid clearance of hyaluronidase activity from plasma after IV administration and limited systemic exposure following ID or SC administration. Moreover, rHuPH20 activity was determined to be transient at the injection site. At the dose of rHuPH20 proposed to be administered SC in patients, measurable systemic concentrations rHuPH20 are not expected.

Bibliographic data on hyaluronidase demonstrate impaired fertility in the Guinea pig model (in vivo) and inhibitory effects of plasma antibodies on in vitro fertilization (in rabbits and primates) after immunization with PH-20 sperm extract. Studies in other laboratory animals such as mouse, rabbit,

sheep, and non-human primates did not indicate potential effects on their fertility. An evaluation of retrospective breeding trials from female primates did not demonstrate an association between fertility and antibody titres. Concerning the effect of antibodies on male fertility it may be assumed that a number of physiological mechanisms including the blood-testis barrier limit the exposure of endogenous PH20.

rHuPH20 was well tolerated at all dose levels and the detected embryo-foetal toxicity at high systemic exposure levels is in line with the mechanism of action for hyaluronidase.

Additional nonclinical studies have been designed to assess the use of IG 10% in combination with rHuPH20 in various animal models. In general, the combination of IG 10% and rHuPH20 is not considered to have a safety profile different from that of the single components because rHuPH20 is acting locally with minimal, if any, systemic absorption. Thus, it is not anticipated that rHuPH20 has an impact on the systemic effects and safety of IG 10%.

The applicant has provided adequate information to support the nonclinical evaluation of recombinant HuPH20 and its proposed use together with IG 10%.

2.3.7. Conclusion on the non-clinical aspects

An appropriate nonclinical programme has been performed to support the use of IG 10% together with recombinant human hyaluronidase (rHuPH20). The presented pharmacodynamic and pharmacokinetic studies support the intended effect of modified permeability of connective tissue through the hydrolysis of hyaluronan through rHuPH20 on the absorption of IG 10%

Based on the above reported data on pharmacology and toxicity the use of rHuPH20 is supported from a nonclinical point of view. Therefore the risk for adverse effects in patients related to systemic exposure to rHuHP20 is considered very low.

From a nonclinical perspective there are no outstanding issues.

2.4. Clinical aspects

2.4.1. Introduction

HyQvia is a preparation of human normal immunoglobulin 10% (IG 10%) for administration with recombinant human hyaluronidase (rHuPH20), which is an enzyme that increases subcutaneous dispersion and absorption of the immunoglobulin. The product is intended for:

Replacement therapy in adults ($\geq$ 18 years) in primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections.

Replacement therapy in adults (≥ 18 years) in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

Applicant's clinical development program includes a pivotal and a supportive study in which the safety, tolerability, efficacy, and pharmacokinetics of IGSC, 10% with rHuPH20 were investigated in patients with PID (Studies 160602 and 160603). Applicant also conducted a study to investigate the pharmacokinetics, tolerability, and efficacy of IGIV, 10% and IGSC, 10% without rHuPH20 in patients with PID (Study 160601). Studies 170901 Part 4 and 161001 were conducted to assess safety and tolerability, infusion pressure, and flow rates in healthy volunteers.

The relevant guidelines are the "Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)" EMA/CHMP/BPWP/94033/2007 rev. 2 and for subcutaneous and intramuscular use EMEA/CPMP/BPWG/283/00 and the core SPC for human normal immunoglobulin for subcutaneous and intramuscular use EMEA/CPMP/BPWG/282/00. The Guideline and core SPC for subcutaneous and intramuscular use are currently under revision.

Scientific advice regarding clinical development was given by CHMP on 19. 02. 2009 (EMEA/H/SA/1170/1/2009/III).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A routine GCP inspection was performed at the sponsor Baxter Healthcare Corporation in Westlake Village, USA and two investigators sites, one in Dallas, USA (site 01) and one in San Francisco, USA (site 10). The inspectors did not find any major inconsistency or any indication of fraud or manipulation of documents. There was no indication that the study was not conducted in accordance with established quality standards and regulations.

- Tabular overview of clinical studies

Study No	**Study**	**No. of Subjects**	**Duration**
Study 160601	Phase I prospective open-label multi-centre study in the USA: tolerability and PK comparison of IGIV, 10% administered iv or sc in PID patients rHuPH 20 was not administered in this study, but compared with data for SCIG + rHuPH20 from study 160603	49 PID	IGIV, 10%: 12 weeks IGSC, 10% 29-53 weeks
Study 160602	Phase I/II prospective open-label multi-centre study in the USA: determination of the dose of rHuPH 20 enabling up to 600 mg/kg of SCIG 10%.	11PID	Arm 1 8-65 days Arm 2 133-165 days

	PK, safety and efficacy		
Study 160603 Pivotal	Phase III prospective open-label multi-centre study in the USA and Canada for efficacy, tolerability and PK comparison of 10% KIOVIG given iv or sc+ rHuPH20 in PID patients	81 PID	IGIV, 10%: 91.0 days IGSC, 10% with rHuPH20 after ramp-up: 366.0 days
Study 170901	A Phase 1 randomized, double blind, controlled study of IGSC administered either alone or in combination with rHuPH20 for safety, tolerability, and optimal rHuPH20-to-IGSC dose ratio in healthy volunteers. Safety and tolerability.	12 healthy subjects	1-3 weeks
Study 161001	A Phase 1 prospective, randomized, within-subject/ between subjects, placebo-controlled, single-centre study in USA for the evaluation of the effectiveness rHuPH20 in enhancing the IGSC 10% in healthy volunteers	53 healthy subjects	1 day (2 infusions)
Study 160902 extension study of 160603	18/48 were converted to a 2 week schedule for exploratory reasons only; **not due to lack of efficacy or to safety concerns**	48 PID patients	

Supportive studies for rHuPH20 were also submitted in the form of synopses and short summaries; they encompass:

R04-0851, a Phase I study; HZ2-05-04 (INFUSE-LR), a Phase IIIb study performed in healthy volunteers to address safety and PK; and studies INFUSE I +II (Study 1838-003 + Study HZ2-08-03), which were performed in children mainly address safety issues and the efficacy of SC rehydration enhanced by rHuPH20.

2.4.2. Pharmacokinetics

Several studies have been addressing the pharmacokinetic evaluation of the preparation. 160601, 160602, 160603 were studies conducted in PID patients divided in two age subgroups (<12, ≥12 and adult). Study 170901 and study 161001 included adult healthy volunteers.

Absorption / Distribution / Elimination

Study 160601(Phase I) was designed to evaluate comparability of IGIV 10% administered IV or SC without the use of rHuPH20 in PID patients. PK equivalence in terms of AUC 0-t/week following IV administration and SC administration of IGIV 10% at an Adjusted/Individually Adapted Dose in was demonstrated within the predetermined margins of equivalence of 80% to 125% in patients ≥12 and adult. The median ratio of the SC dose administered compared to IV administration was 137.3% (range 125.7% to 150.8%), whereby the mean weekly equivalent of the dose administered IV was 133.2 (±36.9) mg/kg, thus, adjustments during SC treatment resulted in a mean weekly SC dose of 182.6 (±48.4) mg/kg.

Bioavailability of IgG in subjects aged 2 to <12 years was determined in terms of trough levels. Median trough levels in the 2 -12 age category of the Full Analysis Data Set (FADS) ranged from 10.10 g/L - 11.50 g/L after IV administration in 3-week intervals, from 9.08 g/L - 10.50 g/L after IV administration in 4-week intervals, and from 11.20 g/L - 13.60 g/L after weekly SC administration. For the age group of >12 years median IgG trough levels (excluding the first SC administration 1 week after the last IV dose in Study Part 1) ranged from 11.05 g/L -14.00 g/L after IV administration in 3-week intervals and from 10.15 g/L - 10.80 g/L after IV administration in 4-week intervals. After weekly SC administration, IgG trough levels ranged from 12.70 g/L - 13.60 g/L for the age group of 12 years and older. These trough levels are all high and fulfil the requirements of the IVIG (EMA/CHMP/BPWP/94038/2007 rev. 3) core SmPC, where trough levels of 5-6 g/L should be achieved.

Study 160602 (Phase I/II) was designed to investigate the administration of half or a full 4-week IVIG dose subcutaneously in a single SC site evaluating tolerability after priming with rHuPH20. The ratio of geometric means for the AUC obtained between IV and SC infusion of IGIV, 10% was 92% (90% CI: 85% to 100%). This indicates that SCIG + rHuPH20 and IVIG may show comparable bioavailability, however, in view of the low sample size and the fact that the study design did not allow for subjects to reach steady state before the actual PK studies, no final conclusions can be drawn.

The median AUC was similar after IV vs. SCIg administration (389.5 vs 369.6 days*g/L). As expected with SCIg, the median Cmax was lower after SC than after IV infusion (16 g/L vs. 24 g/L) while the median time to reach Tmax was longer (5 days vs. 0); clearance and Cmin after SC infusion were similar to the values calculated after IV infusion. For the full SCIG dose a mean 2.9 hours (range: 1.8 – 4.3 h) were required.

IgG trough levels were similar and adequately high after a 4-week IV dose to a 4-week SC dose + rHuPH20. Trough levels after SC + rHuPH20 ranged from 7.84 - 12.92 g/L, after IV infusions they ranged from 8.83 - 13.20 g/L. The minimum dose of rHuPH20 necessary to enhance the SC doses was determined to be 50 U/g IgG.

Study 160603 (pivotal Phase III study) was designed to evaluate safety and efficacy and PK data were collected and compared to those in study 160601. PK equivalence was demonstrated in subjects aged ≥ 12 years with respect to AUC0-t of IgG for SC administration + rHuPH20 at an adapted dose and for IV administration. The ratio of AUC0-t for SC infusions with rHuPH20 and IV infusions was 93.3% (90% CI of 91.4% to 95.2%). Similar results were obtained in SC-naïve subjects (93.9% [90% CI: 91.1; 96.8]). The median ratio of IgG trough levels for SC infusions + rHuPH20 to IV infusions was 103.8% (95% CI: 97.5%; 115.4%) in subjects aged 2 to <12 years,

and 98.5% (95% CI: 94.4%; 102.5%) in subjects aged ≥ 12 years. Comparable results were obtained in SC-naïve subjects. The median IgG trough levels were all well above those recommended in the current IVIg Guideline of 5-6 g/L. The bioavailability of IGSC 10% with respect to AUC per dose/kg was approximately 20% higher when administered SC + rHuPH20 (in Study 160603) than SC without rHuPH20 (in comparison to Study 160601).

Study 170901 (Phase I) was designed to study tolerability of flow rates, in line pressure and dosing of rHuPH20. It was performed in healthy volunteers. The SC infusions were completed with the full dose delivered at a single infusion site; no clear pattern emerged for in-line pressure between infusions that were pre-administered with rHuPH20 as compared to the buffer control. Total volumes infused were similar for IGSC 10% infusions that were pre-administered rHuPH20 or control for both the 0.3 g/kg (~ 250 mL) and 0.6 g/kg (~500 mL) dose groups. Infusion rates were seen to increase from 10 mL/h to 300 mL/h in approximately 10 minute intervals with mild or occasionally moderate local AEs. For the 0.3 g/kg group in 12 subjects the mean infusion time was 1.35 hours (SD 1.28; 1.41); for the 0.6 g/kg group in 10 subjects the mean infusion time was 2.2 hours (SD 2.1, 2.3)

Infusion times did not differ between infusions that were pre-administered with rHuPH20 as compared to the buffer control. Thus, "enhancement" via rHuPH20 is not shown in this study.

Study 161001(Phase I) was conducted in order to assess the effectiveness of rHuPH20 (75 U/g IgG) in facilitating the gravimetric delivery SC infusion of IGSC 10%. The placebo control for the IGSC 10% was a 0.25% human albumin solution and the placebo "enhancer" was lactated Ringer's (LR) solution. Conclusion from the data in 53 healthy volunteers suggest that rHuPH20 pre-administration does not enhance the SC administration of IGSC 10% in terms of time to complete infusions and flow rates when compared to the placebo control with lactated Ringer's (LR) solution.

rHuPH20

The systemic exposure to rHuPH20 is considered very low due to the low dose of rHuPH20 administered subcutaneously and a short plasma half-life of less than 5 minutes. The subcutaneous (SC) dose of rHuPH20 used to facilitate the dispersion and absorption of IGSC, 10% is 0.000625 mg/kg body weight (based on a dose of 1 g/kg IGSC 10% and rHuPH20 of 75 U/g of IGSC 10% and rHuPH20 120,000 U/mg). This low dose of rHuPH20 is expected to be cleared from the SC space without measurable systemic exposure. Assuming the worse-case scenario that the entire 0.000625 mg/kg rHuPH20 dose was delivered IV, PK modelling predicts plasma concentrations < 3 U/mL. Consequently, significant drug exposure to rHuPH20 was not anticipated, and patient blood sampling for plasma rHuPH20 was not considered justifiable.
Furthermore, in a recent publication that compared the SC and IV administration of trastuzumab, plasma samples from 58 human subjects who received SC trastuzumab (formulated with 2,000 U/mL rHuPH20) were analysed for rHuPH20 (0.5, 1, and 24 hours post dose). Plasma concentrations of rHuPH20 were below the limit of quantification (0.3 U/mL, approximately 3 ng/mL) at all-time points (Wynne, J. Clin. Pharmacol. 2013; 53(2):192-201).

With respect to clearance/apparent clearance in Studies 160601, 160602 and 160603, the pooled result for IGSC, 10% with rHuPH20 was 1.53 mL/kg/day (95% CI: 1.40; 1.68), which is comparable to the clearance for IGIV, 10% of 1.37 mL/kg/day (95% CI: 1.24; 1.41), but lower than the result of 2.00 mL/kg/day obtained for IGSC, 10% alone (95% CI: 1.84; 2.12).

In Study 160603, the terminal half-life was longer for IGSC, 10% with rHuPH20 than IGIV 10%; the median values were 45.3 days (95% CI: 41.0; 60.2) for IGSC, 10% with rHuPH20 and 35.7 days for IGIV, 10% (95% CI: 32.4; 40.4)

A longer half-life than with IV administration and a clearance comparable with IV administration were observed for SC administration with rHuPH20. These characteristics support the feasibility of a 3- or 4-week infusion schedule.

IgG and IgG complexes are broken down in cells of the reticuloendothelial system.

In summary, in the table below, 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.

Pharmacokinetic Parameters of HyQvia Compared to Intravenous Administration of IG, 10%		
Parameter	**HyQvia Median (95% CI) N=60**	**IVIG, 10% Median (95% CI) N=68**
C_{max} [g/l]	15.5 (14.5; 17.1)	21.9 (20.7; 23.9)
C_{min} [g/l]	10.4 (9.4 to 11.2)	10.1 (9.5 to 10.9)
AUC per week [g*days/l]	90.52 (83.8 to 98.4)	93.9 (89.1 to 102.1)
T_{max} [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)

Special populations

Subgroup Pharmacokinetic parameters analysis in elderly demonstrates that their PK values are comparable to the characteristics in the whole study population.

Pharmacokinetic interaction studies

Dedicated studies to address pharmacokinetic interaction study have not been performed.

Pharmacokinetics using human biomaterials

Dedicated studies to address pharmacokinetic using human biomaterial have not been performed.

2.4.3. Pharmacodynamics

The pharmacodynamic effect of HyQvia and other IVIgs or SCIgs in replacement therapy is based on the fact that human normal immunoglobulin contains a broad spectrum of opsonising and neutralizing IgG antibodies against infectious agents that are present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Thus, adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range.

Recombinant Human Hyaluronidase is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan and thus facilitates the dispersion and absorption of IG 10%; it is not assumed per se to affect the therapeutic effect of immunoglobulins in replacement therapy, rather the effects pertain to the PK of the product.

No specific pharmacodynamic studies are required.

2.4.4. Discussion on clinical pharmacology

The applicable guideline on Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use requires that for the PK evaluation of a new SCIG trough levels should be determined from at least 15 patients with hypo- or agammaglobulinemia. These values should be comparable with trough values following treatment with the previous product.

In the pivotal study 160603 trough levels were compared after 3 months of IVIG treatment with the levels after ~14 months of SCIG treatment with rHuPH20 for 11 subjects aged 2 to < 12 years of age and 70 subjects aged 12 years and older (FADS), showing similar values for both treatment modalities. Thus the basic pharmacokinetic requirements according to the guideline were exceeded. Furthermore, for subjects aged 12 or older, bioequivalence with respect to AUC0-T for IG 10% administered IV or SC at an adapted dose could be shown.

In addition, for subjects aged 12 years or older, IgG subclass distribution, levels of specific antibodies, AUC, Cmax, Tmax, terminal half-life and clearance were determined in both study 160603 and 160601. The totality of data gives a good overview of the PK characteristics of IG 10% infused after rHuPH20 facilitation in comparison to IG 10% infused IV or SC without rHuPH20 (study 160601). The main clinically relevant PK parameters like AUC, IgG subclass distribution, levels of specific antibodies are comparable between the different treatment modalities. PK equivalence was shown at SC doses 137% of the weekly-equivalent IV doses. Adequately high IgG trough levels were achieved under SC administration of IGIV10% (without rHuPH20). At an SC dose 108% of the weekly equivalent IV dose, PK equivalence was demonstrated in this Phase 3 study for IGIV 10% SC administration + rHUPH20 (75 U/g IgG) compared to the IV administration route.

Furthermore, based on data from preclinical studies and clinical studies with trastuzumab/rHuPH20, systemic exposure to rHuPH20 is expected to be extremely low for subjects administered with HyQvia SC

2.4.5. Conclusions on clinical pharmacology

PK parameters of SC infusion of IG 10% after facilitation with rHuPH20 are similar to those achieved after IV infusion of IG 10% and thus could support the feasibility of infusing 3- or 4-week doses of IG 10% subcutaneously in patients.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Study 160602 – rHuPH20 dose finding study

Study 160602 was a prospective, open-label, non-controlled, two-arm multicenter study in subjects with PID aged 16 years or older with the aim of determining the dose of rHuPH20 necessary to infuse a full 4-week dose, i.e. up to 600 mg/kg BW of IgG in a single SC site with good tolerability. If a subject was to receive more than 600 mg/kg BW/4 weeks, a second infusion site was to be used for administration of IGIV 10% with the appropriate amount of rHuPH20. This was not considered a treatment failure.

In Study Arm 1, 4 adult/adolescent subjects were to receive only SC infusions of IGIV, 10% to determine tolerability. In Study Arm 2, 7 subjects initially were scheduled to receive an IV infusion of IGIV, 10% to determine pharmacokinetics over the ensuing 4 weeks. After completion of the PK evaluation, the subjects received another 4-week dose of IGIV, 10% intravenously. The first SC infusion was administered 1 week after the second IV infusion. Once a full 4-week dose could be infused subcutaneously in a single infusion site, the same dose was repeated and a second PK evaluation was conducted.

This study was conducted using a formulation containing 150 U/ml rHuPH20 for the initial infusions. Then a more concentrated preparation containing 1,500 U/mL in the same buffer was used for subsequent infusions to reduce the volume to be infused.

9 from 11 subjects were able to tolerate the full IG dose with no more than mild ADRs.

In study160602, the ratio of units (U) of rHuPH20 per gram IgG that allowed for administration of large quantities of immunoglobulin was determined. The IgG dose escalation/de-escalation schedule, as per protocol, involved a decrease in the ratio of rHuPH20 to IgG if a SC infusion of IGIV, 10% was tolerated. Data on large immunoglobulin doses obtained from Study 160602 showed that a mean dose of 68 U of rHuPH20/g IgG preceded tolerated SC infusions of three quarters of a full 4-week dose (minimum 66 U/g, maximum 72 U/g) and a mean dose of rHuPH20 of 51 U/g IgG preceded tolerated SC infusions of a full 4-week SC dose of IGIV, 10% (minimum 49 U/g, maximum 51 U/g). When a smaller dose of 25 U/g IgG was attempted, the infusions were not adequately tolerated. Thus, 50 U/g was considered to be the minimum amount of rHuPH20 for a successful infusion.
For Phase III, a dose was chosen that was within the well tolerated range and would provide sufficient margin to ensure that infusions would be consistently well tolerated regardless of potential individual variability. Therefore, a dose of 75 U/g IgG was chosen to be used in the Phase III study 160603. This is approximately 0.37 micrograms per kg for a dose of 0.5 grams IgG/kg or 26 micrograms of rHuPH20 for a 70 kg adult. The amount of rHuPH20 is more than 1,000- fold below the NOAEL in the preclinical studies presented elsewhere in the submission. It also is only 0.5 to 10% of the amount per gram that has been used in clinical trials where the rHuPH20 is co-formulated with the IgG or other drugs (Wynne et al, 2012, *The Journal of Clinical Pharmacology* XX(X) 1–10). The actual use of a higher concentrated rHuPH20 preparation than in study 160602, 150 U/mL versus 160 U/mL in 160603, represents a difference of less than 10 nanograms/mL of

rHuPH20 and is not considered to have any clinical consequence as it had no influence on the administered total amount of enzyme, but only the volume that had to be administered with it. A higher concentration was used to allow higher doses of rHuPH20 to be used, if necessary, without necessitating large volumes to be injected.

2.5.2. Main study

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"

Methods

The planned study duration was 17 months for each subject (3 months for stage 1 and 14 months for stage 2). Subjects who had completed study 160601 (IG, 10% IV and SC) were enrolled into study arm 2 and could proceed directly to stage 2, all other subjects were enrolled into study arm 1 and started treatment with stage 1.

Stage 1(also referred to as Epoch 1) consisted of IV treatment with IG, 10% for 12 weeks at the same dose and frequency each subject received prior to the study start. In subjects who had received prior SC treatment at mean intervals of 5 to 16 days, IV treatment in stage 1 was administered at an interval of 3 or 4 weeks at the discretion of the investigator, and the dose was to be based on the weekly equivalent of SC treatment. If body weight changed by >5% the dose was to be adjusted accordingly. During this stage, a PK assessment was performed. Serum trough levels of IgG >4.5 g/L had to be maintained throughout the study; if levels fell to ≤ 4.5 g/L, the dose was to be adjusted and trough levels re-evaluated at the next infusion. Any changes to the treatment regimen were to be recorded. An initial infusion rate of 0.5 mL/kg BW/h was to be used and increased as tolerated to a maximum rate of 5.0 mL/kg BW/h, at the discretion of the investigator. If a subject experienced an AE of at least moderate severity, the infusion rate was to be reduced to the rate immediately below that at which the AE occurred. If the AE resolved in response to this rate reduction, the infusion was to continue at the adjusted rate for the remainder of the infusion. If the AE continued, the infusion was to be stopped and the AE treated in accordance with the standard of care at the investigative site. The infusion was permitted to be restarted at a lower rate once the AE had resolved. In the case of hypersensitivity reactions (ie, urticaria, low blood pressure, angioedema or wheezing), the infusion was to be stopped immediately and treated according to the standard of care at the investigative site. Total dose for each infusion and any changes in infusion rates were to be recorded. Following the PK assessment, a final 4-week or 3-week dose of IG, 10% was administered and 1 week later, study stage 2 (SC treatment) was to begin.

In stage 2 (also referred to as Epoch 2), all subjects were to be treated SC with IG, 10% at a dose of 108% of the IV dose utilized during Study stage 1 of this study or in Study 160601. The value of 108% was derived from pharmacokinetic data from Study 160602. Prior to each SC infusion, rHuPH20 was to be administered at a minimum dose of 75 U/g IgG.

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 the increasing volume administered SC. The aim was to treat subjects SC at the same intervals (ie, every 3 or 4 weeks) that they had been treated IV before the study.
When a subject reached steady-state at a SC interval equal to the IV interval (after 3 or 4 SC infusions at 4- or 3-weeks intervals, respectively), the IgG trough level (SCIgG) was to be reviewed and compared to the trough level determined during IV treatment (IVIgG). If the trough level ratio was not within 15% of the expected value of 108%, the dose was to be corrected, using the formula:

Dose corrected = Dose*(1+(1.08-SCIg/IVIg)/2) for the next infusion. If the results of the trough adjustment were delayed, dose adjustment was allowed to take place at the subsequent infusion. The IgG trough level achieved with the corrected dose was to be reviewed after 2 infusions. If not within 93% and 123%, a second correction step was to be applied. In this manner, treatment of subjects with a sub-optimal dose for a prolonged time was prevented.

Study Participants

A total of 89 subjects were enrolled into one of 2 study arms, of which 87 were treated, 81 patients were in the Full Analysis Data Set (FADS); 74 in Per-Protocol Analysis Data Set.

Inclusion criteria

1. Subject was 2 years or older at the time of screening
2. Written informed consent was obtained from either the subject or the subject's legally acceptable representative prior to any study-related procedures and study product administration
3. Subject had been diagnosed with a PID disorder requiring antibody replacement as defined by WHO criteria
4. Subject had completed or was about to complete Baxter Clinical Study Protocol No. 160601 or had been receiving a regular IGIV-treatment at mean intervals of 21 ± 3 days or 28 ± 3 days, or SC at mean intervals of 5 to 16 days, over a period of at least 3 months prior to enrollment at a minimum dose of 300 mg/kg body weight (BW)/4 weeks
5. Subject had a serum trough level of IgG > 4.5 g/L at the last documented determination
6. If female of childbearing potential, subject presented with a negative urine pregnancy test and agreed to employ adequate birth control measures for the duration of the study.
7. Subject was willing and able to comply with the requirements of the protocol.

Exclusion criteria

1. Subjects positive at enrolment or screening for one or more of the following: HBsAg, PCR for HCV, PCR for HIV-1

2. Subjects with levels of ALT or AST >2.5 times the upper limit of normal for the testing laboratory
3. Subjects with neutropenia (defined as an ANC $\leq$ 1,000/mm^3)
4. Subjects with serum creatinine levels greater than 1.5 times the upper limit of normal for age and gender
5. Subjects with malignancy other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix
6. Subjects with a history of thrombotic episodes (deep vein thrombosis, myocardial infarction, cerebrovascular accident)
7. Subjects with abnormal protein loss (protein losing enteropathy, nephritic syndrome, severe lung disease)
8. Subjects with anemia that would preclude phlebotomy for laboratory studies
9. Subjects who received any blood or blood product other than an IGIV, SC immunoglobulin, immune serum globulin (ISG) preparation, or albumin within the 6 months prior to study enrolment
10. Subjects with an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IGIV, SC immunoglobulin, and/or ISG infusions
11. Subjects with immunoglobulin A (IgA) deficiency and known anti-IgA antibodies
12. Subjects receiving antibiotic therapy for the treatment of infection within 7 days prior to enrolment
13. Subjects participating in another clinical study involving an investigational product or device - with the exception of Baxter Study 160603 – within 28 days prior to study enrolment
14. Subjects with bleeding disorders or who were on anti-coagulation therapy
15. Subject had total protein >9 g/dL and subjects with myeloma, macroglobulinemia (IgM) and paraproteinemia
16. Subject had a known allergy to hyaluronidase
17. If female, subject was pregnant or lactating at the time of study enrolment
18. Subject had participated in another clinical study and had been exposed to an investigational product (IP) or device within 2 weeks prior to study enrollment (exception: Baxter Study No. 160601) or was scheduled to participate in another non-Baxter clinical study involving an IP or device during the course of this study
19. Severe dermatitis that would have precluded adequate sites for safe product administration

Treatments

IG 10% was supplied in vials of 2.5g, 5g, and 10 g labelled according to the valid regulatory requirements for clinical studies. Storage at 2 to 8°C (36° to 46°F) for a maximum of 36 months was recommended; the product was not to be frozen.

Prior to use, IG 10% vials were to be removed from refrigeration and placed at room temperature for approximately 90 minutes to equilibrate and kept at room temperature during administration. The product was to be inspected visually for particulate matter and discoloration prior to administration and was not to be used if particulate matter and/or discoloration was observed. Only clear or slightly opalescent and colourless or pale yellow solutions were to be administered. The use of an in-line filter was optional. If IG 10% was pooled in a bag, it had to be used as soon as possible, but no longer than 3 hours from the time of pooling.

rHuPH20 was supplied as a single-dose glass vial of 400U/vial for the 2.5 mL fill size and 800U/vial for the 5 mL fill size. The study product was labelled according to the regulatory requirements for clinical studies. Storage at 2° to 8°C (36°to 46°F) was recommended.

Objectives

The *primary objective* was to evaluate the efficacy of IG 10% administered via the SC route after an administration of rHuPH20 in preventing serious bacterial infections in subjects with PID. The *secondary objectives* of the study, in addition to further efficacy assessments, were to evaluate the tolerability of IG 10% and rHuPH20 administered via the SC route. The *exploratory objectives* were to assess quality of life aspects, comparing SC treatment with and without rHuPH20 and IV treatment.

Outcomes / endpoints

The *primary endpoint* was the validated acute serious bacterial infection rate (VASBI), defined as the mean number of validated acute serious bacterial infections per subject per year in the intent-to-treat population.

Acute serious bacterial infections included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognised bacterial pathogen.

The annual rate of all infections, monthly rate of days off school/work, on antibiotics, acute physician visits and in hospital were to be calculated per subject

Exploratory Endpoints:

Quality of life, treatment satisfaction and preference were to be measured in all the subjects:

- Quality of life was to be measured prior to the first SC infusion of stage 2 and at the End-of-Study Visit. The SF-36 was to be used in subjects age 14 and older. In subjects age 2 to 13, Quality of life was to be assessed using the PEDS-QL.7 A parent or primary caregiver was to complete the PEDS-QL on behalf of the subject if under 8 years old.
- Treatment satisfaction was to be measured prior to the first SC infusion of stage 2 and at the End-of-Study Visit using the Life Quality Index (LQI). Subjects 14 years and older were

to complete the LQI on their own, while subjects under age 14 were to have the LQI completed by a parent or primary caregiver.

- Treatment preference questions were to be administered at the End-of-Study Visit to all the subjects in the study. For subjects under 14 years of age, a parent or primary caregiver was to answer on their behalf.

Sample size

It was calculated that with 80 patients and an assumed yearly rate of 0.7 new serious bacterial infections per patient a one-sided test with a type I error of 0.01 would have about 80% power to exclude an annual serious bacterial infection rate $\geq$ 1.

Randomisation

This was a prospective, open-label, non-controlled study. Due to the uncontrolled study design, no randomisation was possible. Subjects were to be enrolled into one of 2 study arms (i.e. cohorts):

- Study Arm 1 comprised subjects who previously participated in the Clinical Study 160601.

- Study Arm 2 comprised all other subjects

Blinding (masking)

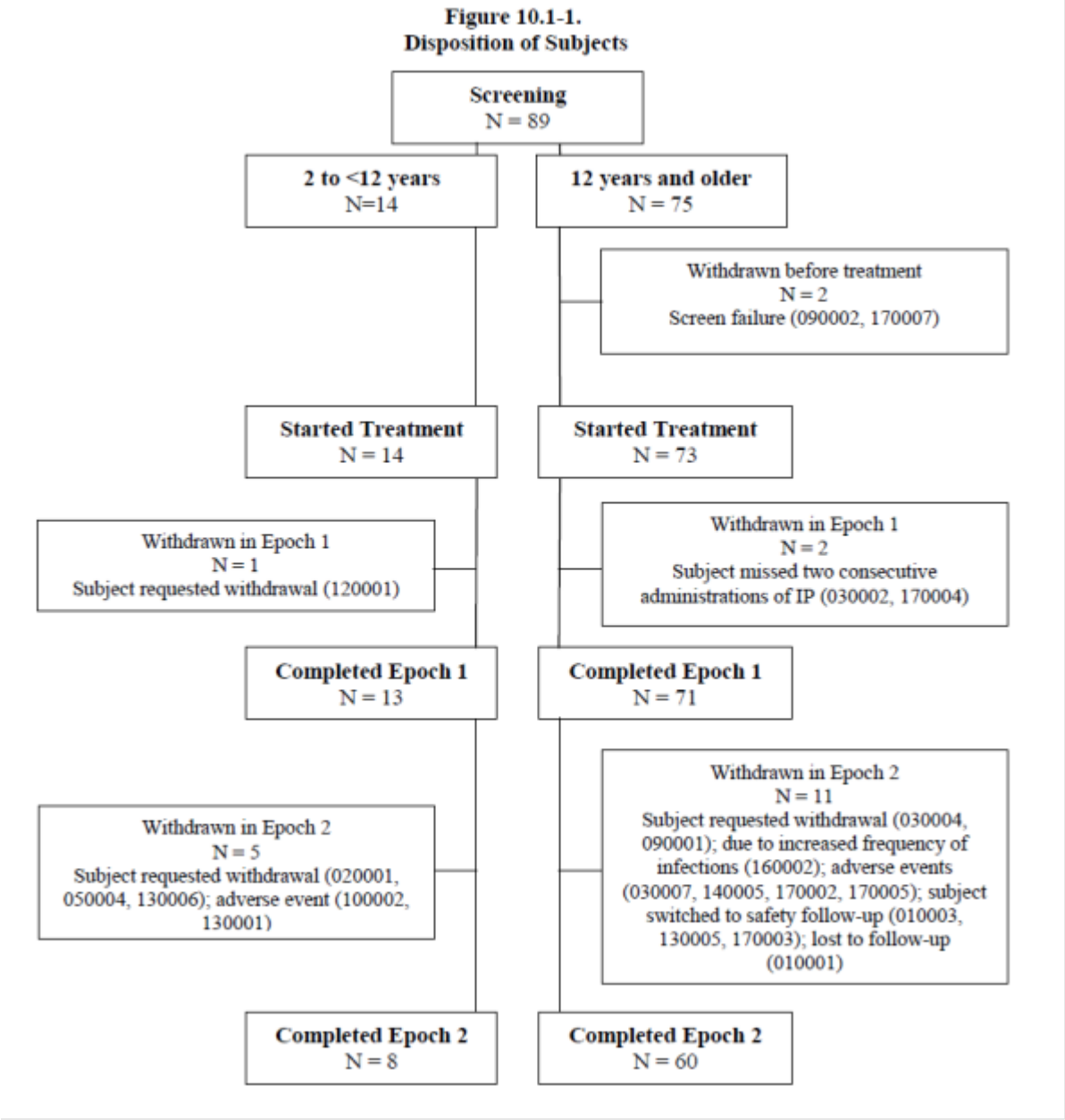
Study160603 was performed open label.

Statistical methods

The method of analysis for the primary endpoint was based on a Poisson model. A generalized linear model assuming the Poisson distribution for the number of validated acute serious bacterial infections (VASBI) with the logarithm as link function was used. Two sensitivity analyses for the rate of infections was performed to address the potential effects of subjects not completing the full year of SC treatment.
Monthly rates of days off school/work, days on antibiotics, and days in hospital were calculated per subject. Point estimates and 95% CIs for the monthly rates were calculated using a Poisson model and the same methodology including allowance for over-dispersion as described for the primary endpoints. Monthly rates of acute physician visits were calculated per subject. Point estimates and 95% CIs for the monthly rates were calculated using a Poisson model and the same methodology including allowance for over-dispersion as described for the primary endpoints.

Results

Participant flow



Overall, 16/87 subjects (18.4%) withdrew or were discontinued from the study, whereby 7 requested withdrawal and 6 withdrew due to AEs (6.8%); 3 subjects reduced their participation to safety follow-up only.

Recruitment

Initiation (first subject in): 18 Dec 2008

Completion (last subject out): 11 Nov 2010

Total study duration: approximately 1 year and 11 months

Conduct of the study

Three Amendments were made to the original study Protocol (Version 23 Sep 2008).

Significant non-compliance was detected at Site 11. A sponsor audit and an inspection by the FDA (22 Feb 2011-02 Mar 2011) identified significant departures from Good Clinical Practice at Site 11, resulting in discussions regarding whether to censor the data from this site (n=6). However, exclusion of these data from the analyses would have introduced bias in Baxter's favour. Therefore, the data from Site 11 were included in all analyses.

A total of 15 major protocol deviations were reported during the study. The most common major deviations were administration of an incorrect dose (n=7) and failure to conduct PK assessments (n=4). In addition, 1 subject violated an inclusion criterion, 1 received IG 10% from an incorrect lot, 1 received rHuPH20 approximately 3 weeks after its expiration date, and for 1 subject a dose adjustment due to insufficient serum IgG trough levels was not conducted at the next infusion, but at the second infusion following the identification of low trough levels. Subjects were not excluded from the per-protocol analysis due to major protocol deviations.

Baseline data

Common variable immune deficiency (CVID) was the most commonly diagnosed PID (49/87 subjects), followed by hypogammaglobulemia (17/87 subjects) and X-linked agammaglobulinemia (6/87). In the SNDS, the most frequently diagnosed PIDs were CVID (24/44 subjects), hypogammaglobulemia (7/44), and IgG subclass deficiency (4/44).

Subjects were distributed evenly by gender. The majority of subjects (79/87; 90.8%) were white; 2 (2.3%) were black/African American, 3 (3.4%) were Asian, 1 (1.1%) was American Indian or Alaskan Native, and 2 (2.3%) were of multiple race. With respect to ethnicity, 8/87 (9.2%) of subjects were Hispanic or Latino. The median age was 35.0 years (range: 4-78 years). The median height and weight were 165.0 cm (range: 94.0-193.0 cm) and 63.8 kg (range: 15.0-135.9 cm), respectively. Similar demographic characteristics were observed in the 44 subjects who were naïve to SC IgG before the study (SNDS), except that no black/African American, American Indian or Alaskan Native subjects were included in this data set.

Numbers analysed

The following data sets were analysed:

- Full Analysis Data Set (FADS; n=81): All subjects who had been exposed to either or both study drugs and who provided data for the primary endpoint for any period of time.
- Per-Protocol Data Set (PPADS; n=74): A subset of the FADS including only subjects who completed at least 6 months of SC treatment after the ramp-up.
- Safety Analysis Data Set (SADS, n=87): All subjects exposed to either or both study drugs.

- Subcutaneous Immunoglobulin Naïve Subjects Data Set (SNDS; n=44): Subjects who had not previously been exposed to immunoglobulins by the SC route.

The numbers of eligible subjects in each data set by age group (2-<12 years and ≥ 12 years) are provided in Table 14.1-1. The numbers of subjects in each data set who completed study stages 1 and 2 are shown in Table 14.1-3.

Table 14.1-1.
Subjects Who Were Eligible to Participate in the Study According to the Inclusion/Exclusion Criteria (Study 160603)

Analysis Set	Age Group	n of N (%)
Safety Analysis Set	Subjects aged 2 to <12 years	14 of 14 (100.0%)
	Subjects aged 12 years and older	72 of 73 (98.6%)
	Total	86 of 87 (98.9%)
Full Analysis Set	Subjects aged 2 to <12 years	11 of 11 (100.0%)
	Subjects aged 12 years and older	69 of 70 (98.6%)
	Total	80 of 81 (98.8%)
Per-Protocol Analysis Set	Subjects aged 2 to <12 years	9 of 9 (100.0%)
	Subjects aged 12 years and older	64 of 65 (98.5%)
	Total	73 of 74 (98.6%)
SCIG Naive Subjects Analysis Set	Subjects aged 2 to <12 years	5 of 5 (100.0%)
	Subjects aged 12 years and older	38 of 39 (97.4%)
	Total	43 of 44 (97.7%)

Table 14.1-3.
Subjects Who Completed Study Epoch 1 and 2 (Study 160603)

Analysis Set	Age Group	Study Epoch 1 n of N (%)	Study Epoch 2 n of N (%)
Safety Analysis Set	Subjects aged 2 to <12 years	13 of 14 (92.9%)	8 of 14 (57.1%)
	Subjects aged 12 years and older	71 of 73 (97.3%)	60 of 73 (82.2%)
	Total	84 of 87 (96.6%)	68 of 87 (78.2%)
Full Analysis Set	Subjects aged 2 to <12 years	11 of 11 (100.0%)	8 of 11 (72.7%)
	Subjects aged 12 years and older	70 of 70 (100.0%)	60 of 70 (85.7%)
	Total	81 of 81 (100.0%)	68 of 81 (84.0%)
Per-Protocol Analysis Set	Subjects aged 2 to <12 years	9 of 9 (100.0%)	8 of 9 (88.9%)
	Subjects aged 12 years and older	65 of 65 (100.0%)	60 of 65 (92.3%)
	Total	74 of 74 (100.0%)	68 of 74 (91.9%)
SCIG Naive Subjects Analysis Set	Subjects aged 2 to <12 years	4 of 5 (80.0%)	1 of 5 (20.0%)
	Subjects aged 12 years and older	38 of 39 (97.4%)	29 of 39 (74.4%)
	Total	42 of 44 (95.5%)	30 of 44 (68.2%)

Outcomes and estimation

Serious bacterial infections (SBIs)

Two validated acute serious bacterial infections (one each in Subjects 010010 and 060001) were reported during the prospectively planned observation period, which began with the day of the first SC infusion at the final infusion interval after the ramp-up. In addition, 1 validated acute serious bacterial infection occurred during the ramp-up (in Subject 110005), which was not included in the observation period.

The rate of acute SBIs per year during SC administration of IGIV 10% with rHuPH20 was 0.025, (upper limit of the one-sided 99% CI of 0.046), in SC-naïve subjects it was 0.000, (upper limit of

the one-sided 99% CI of 0.130), both when considering the observation period only. When the ramp-up was included the rate of acute SBIs per year during SC administration of IGIV 10% with rHuPH20 was 0.03, with an upper limit of the one-sided 99% CI of 0.06. In all three cases, the rate of SBIs year was significantly lower than 1.0 ($p<0.0001$).

All infections

The point estimate of the annualized rate of all infections was lower during SC administration with rHuPH20 at the final infusion interval (2.97 [95% CI: 2.51; 3.47] compared to IV infusions (4.51 [95% CI: 3.50; 5.69]). When the ramp-up was included the estimated rate of all infections was 3.09 [95% CI: 2.61; 3.63] per year under SC administration with rHuPH20.

The monthly rate of days off school/work, on antibiotics, acute physician visits and in hospital per subject was similar in the SC and IV groups.

Quality of life, treatment satisfaction and preference

QoL, treatment satisfaction and preference were evaluated as exploratory endpoints. QoL was evaluated by mode of administration (SCIG + rHUPH20, SCIG without rHuPH20 and the IV route). Quality of life assessment in subjects aged 2-7 years (by parents) and 8-13 years was the Paediatric Quality of Life Inventory (PEDS-QL) questionnaire. In subjects aged 14 years and over, quality of life was assessed using the SF-36 6 survey. All scores were transformed to a scale of 0- 100, higher scores indicating better quality of life.

Similar QoL was achieved for all 3 routes. The median total scores were comparable for SC administration with rHuPH20, SC administration without rHuPH20 (in Study 160601), and for IV infusions either in young subjects (subgroups 2-7 and 8-13 year) or in subject aged 14 years and over. Higher median total scores were observed in subjects who were previously naïve to SC IgG.

	SC administration with rHuPH20	SC administration without rHuPH20 (in Study 160601)	IV infusions
2-7 years	88.04	71.43	78.26
SC-naive	96.88	97.83	78.26
8-13 years	78.26	70.65	83.15
SC-naive	79.35	n.a.	83.15
≥ 14 years mental component	52.26	53.74	51.17
≥ 14 years physical component	44.76	47.52	44.65

Treatment satisfaction also showed that the median scores were similar for each mode of administration. Treatment satisfaction was assessed using the Life Quality Index (LQI) survey developed for patients with PID by Daly et al. Two age groups (2-13 years and ≥ 14 years) were assessed separately for SC administration with rHuPH20, SC administration without rHuPH20, and IV administration. For all subjects combined, the results for administration SC with rHuPH20, SC without rHuPH20 and IV ranged from 34.0-35 for treatment interference, 21.0-23.0 for therapy-related problems, 18.0-19.0 for therapy settings, and 10.0-11.0 for costs. The results for

subjects who were naïve to SC IgG were comparable to the results for subjects who had previously been treated with SC IgG.

With regard to preference 100% of parents/caregivers of subjects aged 2-13 years (n= 13) and 78.6% (44/56) of subjects aged ≥ 14 years would have chosen continued SC IgG treatment with rHuPH20. Of the 12 respondents who did not state a preference for SC treatment with rHuPH20, 8 preferred the IV route and 4 preferred SC administration without rHuPH20.

The median number of infusion sites per month was 1.09 for SC administration with rHuPH20, and 1.34 for IV administration. During Study 160601, subjects that received SC infusions without rHuPH20 had a median of 21.43 sites per month.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial 160603

Title: 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 identifier	**160603**		
Design	Prospective, open-label, non-controlled study in subjects with PID.		
	Duration of IV phase (Stage 1): Duration of Ramp-up phase in Stage 2: Duration of main SC phase (Stage 2): Duration of Extension phase:		Approx. 3 months Approx. 6 weeks Approx. 12 months not applicable
Hypothesis	The null hypothesis of one or more validated acute serious bacterial infections per subject per year was to be tested against the alternate hypothesis of less than 1 validated acute serious bacterial infection per subject per year.		
Treatments groups	Arm 1: Subjects from study 160601; SC experienced		Could proceed directly to stage 2: SC treatment with IG 10% after facilitation with rHuPH20
	Arm 2: Subjects not previously enrolled in 160601; SC experienced and SC naïve subjects		Completed stage 1 first: IV treatment and PK assessment with IG 10%
Endpoints and definitions	Primary endpoint	VASBI	Mean number of validated acute serious bacterial infections per subject per year in the FAS (=ITT population)
	Secondary endpoint	infections	Annual rate of all infections
	Secondary endpoint	trough	Median Trough levels of IgG

	Secondary endpoint	days	Monthly Rate of Days off school/work

Results and Analysis

Analysis description	**Primary Analysis**							
Analysis population and time point description	Intent to treat population; During stage 2 after ramp-up until end-of-study visit							
Descriptive statistics and estimate variability	Treatment group	Full Analysis Set		Per-Protocol Analysis Set		SCIG Naïve Analysis Set		
	Age	2-<12	≥12	2-<12	≥12	2-<12	≥12	
	Number of subjects	11	70	9	65	5	39	
	VASBI	0.025		0.025		0.000		
	Upper limit of (one-sided) 99% CI	0.046		0.048		0.130		
	Infections	2.97		2.95		3.50		
	95% CI (two-sided)	2.51 – 3.47		2.48 – 3.48		2.79 – 4.32		
	trough	9.95	10.7	9.14	10.6			
	95% CI (two-sided)	7.87-15.00	9.46-11.80	7.83-11.40	9.42-11.70			
	days	0.28		0.27				
	95% CI (two-sided)	0.20-0.37		0.19-0.37				
Notes	The observation period for the primary endpoint as predefined in the protocol does not include the ramp-up period, which is not in accordance with ITT principles. One patient experienced an acute serious bacterial infection during that phase, which was excluded from the primary analysis. To obtain an estimate of the incidence of VASBI in the true ITT population a reanalysis including the ramp-up was submitted. In this analysis the annual rate of VASBI was estimated as 0.03. Thus, it could be confirmed that the estimate on the rate of VASBI was not biased.							

Clinical studies in special populations

In trial 160603, 14 subjects aged 2 to <12 and 11 adolescents ages 12 to <16 were enrolled. Additionally, children and adolescents were included in study 160601, which investigated the effects of SC administration of IG 10% without rHuPH20. The following was noted:

The two youngest subjects included into the pivotal trial were 4 years of age. Local tolerability is considered to be even more relevant in the treatment of babies and toddlers. The trade-off of

increased local reactions versus increased treatment intervals is likely to be understood by older children only.

In study 160603, at least 7 subjects were 65 years or older, the supportive studies 160601 and 160602 did also enrol subjects in this age range.

Supportive study(ies)

Study 160601

Clinical Study 160601 was designed as a prospective, open-label, non-controlled, multi-centre study in subjects with PID with the aim of determining tolerability and pharmacokinetics of IGIV, 10% given subcutaneously. Pharmacokinetics of IGIV 10% administered subcutaneously was compared to the pharmacokinetics of IGIV 10% administered intravenously. Efficacy was determined in terms of acute serious bacterial infections.

Bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess were categorized as serious acute bacterial infections. These infections were diagnosed according to the FDA Guidance for Industry, November 2005. The monthly rate of serious acute bacterial infections was calculated per subject. Point estimates and 95% confidence intervals for the annual rates were calculated using a Poisson model.

Furthermore, rates for all infections, antibiotic use, hospitalisations due to infections and days out of work, school are reported.

The study consisted of 4 parts plus an optional Study Extension Part: Study Part 1, which included IV treatment, and Study Parts 2, 3a, 3b, and the Study Extension Part with SC treatment.

This supportive study encompassed patients with PID as defined by WHO criteria, at least 2 years of age. Nine (9) study sites enrolled a total of 49 subjects who received treatment in the study (Full Safety Dataset [FSDS]). Between 2 and 13 subjects were enrolled and treated per study site. Of the subjects enrolled and treated, 14 were aged 2 to <12 years and 35 were at least 12 years old.

A total of 38 subjects were naïve to SC immunoglobulin replacement, 14 in the 2 to <12 years age group, and 24 in the 12 years and older age group. Four of these naïve subjects (2 per age group) did not meet all inclusion/exclusion criteria.

Of all subjects treated (FSDS), 44.9% (22/49) were female, and 55.1% (27/49) were male. In the age group of 2 to <12 years, the ratio of females and males was 42.9% (6/14) and 57.1% (8/14), respectively, and in the age group of 12 years and older, the ratio was 45.7% (16/35) and 54.3% (19/35), respectively.

Among the subjects treated, 93.9% (46/49) were Caucasian, 4.1% (2/49) were Black, and 2.0% (1/49) were of Hispanic ethnicity. In the age groups of 2 to <12 years and 12 years and older, 92.9% and 94.3% of subjects, respectively, were Caucasian. There was one Black subject in each of these age groups (7.1% of subjects in the lower and 2.9% of subjects in the higher age group). The subject of Hispanic origin was in the age group of 12 years and older (2.9% of subjects).

The median age at enrolment in the FSDS was 20 years with a range of 3 to 77 years. Among the subjects aged 2 to <12 years, the median age at enrolment was 7.5 (range 3 to 11) years; among the subjects aged 12 years and older, it was 36 (range 14 to 77) years

IV administration was to be used in Study Part 1 only. The dose to be infused was 300-1,000 mg/kg BW/4 weeks depending on the subject's previous dose and previous treatment interval. The dose (on a gram IgG/kg BW basis) was to be kept constant during the whole study part.

SC administration was used in Study Part 2 (dose per administration: 130% of the weekly equivalent of the dose used during IV treatment) and in Study Parts 3a and 3b (dose adjusted for Study Parts 3a and 3b based on AUC determined in Study Parts 1 and 2, or dose individually adapted for Study Part 3b, if necessary, according to IgG trough level increase in Study Part 3a). Furthermore, the subjects could be treated subcutaneously in the optional Study Extension Part, where all subjects received the same dose as in Study Part 3b.

In 26 subjects, the duration of SC treatment with IGIV 10% was at least 53 weeks. Seventeen subjects received SC treatment for 30 to 52 weeks, and 4 for up to 29 weeks.

The efficacy endpoints were

- serious bacterial infections
- other infections
- use of antibiotics
- patient reported outcomes

A total of 3/49 subjects had acute serious bacterial infections (SBI) while on SC treatment (without rHuPH20). The annual rate of SBI while on SC treatment (Part 2, 3a, 3b and extension) with IGSC 10% was 0.067 and the 99% upper confidence limit was 0.134 (no SBIs occurred in the 12 week IVIg study part 1).

The annual infection rate of other infections (i.e. excluding SBIs) under IVIG and SCIG was similar (5.1 vs. 4.1; with overlapping 95% CIs).

The patient reported outcomes (Days of use of systemic antibiotics, days of prophylactic and therapeutic use of systemic antibiotics, days missed from school/work due to fever, infection or other illness, and non-study required out-patient visits) and the use of antibiotics show similar point estimates and overlapping CIs between the IGIV 10% and IGSC 10% arms, therefore no clear distinction can be made for the 2 administration routes for these parameters.

Study 160902 – extension study enrolling patients from 160603

An interim report on the extension study 160902 was submitted. In Study 160902, subjects began on the same doses of IGSC, and rHuPH20 and on the same dosing intervals that were used for the last infusions in stage 2 of Study 160603.

18 of the remaining 48 subjects receiving rHuPH20 + IG, 10%, were changed to a 2-week infusion interval. The interim study report states that this was done to evaluate whether a more frequent administration of IGSC leads to improved IgG trough levels. To address the concern that trough levels observed at the end of study 160603 or at the beginning of study 160902 were not optimal, the applicant provided data showing that subjects were switched from a 3- or 4-week to a 2-week treatment interval in Study 160902 with the sole purpose of assessing the effect of treatment intervals on IgG trough levels and not on the grounds of safety or efficacy. The data show that

trough levels were in the therapeutic range before and after the change in infusion interval and that trough levels increased only slightly with the shorter interval.

2.5.3. Discussion on clinical efficacy

One pivotal study (160603) was submitted for the evaluation of the clinical efficacy of the SC administration of a 3- or 4 week dose of IG 10% after infusion of the permeation enhancer, rHuPH20. The other studies included in the dossier provide supportive information on tolerability of SC administration of IG 10% alone in subjects with PID (160601), investigated the dose of rHuPH20 needed to infuse a monthly bolus of IG 10 % subcutaneously (160602) or enrolled healthy volunteers (170901, 160001).

Design and conduct of clinical studies

The design of the pivotal study 160603 (open-label, non-controlled multi-centre study) is adequate to fulfil guideline requirements of SCIGs and was also agreed on in the EMA scientific advice. The patient population selected, i.e. subjects with PID as defined by WHO criteria, is relevant for the intended indication. The study included children and adolescents in a sufficient number to fulfil PIP and GL requirements. However, due to potential concerns regarding the use of the excipient (rHuPH20) in children and adolescents, the patient population was restricted to adults (see Discussion on clinical safety).

Study centres were located in the US and Canada, but subject demographics illustrated that the enrolled subjects can also be regarded as representative for European patients with PID.

The duration of the study, 3 months on IGIV therapy and 12 months on IGSC plus rHuPH20 (following an SC ramp-up phase of approximately 6 weeks) treatment exceeded current GL requirements for new SCIg (6 months), but in light of the new facilitation principle introduced is considered adequate for the evaluation of efficacy.

Efficacy data and additional analyses

The primary endpoint, rate of validated serious acute bacterial infections per subject per year, is in line with the newly revised guideline on IVIg and was also agreed in the scientific advice procedure. However, the CHMP initially questioned the definition of the observation period as the observation period for the primary endpoint as predefined in the protocol did not include the ramp-up period. To address this concern the applicant provided additional analysis including the ramp-up (and 2 patients who had dropped out during the ramp up) provided results, which differed only to an irrelevant extent. The additional acute SBI that was included in this analysis, was balanced with the addition of further exposure time for the other patients and in summary this did not impact on the treatment effect estimate. The secondary efficacy endpoints, overall infections, days off school/work, days on antibiotics, days in hospital, physician visits are in line with the applicable guidance and of clinical relevance. Furthermore, quality of life and treatment satisfaction as well as treatment preference were evaluated. Results from the secondary efficacy endpoints are generally in line with those seen with other licensed IVIg and SCIg products.

The evaluation on quality of life and treatment satisfaction did not reveal differences between the IV and the SC administration with rHuPH20. Results on treatment preference show that of the 68

respondents, 2 subjects intended to stay on treatment because of medication costs outside a trial. Of the 12 subjects who intended not to continue treatment with rHuPH20, 8 were SC naïve. The reasons stated for not continuing were mostly pain and the complexity of the procedure. Only 25 % of infusions at the final dosing interval were administered in the home setting.

The vast majority of subjects (78) reached the same dose interval for IG 10% SC with rHuPH20 treatment as for IV treatment. Only 3 subjects, all of them SC naïve, did not achieve their prior dosing interval. A meaningful reduction of infusion sites needed per month was observed for IG 10 % SC with rHuPH20 treatment versus IG 10% SC (for subjects who also participated in trial 160601): The median number of infusion sites was reduced from 21.43 to 1.09, which is comparable to the median number of 1.34 infusion sites needed during the IV treatment stages in both trials, 160601 and 160603. 18 of the remaining 48 patients in the extension study 160902 were converted to a 2-week infusion interval. The interim study report states that this was done to evaluate whether a more frequent administration of IGSC leads to improved IgG trough levels. Additional data submitted by the applicant show that trough levels were in the therapeutic range before and after the change in infusion interval and that trough levels increased only slightly with the shorter interval.

While the analysis plan to use a Poisson regression is appropriate for the type of primary endpoint, a discussion of the appropriateness of the assumptions made with respect to their applicability to the final data was lacking. Only few events had been observed for the primary endpoint, and it was likely that this was indeed not problematic for the primary endpoint. Following a request, sensitivity analyses were provided, accompanied by an appropriate discussion on the suitability of the primary analysis model to the data. This also included a discussion on the impact of missing data (68 of 83 patients having initiated SC treatment in study 160603 completed the trial), and this convincingly demonstrated efficacy regarding acute SBIs.

Similar comments also applied to the other efficacy endpoints, for which the ramp-up has been consistently excluded, and the same analyses as for the primary endpoint had been applied. It could be demonstrated that inclusion of the ramp-up also had no impact on these secondary efficacy endpoints.

2.5.4. Conclusions on the clinical efficacy

The primary endpoint VASBI in the observation period is 0.025 in the full analysis set, which formally meets the required study hypothesis. In an additional analysis following the ITT principle, i.e. including the ramp-up, the annual rate of VASBI was estimated as 0.03. Thus, it could be confirmed that the estimate on the rate of VASBI was not biased.

Robustness could be confirmed in additionally requested analyses including the ramp-up and the results presented for the other endpoints were in line with those seen for other licensed IVIg and SCIg products. Regarding quality of life and treatment satisfaction outcomes, SC IG, 10% in combination with rHuPH20 was perceived similar to IG 10 % IV. The low number of SC infusions with rHuPH20 administered at home and reasons cited by subjects who did not continue IG 10% with rHuPH20 treatment imply a complexity of the infusion procedure that is deterring for subjects, especially those who were SC naïve. A true advantage of the treatment with IG, 10% SC combined with rHuPH20 is the low number of infusion sites per month, which is comparable to those needed for IV treatment and meaningfully lower than those needed for SC treatment without rHuPH20.

Equal quality of life and treatment satisfaction in comparison to IV treatment illustrates that SCIG + rHuPH20 is perceived as having comparable convenience to the IV modality. The fact that the pivotal and all supportive studies were performed in the US (and Canada) made questionable whether these data on perceived treatment convenience and quality of life can be extrapolated to European patients is considered uncertain.

The Applicant has restricted the indication to adults due to potential concerns regarding the use of the excipient (rHuPH20) in children and adolescents. For this patient population, no VASBI has been observed during the entire treatment period. The upper limit of the two-sided 98%-confidence interval for the VASBI rate/year/subject is estimated as 0.0707 and is thus significantly below the acceptable value of 1 VASBI/patient/year. The rate of all infections (3.1005) in the suggested patient population is similar to the rate of infections in the overall population in study 160603, which is 2.97. Therefore, the efficacy in this patient population is confirmed.

2.6. Clinical safety

The safety database comprises a pivotal and a supportive study in which the safety and tolerability of IGSC 10% with rHuPH20 were investigated in patients with PID (Studies 160602 and 160603). In addition, a study to investigate the tolerability, of IGIV, 10% and IGSC 10% without rHuPH20 in patients with PID (Study 160601) was conducted. Studies 170901 Part 4 and 161001 were conducted to assess, besides infusion pressure and flow rates, the safety and tolerability in healthy volunteers. 4 of these clinical studies were completed (160601, 160602, 160603 and 161001) and one was terminated (170901).

In addition to the studies with IGSC 10% and rHuPH20 performed in subjects with PID and healthy volunteers, for 4 additional studies investigating sensitivity to rHuPH20 and the safety of large volume subcutaneous fluid administration with rHuPH20, study synopses were provided (studies R04-0851 and HZ2-05-04 in HV; studies 1838-003 and HZ2-08-03 in dehydrated paediatric patients). In these studies follow-up period was no longer than 30 days in healthy volunteers and 7 days in dehydrated paediatric patients respectively. Furthermore, the dose of rHuPH20 was 15 U in study R04-0851 and 150 U in the other three studies which is much lower than in the targeted PID patient population.

Patient exposure

In **Study 160601** 49 PID patients were exposed to 207 IGIV 10% infusions (thereof 162 in SC naïve patients) over a period of ~84 days and 2294 IGSC 10% infusions (thereof 1757 in SC naïve patients) over a period of approx. one year.

In **Study 160602** 11 PID patients were exposed to 14 IGIV 10% infusions and approx. 47.75 IGSC 10%+ rHuPH20 infusions over ~ half a year.

In **Study 160603** 87 PID patients (thereof 44 SC naïve patients) were exposed to 365 IGIV 10% infusions for 91 days and 83 PID patients were exposed to 1359 IGSC 10% + rHuPH20 infusions (thereof 230 infusions in the ramp-up phase and 1129 in stage 2) for one year. The mean weekly dose was 0.143g/kg in stage 1, 0.155g/kg in stage 2 and 0.144g/kg in the ramp-up phase.

In **Study 170901** 12 healthy volunteers were over the course of 21 days exposed to the following:

Treatment 4A: IGSC 10% (0.3 g/kg BW/infusion) + Buffer Control: 253 ± 27 mL
Treatment 4B: IGSC 10% (0.3 g/kg BW/infusion) + rHuPH20 75 U/g IgG: 252 ± 26 mL
Treatment 4C: IGSC 10% (0.6 g/kg BW/infusion) + Buffer Control: 490 ±38 mL
Treatment 4D: IGSC 10% (0.6 g/kg BW/infusion) + rHuPH20 75 U/g IgG: 504 ± 55 mL

In **Study 161001** 53 healthy volunteers were, on one day, exposed to the following:

IGSC 10% (min-max): 0 – 246ml
Albumin 0.25% (min –max): 158 – 228 ml
LR control: 0.046ml/ml
rHuPH20: 75 U/ml

Supportive studies with rHuPH20 encompassed the following:

	Patients exposed	Subjects on IV infusions	Subjects on SC infusions + rHuPH20
R04-0851	100 healthy volunteers	-	All:0.1 ml rHuPH20 intradermally
HZ2-05-04	54 healthy volunteers	-	18: 400 ml LR + 150 U rHuPH20 or saline 15: 400 ml LR + 1500 U rHuPH20 or saline 16: 400 ml LR + 750 U rHuPH20 or saline
1838-003	51 children		
HZ2-08-03	148 children	75	73 (150 U dose of rHuPH20)

Adverse events

Study 160601

49 patients were included in the phase II/III study 160601 - no rHuPH20 was administered. All 49 subjects were included in the safety dataset.

A total of 226 AEs were reported during the IV treatment period (Study Part 1), and 634 AEs were reported during the SC treatment periods (Study Parts 2, 3a, 3b, and Extension). Among these, 85 AEs were considered related to the use of the investigational product during IV treatment (12 weeks), and 150 AEs were considered related during SC treatment (30 – 53 weeks). Most related AEs were mild to moderate in severity in the IV group, and mainly mild in the SC groups.

The median maximum infusion rates of 20.0 mL/h (ages 2 to <12 years) and of 30.0 mL/h (ages ≥12 years) were achieved for SC infusion of IGIV 10%. The proportion of subjects for whom the infusion rate had to be reduced, interrupted or stopped for tolerability reasons was 16.3% during IV treatment in Study Part 1 and 4.3% in the SC study parts; the proportion of infusions that had to be stopped etc. was 6.2% for IV and 0.2% for SC. The median rate of temporally associated AEs per infusion was 0.25 after IV and 0.08 after SC infusions.

Local AEs were higher in the SC groups compared to the IV group, but diminished over time from 4.9% to 1.1% in the Study Extension Part.

The proportion of temporally associated systemic AEs (excluding infections) was 28.0% for the IV treatment and 6.8% for the SC replacement. Both the increase in local and decrease in systemic AEs for the SC route is to be expected and has been described in the literature.

Symptoms that were related to the SC infusion mainly encompassed infusion site pain/hematoma/pruritus, headache, increased heart rate, fatigue, increased systolic blood pressure, pyrexia, nausea, upper abdominal pain, and vomiting – these AEs have been described in the literature for IVIgs and SCIgs.

No related SAEs occurred.

Study 160602

This Phase I/II study in 11 PID patients showed that (after a gradual dose escalation) an SC administration of a full 4-week dose of IGIV 10% when preceded by a mean dose of 51 U/g IgG rHuPH20 was tolerated by 9/11 at a single infusion site and a mean infusion duration of 2.9 hours. A reduction of rHuPH20 to approximately 25 U/g IgG resulted in failure to tolerate the full dose of study drug due to the occurrence of related AEs or increase in infusion time. The proportion of infusions not interrupted/ stopped as estimated by the Poisson model was 0.97. No AEs led to a discontinuation of the treatment. However, there was 1 subject who returned to IV treatment due to AEs after SC treatment. For proportion of SC infusions associated with 1 or more AEs within 72h + moderate or severe AEs + AEs by periods corresponding to dose categories, more AEs in the full dose category were seen.

At the full SC 4-week dose within 72 hours post infusion, 7% of SC infusions were associated with systemic AEs and 46% were associated with local AEs. The latter is deemed rather high and is not seen in the pivotal study. (160602 Study Arm 1: 20%, Study Arm 2: 14.3% vs. 160603 stage 2 after the ramp-up phase: 0.44%). The rate of AEs per infusion as well as the percentage of subjects with related AEs in study 160602 is considered quite high compared with the rate of AEs per infusion and the percentage of subjects with related AEs in study 160603 (160602 Study Arm 1 + 2: 1.951 vs. 160603 stage 2 after the ramp-up phase: 0.96, 160602 Study Arm 1: 100/Study Arm 2: 85.7 vs. 160603 stage 2 after the ramp-up phase: 71.6 respectively). Moreover, when compared with the phase III study 160603 AE rates per infusion of infusion site pain, infusion site erythema and infusion site pruritus are considered quite high (160602 study arm 1 + 2 / 160603 final infusion interval/ramp-up phase: infusion site pain 0.607 vs. 0.081/0.161, infusion site erythema 0.41 vs. 0.25/0.08 and infusion site pruritus 0.082 vs. 0.015/0.017), but due to the small patient number of study 160602, this should be evaluated with caution.

The type of AEs is in keeping with the SC administration of immunoglobulin (injection site reactions, headache) or the underlying illness (decrease in lymphocytes, sinusitis, and congestion) and/or co-medication.

Study 160603

In the pivotal study 365 infusions were administered IV to 87 PID patients (stage 1) and 1359 were administered SC with rHuPH20 to 83 patients treated during ramp-up, 81 treated during stage 2 patients (230 infusions in the ramp-up phase and 1129 in stage 2). Stage 1 lasted approximately 90 days, the ramp-up 42 days and stage 2 one year. A total of 68 patients completed stage 2, (60 adults and 8 pediatric patients).

Category	**Number (%) of subjects (N=87 IV)**	**Number (rate) of AEs (n=365 IV infusions)**	**Number (%) of subjects (N=81 SC+rHuPH20)** Excluding ramp-up	**Number (rate) of AEs (n=1129 SC+rHuPH20 infusions)** Excluding ramp-up	**Number (%) of subjects (N=83) SC+rHuPH20** Including ramp-up	**Number (rate) of AEs (N=1359 SC+rHuPH20 infusions)** Including ramp-up
AEs	78 (89.7)	387 (1.06)	81 (100)	1085 (0.96)	82 (98.8)	1317 (0.969)
Related AEs (IGSC and/or rHuPH20)	42 (48.3)	109 (0.30)	58 (71.6)	384 (0.34)	62 (74.7)	501 (0.369)
Related AEs (IGSC+rHuPH20)	n.a.	n.a.	41 (50.6)	196 (0.17)	47 (56.6)	261 (0.192)
Related AEs (IGSC)	n.a.	n.a.	37 (45.7)	134 (0.12)	45 (54.2)	172 (0.127)
Related AE (rHuPH20)	n.a.	n.a.	11 (13.6)	54 (0.05)	14 (16.9)	68 (0.050)
Non-serious AEs	79 (90.8)	383 (1.05)	80 (98.8)	1074 (0.95)	81 (97.6)	1303 (0.959)
Local AEs	5 (5.7)	5 (0.01)	43 (53.1)	235 (0.21)	53 (63.9)	335 (0.247)
Related AEs (IGSC and/or rHuPH20)	2 (2.3)	2 (0.005)	41 (50.6)	229 (0.2)	50 (60.2)	325 (0.239)
Related AEs (IGSC+rHuPH20)	n.a.	n.a.	33 (40.7)	146 (0.13)	40 (48.2)	206 (0.152)
Related AEs (IGSC)	n.a.	n.a.	19 (23.5)	37 (0.03)	25 (30.1)	59 (0.043)
Related AE (rHuPH20)	n.a.	n.a.	9 (11.1)	46 (0.04)	13 (15.7)	60 (0.044)
Systemic AEs	79 (90.8)	378 (1.04)	80 (98.8)	839 (0.74)	81 (97.6)	968 (0.712)
Related AEs (IGSC and/or rHuPH20)	41 (47.1)	107 (0.3)	39 (48.1)	155 (0.14)	42 (50.6)	176 (0.130)
Related AEs (IGSC+rHuPH20)	n.a.	n.a.	18 (22.2)	50 (0.04)	20 (24.1)	55 (0.040)
Related AEs (IGSC)	n.a.	n.a.	27 (33.3)	97 (0.09)	30 (36.1)	113 (0.083)
Related AE (rHuPH20)	n.a.	n.a.	3 (3.7)	8 (0.01)	3 (3.6)	8 (0.006)
Serious AEs	3 (0.03)	4 (0.01)	8 (9.88)	11 (0.01)	11 (13.3)	14 (0.010)
Related serious AEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.000)
AEs leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.000)
AEs, where **infusion** had to be stopped	0 (0)	0 (0)	1 (1.23)	2 (0.002)	1 (1.2)	3 (0.002)
AEs leading to discontinuation of the subject	0 (0)	0 (0)	6 (7.41)	25 (0.022)	7 (8.4)	35 (0.026)
Related AEs leading to discontinuation of the subject	0 (0)	0 (0)	5 (6.17)	24 (0.021)	6 (7.2)	34 (0.025)
Temporally associated AEs	58 (66.7)	158 (0.433)	70 (86.4)	2453 (0.401)	73 (88.0)	601 (0.442)
Temporally associated	56 (64.4)	154 (0.422)	61 (75.3)	228 (0.202)	65 (78.3)	277 (0.204)

systemic AEs						
Temporally associated local AEs	4 (4.6)	4 (0.011)	42 (51.9)	225 (0.2)	52 (62.7)	324 (0.238)
Temporally associated related AEs	40 (46.0)	100 (0.274)	56 (69.1)	346 (0.306)	61 (73.5)	460 (0.338)
No reduction, interruption, stop of infusion	77 (88.5)	350 (0.959)	68 (84)	1103 (0.977)	68 (81.9)	1322 (0.973)
Reduction of infusion	6 (6.9)	10 (0.027)	8 (9.9)	19 (0.017)	9 (10.8)	29 (0.021)
Interruption of infusion	4 (4.6)	5 (0.014)	4 (4.9)	5 (0.004)	5 (6.0)	6 (0.004)
Stop of Infusion	0 (0)	0 (0)	1 (1.2)	2 (0.002)	1 (1.2)	2 (0.001)

IV intravenous treatment, SC subcutaneous treatment, n.a. not applicable, N total number of subjects, n total number of infusions

From the multitude of safety endpoints investigated by the applicant the following can be deduced:

No major, clinically relevant differences between IV and SC +rHuPH20 including ramp-up in:
- rate of AEs related to the study drug(s) per infusion (0.3 vs. 0.37),
- Serious AEs (rate of AEs/infusion), related serious AEs, AEs leading to death
- AEs, where infusion had to be stopped
- no reduction, interruption, stop of infusion

With **IV showing a favourable profile** with regard to:

- rate of subjects with related AEs (48.3% vs. 74.7%)
- rate of patients with (total) temporally associated AEs including infections (66.7% vs. 88%)
- rate of patients with systemic temporally associated AEs including infections (64% vs. 78.3%)
- rate of infusions temporally associated with one or more local AEs (0.011 vs. 0.238)
- rate of patients with infusions temporally associated with one or more local AEs (4.6% vs. 62.7%).
- rate of patients with temporally associated related AEs (46.,% vs. 73.5%)
- rate of infusions temporally associated with related AEs (0.274 vs. 0.338)

SC + rHuPH20 administration compared to IV showing a favourable profile for:
- rate of infusion with related systemic AEs (0.3 vs. 0.130)
- rate of infusions with non-serious systemic AEs (1.04 vs. 0.71)
- rate of infusions with temporally associated systemic AEs (0.422 vs. 0.204)

The threshold for high dose SC infusions with rHuPH20 was defined as the highest dose at which at least 30 subjects' median doses per site were above the threshold, which was 36 g per infusion site. The rates of mild AEs per high-dose SC infusion were similar to those for all SC doses. The most common IV (stage 1) related AEs were headache, chills, nausea, fatigue, pyrexia and vomiting.

The most common AEs related to both IGSC 10% + rHuPH20 in stage 2 (excluding the ramp-up) were infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritus, infusion site oedema, and infusion site swelling. AEs related only to rHuPH20 included infusion site pain and infusion site pruritus. The majority of AEs were mild; very few severe AEs occurred. The 3 severe AEs related to both IGSC 10% and rHuPH20 were infusion site pain, infusion

site swelling, and genital oedema. One severe AE was related to IGSC 10% only (migraine), and one was related to rHuPH20 only (oral pain).

AEs by comparison of data from study 160603 and study 160601

To explore the impact of rHuPH20 enhancement on the safety profile, mean / median rates of AEs between Study 160601 (without rHuPH20) and study 160603 were compared. However, it has to be taken into account that the clinical studies 160601 and 160603 were not designed to be compared directly (different observation time, volumes etc) and that any conclusion should therefore be undertaken with caution. The rate of related AEs per infusion as well as the rate of related AEs per subject-year was higher in subjects who received IGSC + rHuPH20 than in subjects who received IGSC alone. This is mainly contributed to the considerable higher (related) local AEs after administration of IGSC + rHuPH20, while the rates of systemic AEs are more or less comparable. The difference in local tolerability is expected due to higher doses, volumes and flow rates when compared to subcutaneous administration of IG without rHuPH20.

Summary of AEs attributed to rHuPH20 alone

Unintentional intravenous administration of rHuPH20 has not been reported.

Injection site pain or infusion site pain were the most notable AEs by MedDRA preferred terms attributed to rHuPH20 alone occurring at higher frequencies in most of the treatment arms with IGSC 10% and rHuPH20 across all studies. In addition, in study 161001 in healthy volunteers more cases of administration site pain were classified as moderate or severe in the rHuPH20 group compared with the lactated Ringer control group.

Study 170901 (Part 4)

This Phase 1 randomized, double blind, controlled, 2 dose study of IGSC (0.3 g/kg or 0.6 g/kg) administered either with a prior buffer control or with rHuPH20 was carried out in 12 healthy volunteers to assess infusion site reactions, tolerability and other AEs. It lasted between 7 and 21 days.

All 12 patients experienced treatment related adverse events. Systemic-related AEs were reported more frequently for 0.6 g/kg BW IGSC 10% infusions (11/20 infusions, 55.0%) compared to 0.3 g/kg BW IGSC 10% infusions (3/24 infusions, 12.5%). The most notable related systemic AEs were haemolytic anaemia (2/12 subjects, 16.7%), leukopenia (3/12 subjects, 16.7%), and nausea (2/12 subjects, 16.7%) and were reported only for the 0.6 g/kg BW IGSC 10% treatments with or without rHuPH20.

Most of the infusions were associated with mild local site reactions including induration, discoloration, pain, pruritus, and swelling. Administration of IGSC 10% with rHuPH20 elicited lower rates of infusion site induration than IGSC, 10% alone (0.591 vs. 0.818), and higher rates of infusion site pain (1.277 vs. 0.727), injection site pain (0.318 vs. 0.136), infusion site discoloration (1.000 vs. 0.773) and infusion site pruritus (0.545 vs. 0.409).

Study 161001

In this Phase 1 prospective, randomized, placebo-controlled, single-centre study, evaluation of the effectiveness and safety/tolerability of rHuPH20 in enhancing the IGSC, 10% in 53 healthy volunteers was assessed, 52 subjects were included in the safety dataset.

The control for rHuPH20 was lactated Ringer's (LR) solution and the control for IGSC 10% was albumin. The study was divided into 2 stages; one was a pilot phase where each subject (n=8) received 2 simultaneous treatments (IGSC 10% with rHuPH20 and IGSC 10% with LR control) in the thighs and stage 2 compared all four above mentioned study drugs in 45 subjects. The main safety focus thus was on stage 2.

A total of 363 AEs were reported in 52 (98.1%) subjects, whereby 337/363 (92.8%) were considered related to the administration of study drugs. The majority of the related events were mild (211; 58.1%) or moderate (107; 29.5%) in severity.

Local AEs: Practically all local AEs were related in all 4 study arms, most AEs were mild to moderate in severity with no clear distinction between the study arms. More subjects (21%) had severe, related local AEs who were receiving IGSC 10% + rHuPH20 compared with the other 3 study arms (8.3 – 15.2%).

Of 90 local AEs in the IGSC 10% + rHuPH20 group, 30 (33%) were deemed related to rHuPH20

Of 116 local AEs in the IGSC 10% + LR group, 29 (25%) were deemed related to LR control. There was a similar proportion of infusions with temporally associated local, moderate or severe AEs for both pre-administrations in the IGSC 10% groups.

Local AEs in >5% subjects who received infusions with rHuPH20 pre-administration included infusion site pain (93.9%) and discoloration (54.5%), whereas with LR control pre-administration these local AEs were infusion site induration (97.0%), pain (87.9%), and discoloration (63.6%). The incidence of administration site pain seems to be more or less similar in both groups but more cases of administration site pain were classified as moderate or severe in the rHuPH20 group compared with the LR group.

Systemic AEs: Regardless of the pre-administration (rHuPH20 or LR) the majority (14/15) of the systemic AEs in stage 1 and approximately half (13/27) of the AEs in stage 2 were related to the administration of IGSC10% (only one was related to rHuPH20 and IGSC 10%); in contrast none of the AEs in the albumin arms (with rHuPH20 or LR) were related to albumin. Because of simultanous application in both thighs, the relatedness of systemic AEs is difficult to assess.

Treatment preference for rHuPH20 vs. LR enhancement of an IGSC, 10% infusion 59.4%; (95% CI: 42.3, 74.5%) vs. 34.4% (95% CI: 20.4, 51.7%).

Supportive studies

The supportive studies with regard to rHuPH20 application in healthy subjects and pediatric patients diagnosed with dehydration (who received rHuPh20 prior to saline for rehydration) did not reveal any new safety concerns and the type of AEs is similar to those seen in the main studies.

Serious adverse event / deaths / other significant events

A total of 27 serious adverse events (SAEs) in 21 subjects occurred across all 5 studies in the IGSC 10% with rHuPH20 clinical program. One death occurred due to cardiorespiratory failure in study 160601; the event occurred prior to the subject starting treatment therefore the SAE was assessed as being unrelated to the study drug.

Across all 5 clinical studies, 2 SAEs in 2 subjects were considered to be possibly related to a study drug; both were instances of haemolytic anaemia in study 170901 part 4:

- Subject 010005, a previously healthy 32-year-old, black male, was withdrawn from the study due to a SAE of hemolytic anemia (moderate; unlikely related to rHuPH20 and possibly related to IGSC 10%) and a non-serious AE of lymphopenia (severe; unlikely related to rHuPH20 and possibly related to IGSC 10%) both of which began on Day 21 approximately 6 days after receiving Treatment 4C (IGSC 10% [51.4 g] + formulation buffer control).
- Subject 010015, a previously healthy 47-year-old, white male, completed dosing, but experienced an SAE of hemolytic anemia (moderate; possibly related to rHuPH20 and possibly related to IGSC, 10%) that began on Day 30 (end of study) approximately 8 days after receiving Treatment 4D (IGSC 10% [43.3 g] +rHuPH20 [3249 U]).

Dosing was halted for study part 4 and the study was terminated early after these subjects.

One thromboembolic event occurred in a 19 year-old male subject (010011; study 160603) who experienced a right subclavian vein thrombosis caused by an indwelling port catheter. It is apparent that having an indwelling venous access device is a significant risk factor independent of the treatment with intravenous or subcutaneous gammaglobulin. A contribution of the gammaglobulin cannot be ruled out, but clearly the indwelling port, thrombophilia, and family history of thrombosis are all major risk factors and sufficient to explain the thrombotic episode in the absence of gammaglobulin.

Laboratory findings

Thromboembolic events and cases of haemolysis/haemolytic anaemia have been observed. The cases of haemolytic anaemia occurring only at the higher dosage of 0.6mg/kg IGSC 10% as described in the terminated study 170901 (first study in healthy subjects) are considered possibly related to IGSC 10%. In these two instances, it is conceivable that the administration of immunoglobulin and the simultaneous infection with pandemic influenza H1N1v, demonstrated as seroconversion to the H1N1 strain of Influenza A virus in these patients, could play a role in causing this adverse event, which was not observed in any of the patients in studies 160601, 160602 or 160603.

In several patients and healthy subjects treated with IGSC 10% with rHuPH20 significant (> 2g/dl) and insignificant (< 2g/dl) declines in haemoglobin have been observed in all 5 clinical studies. Most instances of drop in haemoglobin were observed in laboratory assessments that were temporally far removed from each other or could be interpreted as lab errors, and in no case there were clinical signs or symptoms of haemolysis.

Safety in special populations

Safety of IGSC 10% and/or rHuPH20 has been studied in healthy volunteers, PID patients and supportively in children with dehydration. However, there is no clinical data on administration of IGSC 10% with rHuPH20 provided for the age group of 0 to 4 years.

Immunological events

A listing of all AEs (related and unrelated) together with their time of onset, duration, severity and temporal relationship to the anti-rHuPH20 antibody titres for all subjects in study 160603 with antibody titres ≥ 160 was provided. A temporal analysis of all ADRs in subjects with at least one antibody titer ≥ 160 during the observation period was also submitted to assess any potential temporal relationship between anti-rHuPH20 titres and AEs. An identical analysis on safety data for all subjects in study 160603 and 160902 with antibody titres ≥ 160 was submitted to assess any potential temporal relationship between anti-rHuPH20 titres and AEs.

In this analysis, for each subject, the observational period before and after the initial detection of rHuPH20 antibodies was calculated, and the ADRs were assigned to the respective period. As a threshold between the two periods, the date of the measurement which preceded the date of the 1st measurement with anti-rHuPH20 antibody titres ≥ 160 was used. Thus subjects act as their own control regarding the incidence of AEs, which is considered to be more meaningful than an inter-individual comparison. The Applicant concludes that the majority of those who had observational periods before and after antibody development had a similar or even lower rate of ADRs after the development of antibodies. This conclusion is supported, although the tendency of SCIGs to cause less AEs with longer treatment duration might influence this analysis.

Two separate analyses of potentially immune-mediated local reactions were conducted: (a) data from all 83 subjects who participated in Study 160902 and/or in Study 160603 and who received HyQvia treatment were analysed (i.e., this analysis included also subjects from study 160603 who did not roll-over into study 160902) to compare the rates of these local AEs in antibody-positive and negative subjects, and (b) data for the 14 subjects who developed an antibody titer of 160 or higher during study 160603 and/or 160902 until cut-off date Apr 6, 2012 were analysed to identify any temporal relationship between the presence of antibody titres and the incidence of immune-mediated local AEs in these subjects.

Sixty-six (66) events of local erythema were observed during the whole observational period on HyQvia treatment, 28 of them in subjects who at any time during the observation period had an anti-rHuPH20 antibody titre of ≥ 160. In total, 16 of the 66 local erythema events occurred during a period when the subjects had titres ≥ 160. The majority of the episodes (55 out of 66) were mild and all were self-limiting. No severe episode was observed.

Forty-three (43) events of local pruritus were reported during the entire observational period of HyQvia treatment, 13 of them in subjects who at any time during the observational period had an anti-rHuPH20 antibody titer of ≥ 160. 6 events of all 43 events of local pruritus occurred during a period when the subjects had titres ≥ 160.

The conclusion of the Applicant, that there was no association between the occurrence of local erythema and/or pruritus and elevated antibody titres to rHuPH20 is therefore supported.

Safety related to drug-drug interactions and other interactions

Concomitant use of immunoglobulins or of rHuPH20 with other drugs has not been evaluated. It is generally recommended that immunoglobulins are administered separately from other drugs or medications that the patient may be receiving. The product should not be mixed with immunoglobulins from other manufacturers. No other drug interactions or compatibilities have been evaluated. Antibodies in immunoglobulin preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, rubella, and varicella. The immunizing physician should be informed of recent therapy with immunoglobulins so that appropriate precautions can be taken.

For IGIV 10% no drug-drug interactions have been investigated and are normally not requested. To investigate a\ny potential impact of rHuPH20 on the efficacy of IGSC 10%, data from studies 160602 and 160603 in PID patients has been analysed. From these studies no distinct action of rHuPH20 is seen on the beneficial effects of the immunoglobulin i.e. the efficacy profile does not seem to change. By altering the PK of the SC administration of immunoglobulins through rHuPH20 to be more similar to that of IV administration the safety profile also shifts in this direction, however, new adverse events outside the range of the known ones for SCIG/IVIG were not identified.

Discontinuation due to adverse events

Study 160601

One subject (1/49) withdrew from the study because of decreased QoL and increase in fatigue and general malaise.

Study 160602

None of the AEs reported in the 11 PID patients led to the discontinuation of IGIV, 10% treatment. However, 1 subject returned to IV treatment after 2 SC infusions due to mild and moderate AEs.

Study 160603

6 patients withdrew due to AEs; in 5 of those AEs were at least possibly related to either IG 10% (1) or rHuPH20 (1) or both (3), in the IGSC with rHuPH20 group compared to no discontinuation due to AEs in the IVIg group respectively one discontinuation in the IGSC without rHuPH20 group in the phase II/III study 160601. 5 out of 6 patients were naive to SCIg treatment.

Ages 2- 12

- 100002, Subject had adverse events. IgG infusions were discontinued to see if the specific antibody deficiency associated with congenital anomalies had resolved
- 130001 not specified

Ages >12

- 030007, not specified
- 140005, discomfort from infusion site, erythema, induration and extravasation of serous fluid
- 170002, pain and discomfort in abdomen and groin from fluid shifting post-SC infusions
- 170005 not specified

Study 170901

Two subjects (Subject 010005 and Subject 010020) out of 12 (16.6%) were discontinued due to (S)AEs (see above)

Subject 010020 [4008]) was withdrawn from the study due to a non-serious AE of flu-like illness and concern regarding the 2 SAEs (one SAE led to withdrawal in Subject 010005, the other patient (010015) experiencing an SAE had completed the study).

In addition, 5 subjects including the 2 SAE subjects (Subjects 010005, 010015, 010020, 010001, and 010016) experienced a flu-like clinical syndrome that was associated with a number of laboratory abnormalities. As a result of these occurrences, dosing was halted for Study Part 4 and the study was terminated early. These 5 subjects, as well as 5 asymptomatic subjects, were later found to have seroconverted to the H1N1 strain of Influenza A virus during the course of the study. This study had been conducted during the peak 2009 outbreak of pandemic H1N1 influenza. The subjects also had increases in muscle, liver, and pancreatic enzymes that are not a plausible consequence of autoimmune haemolytic anaemia. Therefore, it was determined that an influenza infection was the most likely cause of all of the laboratory abnormalities, including the haemolysis. However, the haemolysis was conservatively assessed as possibly related to IGSC 10% with rHuPH20.

Study 161001

Subject 010058 (1/53) was withdrawn from treatment due to a moderate event of hypotension at the end of rHuPH20/LR control injections but before IGSC 10% infusions.

Post marketing experience

No post-marketing experience is available yet.

2.6.1. Discussion on clinical safety

The current SCIg Guideline CHMP/BPWP/761007/2010 is under revision therefore the IVIg Guideline EMA/CHMP/BPWP/94033/2007 Rev. 2 is also used in the assessment for safety requirements. For a PID indication application with an unmodified IVIG this would be based on data from 40 PID patients, all other pertinent safety findings and a comprehensive risk management plan (RMP). However, as HyQvia employs a new approach by administering a SCIg product preceded by rHuPH20, the data base is expected to be more comprehensive than the current IVIg Guideline recommends in order to assess the safety outcomes of the combination.

The safety database comprises a pivotal and a supportive study in which the safety and tolerability of IGSC 10% with rHuPH20 were investigated in patients with PID (Studies 160602 and 160603). In addition, a study to investigate the tolerability of IG 10% administered IV and SC without rHuPH20 in patients with PID (Study 160601) was conducted. Studies 170901 Part 4 and 161001 were designed to assess, besides infusion pressure and flow rates, the safety and tolerability in healthy volunteers. 4 of these clinical studies were completed (160601, 160602, 160603 and 161001) and one was terminated (170901).

In the 5 clinical studies 65 healthy subjects and 147 patients with PID including children were enrolled. Of those subjects, 94 patients and 52 healthy subjects were treated with SC infusions with rHuPH20. 32 healthy subjects were exposed to the proposed dose range once. 81 patients were exposed to the proposed dose range including children followed for up to 366 days. In studies 160602 and 170901 a different concentration of rHuPH20 (1,500 U/ml) was used compared to the studies 160603 and 161001 (160 U/ml). Therefore, the results of studies 160602 and 170901 are of limited applicability.

IV and SC+rHuPH20 administration showed a comparable safety profile with respect to serious AEs (rate of AEs/infusion), related AEs (rate of AEs/inf.), related SAEs, AEs leading to death, AEs where infusion had to be stopped and infusions with no reduction, interruption, stop of infusion.

IGIV was better tolerated than IGSC + rHuPH20 administration with regard to infusions with temporally associated related AEs, related AEs (rate of subjects) and temporally associated systemic AEs including infections (rate of patients), (total) temporally associated AEs including infections and rate of infusions temporally associated with local AEs.

IGSC + rHuPH20 administration compared to IV proved more favourable for related systemic AEs (rate of AEs/ infusion), non-serious systemic AEs (rate of AEs/ infusion) and temporally associated systemic AEs (rate of AEs/ infusion).

Acceptance of therapy in patients is an important factor and often influenced by individual tolerability and convenience with respect to handling/administration of a product. In the submitted Treatment Preference analysis, all parents/caregivers of subjects aged 2-13 years and 78.6% of subjects aged ≥ 14 years who experienced moderate or severe temporally associated AEs, would have chosen to continue with IGSC treatment with rHuPH20. The majority of respondents for both age groups gave a positive rating and quoted as an advantage of IGSC + rHuPH20 the frequency of administration, number of needle sticks per month, ease of administration, potential to self-administer, ability to fit treatment into own schedule, overall convenience and ability to self-administer without medical supervision. The rates of subjects who gave positive ratings for each parameter were generally lower among SC-naïve subjects than in subjects previously exposed to SCIG. Based on a subgroup analysis, patients who preferred treatment with IGSC + rHuPH20 compared to that in patients who preferred treatment with IGSC alone or IGIV had a lower rate of infusions associated with one or more moderate or severe temporally associated AEs. The data suggest that treatment preference may indeed be influenced by the frequency/severity of AEs. However there are limitations regarding this evaluation as for 14 out of 83 subjects no preference is available.

Immunogenicity

Although the targeted patient population represents a group of different immunodeficiency syndromes, a substantial proportion of patients is not totally incapable to develop immune responses. In fact in study 160603 13 out of 83 patients (15.66%) were seropositive (titre ≥ 1:160) for anti-rHuPH20 antibodies. Most of these patients participated in the extension study 160902. Overall, 15 out of 83 patients (18%) were seropositive (titre ≥ 1:160) for anti-rHuPH20 antibodies in study 160603 and study 160903. 3 of these 15 subjects were children or adolescents <18 years.

The permeation enhancer rHuPH20 has the identical primary protein structure as the human hyaluronidase PH20 devoid of the carboxy terminal glycosylphosphatidyl-inositol (GPI) anchor present in the native molecule. Consequently a (cellular or humoral) immune response may cross-react with the endogenous structure, with the potential to impair the physiological function of PH20. To date it seems justified to anticipate, that treatment emergent rHuPH20-reactive antibodies can interact with endogenous PH20.

The majority of nonclinical in vivo studies with rHuPH20 report that rHuPH20 specific immune responses were generated.

The CHMP raised concerns regarding the long-term effects of rHuPH20 administration, the impact of anti-rHuPH20 antibodies on neurogenesis/neuronal repair and on fertility. The applicant addressed these with additional analyses on the available clinical patient data, with additional clinical data from healthy volunteers and with several non- and preclinical investigations (see also Nonclinical aspects).

With regard to the concerns on neurogenesis/neuronal repair, taken together the available data are reassuring. Additionally, a warning statement is added to the SmPC indicating that women of childbearing potential should not use HyQvia if pregnant or planning to become pregnant. Furthermore, if a woman becomes pregnant, treatment with HyQvia should be stopped and an alternative IgG treatment that does not contain recombinant hyaluronidase should be considered. The lack of information on safety in pregnant and lactating women has also been included as important missing information in the risk management plan. In order to acquire safety data regarding the course and outcome of pregnancy and foetal and neonatal development in female subjects who become nevertheless pregnant during HyQvia administration, the applicant will perform a pregnancy registry, as stated in the risk management plan.

With regard to the concerns on fertility, the preclinical data in several different animal species have not shown a potential impact of anti-PH20 antibodies, which is reassuring. The SmPC provides appropriate information. Furthermore, to further alleviate possible remaining concerns, the applicant proposed a label for HyQvia that excludes children and adolescents aged 0 to 18 years of age; this was considered acceptable by the CHMP. Thus adult patients will be able to make an informed decision for a SC immunoglobulin treatment with an extended infusion interval. At the same time minors will be protected from a possible adverse event which may have consequences later in their adult life. The risk management plan specifies the lack of clinical data on the potential consequence of antibody development against recombinant human hyaluronidase, e.g., on fertility in men and women, as important missing information.

The evaluation of long-term local and systemic effects for the observed time period of up to 3 years in the clinical trials does not reveal a specific safety signal. A potential loss of efficacy with a longer duration of administration due to local reactions has not been identified. To further evaluate the long term local and systemic effects the Applicant will perform a post-authorisation safety study, as indicated in the risk management plan.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

HyQvia is a human normal immunoglobulin preparation (IG 10%) for subcutaneous use in primary and secondary immunodeficiency disorders, administered with the excipient recombinant human hyaluronidase (rHuPH20) to facilitate subcutaneous administration of the IG 10% preparation. The recombinant human hyaluronidase component modifies the permeability of connective tissue through the hydrolysis of hyaluronan. This combined use of IG 10% preceded by rHuPH20 is a novel approach hence a more comprehensive safety data set compared to guideline requirements for IGSC preparations is required. The extent of the available data for HyQvia allows adequate characterisation of the safety profile.

The observed safety profile of IGSC + rHuPH20 administration is considered manageable in clinical practice with the guidance provided in the SmPC. Specific for the excipient hyaluronidase the potential concerns regarding long-term effects of rHuPH20 administration, and impact of anti-rHuPH20 antibodies on neurogenesis/neuronal repair and on fertility, have been adequately addressed through SmPC statements and risk management activities including educational programme. Also the patient population was restricted to adults only. Additional data will be generated through a pregnancy registry as well as a post-authorisation safety study to evaluate the long term local and systemic effects of HyQvia.

In conclusion, based on the safety data presented and the minimisation of the risks introduced in the SmPC and RMP, the safety profile of the product is considered acceptable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 3. Summary of the risk management plan

Safety issue	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Important Identified Risks		
Allergic/hypersensitivity responses including	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.3:

anaphylactic reactions, especially in patients with IgA deficiency		Contraindications and Section 4.4: Special Warnings and Precautions for Use
Altered immune response: • Reduced efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella • Interference with serological testing after infusion of immunoglobulin	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use* and SmPC Section 4.5: *Interaction with Other Medicinal Products and Other Forms of Interaction*
Infusion site reactions (including Discomfort/Pain, Erythema, Swelling/Edema, Pruritus, Infusion site mass, Nodule, Infusion site warmth, Infusion site hematoma, and Infusion site haemorrhage)	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use* Local reactions and Infusion site reactions (including Discomfort/Pain, Erythema, Swelling/Oedema, Pruritus, Infusion site mass, Nodule, Infusion site warmth, Infusion site hematoma, and Infusion site haemorrhage) are included in SmPC Section 4.8: Undesirable Effects.
Thromboembolic events	Routine Pharmacovigilance: • Expedited reporting of all thromboembolic events • Evaluation of safety data in the PSUR • Proposed thromboembolic adverse event questionnaire	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Haemolysis/Haemolytic anaemia	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Important Potential Risks		
Transmittable infectious	Routine	Routine Risk Minimization:

agents	Pharmacovigilance	Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Spread of localized infection	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Renal dysfunction/failure	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Aseptic meningitis syndrome (AMS)	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Drug administration error (Incorrect sequence of administration of vials)	Routine Pharmacovigilance	Routine Risk Minimization: The dual vial content of the HyQvia kit is discussed in SmPC Section 2: *Qualitative and Quantitative Composition*. The correct method of administration is discussed in SmPC Section 4.2: *Posology and Method of Administration*.
Important Missing Information		
Lack of information on safety in pregnant and lactating women	Routine Pharmacovigilance Additional Pharmacovigilance: • Proposed pregnancy registry	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use* and Section 4.6: *Fertility, Pregnancy and Lactation* Additional Risk Minimization: • Proposed HyQvia Patient Educational Material
Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.2: *Posology and Method of Administration,* Section 4.8: *Undesirable Effects*, and Section 5.1: *Pharmacodynamic Properties*
Limited information on safety in geriatric populations	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special*

		Warnings and Precautions for Use
Limited clinical data on treatment in patients with myeloma	Routine Pharmacovigilance	Routine Risk Minimization: None
Lack of clinical data on the potential consequence of antibody development against recombinant human hyaluronidase, e.g., on fertility in men and women	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.2: *Posology and Method of Administration,* Section 4.6: *Fertility, Pregnancy and Lactation*, and Section 4.8: *Undesirable Effects* Additional Risk Minimization: Proposed HyQvia Patient Educational Material
Limited clinical data on the influence of the type of PID on the immunogenicity of recombinant human hyaluronidase	Routine Pharmacovigilance: • Proposed immunological adverse event questionnaire • Evaluation of safety data in the PSUR	Routine Risk Minimization: None
Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against recombinant human hyaluronidase	Additional Pharmacovigilance: • Proposed PASS on long term local and systemic effects • Evaluation of safety data in the PSUR	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use*
Limited clinical data on patients with serum creatinine levels greater than 1.5 times the upper limit of normal for age and gender	Routine Pharmacovigilance	Routine Risk Minimization: Discussed in SmPC Section 4.4: *Special Warnings and Precautions for Use* and Section 4.8: *Undesirable Effects*

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
PASS on long-term local and systemic effects	Draft protocol to be submitted by August 2013

Description	Due date
	Preliminary study report to be included in each PSUR Final report estimated for 2019
Pregnancy registry	Draft protocol to be submitted by August 2013 Preliminary study report to be included in each PSUR Final report estimated for 2019

Furthermore, the CHMP is of the opinion that additional risk minimisation activities were required. The list of these measures is reported in the section 3 of this report under the heading “Additional risk minimisation measures”.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet initially submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

During the assessment changes were made to the package leaflet affecting the key safety messages, as well as inserting pictograms on how to administer the product.

Therefore, the applicant will perform a targeted user testing upon finalization of the package leaflet with special focus on the pictograms and submit the final report as soon as it becomes available.

3. Benefit-Risk Balance

Benefits

Beneficial effects

A measure of the beneficial effect of restoring IgG is the reduction of the incidence of serious bacterial infections ((SBIs) such as bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess) to below one per patient per year. In the pivotal study 160603, a prospective, open-label, non-controlled, two-arm multicentre study, which investigated the efficacy, tolerability and safety of IG 10% with rHuPH20 treatment in 83 subjects with PID, efficacy was shown on the endpoints incidence of acute serious bacterial

infections (0.025/year when the ramp up was excluded, resp. 0.03/year when the ramp-up was included) and in the incidence of all infections (2.97/year, when the ramp-up was excluded, resp. 3.09/year when the ramp-up was included). The observed efficacy was similar to other licensed immunoglobulin products.

The additional benefit of hyaluronidase is the ability for the patient to deliver the equivalent of an IVIG monthly dose at one SC site also in a 4-weekly schedule, which also reduces the number of administration sites. The median number of infusion sites per month needed for SCIg infusions with rHuPH20 was substantially lower (1.09) than the number of sites needed for SCIg infusions without rHuPH20 (21.43); at the same time it was comparable to the number of sites needed for IVIG infusion (1.34). 78 of 83 subjects treated with SCIg + rHuPH20 achieved the same dosing interval as for IVIg substitution. Treatment satisfaction and quality of life evaluation were comparable for the IVIg and the SCIg + rHuPH20 treatment phases (3 months and approx. 14 months, respectively) in study 160603.

Uncertainty in the knowledge about the beneficial effects.

Although a patient perception of comparable convenience between SCIG + rHuPH20 and IVIG has been shown based on the available data, it is noted that all studies were performed in the US and Canada. Given the different healthcare systems there is an uncertainty whether this perceived treatment convenience and quality of life can be extrapolated to European patients. However this uncertainty can be accepted.

Risks

Unfavourable effects

As would be expected from the SC administration of an IgG product the main adverse events with HyQvia are local infusion site reactions with mainly mild to moderate swelling, pain, pruritus and discoloration. Systemic adverse events are similar in type to the common ones seen with IVIG treatment (headache, back ache, chills, nausea etc.).

The local tolerability is impacted by the higher doses, volumes and flow rates leading to a tendency of more local adverse events when compared with SC alone. Likewise, the subcutaneous administration of HyQvia is associated with a different local tolerability profile compared to intravenous administration, which led to higher rates of related non-serious local adverse events and temporally associated local adverse events observed in HyQvia treated patients in the clinical studies.

Uncertainty in the knowledge about the unfavourable effects

The studies show the ability of PID patients to form anti-drug antibodies (anti-rHuPH20) after repeated administration of HyQvia, resulting in higher titres than observed in healthy subjects, who were exposed only up to two infusions to rHuPH20. There is cross-reactive potential of

anti-rHuPH20 antibodies with endogenous PH20 and thus potential interference with the physiological functions of endogenous PH20. The available clinical and nonclinical data are reassuring with regard to the uncertainty on neurogenesis/neuronal repair. Appropriate guidance is included in the SmPC. In order to acquire safety data regarding the course and outcome of pregnancy and foetal and neonatal development in female subjects who nevertheless become pregnant during HyQvia administration, a pregnancy registry is described in the risk management plan. Likewise, the uncertainty regarding the possible impact of anti-PH20 antibodies on fertility have been addressed by preclinical data in several different animal species. The majority of these studies do not indicate a safety signal. Nevertheless, to address any potential risk of recombinant human hyaluronidase antibodies especially in children/adolescents on their future fertility the patient population in the SmPC for HyQvia was restricted to adults. Additionally, information regarding fertility has been added to the SmPC and educational material will be provided.

The evaluation of long-term local and systemic effects for the observed time period of up to 3 years in the clinical trials does not reveal a specific safety signal. Equally, concerns regarding a possible loss of efficacy with a longer duration of administration due to local reactions have not been substantiated. To further evaluate the long term local and systemic effects, the Applicant will perform a post-authorisation safety study, as indicated in the risk management plan.

Benefit-risk balance

Importance of favourable and unfavourable effects

The PK and efficacy data indicate favourable effects of HyQvia on the incidence of acute serious bacterial infections, incidence of all infections, number of days missed at school/work and number of days in hospital, which are comparable to other licensed IG (SC and IV) preparations. Quality of life and treatment satisfaction of patients in the pivotal study did not differ significantly between the IVIG and the SCIG + rHuPH20 treatment periods. With regard to preference, most of patients or parents/caregivers would have continued with SCIg + rHuPH20 treatment. The reduction of infusion sites per month compared to SC administration of IG alone is considered substantial. Patient statements indicate that pain and the complexity of the infusion procedure are the main reasons for discontinuing treatment with rHuPH20.

Overall the observed safety profile of HyQvia administration is considered manageable in clinical practice with the guidance provided in the SmPC.

Benefit-risk balance

For the evaluation of the benefit-risk balance of HyQvia one has to take already licensed SCIg products into consideration, as the main claimed benefit of HyQvia is the extension of the infusion interval for SC replacement therapy. 78 of 83 patients achieved the same treatment interval as established for IVIg substitution, and the reduction in monthly infusion sites vs. SC administration of IG 10% alone is dramatic. The efficacy of HyQvia appears to be approximately equivalent to other licensed IG products.

The convenience of extended infusion intervals with comparable clinical efficacy is offset by an increase in mainly local adverse infusion reactions. It is expected that most adult patients would accept a slight increase of local reactions in exchange for a much longer treatment interval. The uncertainties regarding the effects of anti-PH20 antibodies on the physiologic function of

endogenous PH20, i.e. mainly on fertility have been adequately addressed. This includes the restriction to adult patients given the uncertainties regarding the possible future effects of anti-PH20 antibodies on fertility.

Based on the available data and taking into account the SmPC / Package Leaflet and the risk management plan, reason reported above the CHMP considers the overall Benefit/Risk of HyQvia is positive.

Discussion on the benefit-risk balance

The therapeutic effect of HyQvia and other IVIgs or SCIgs in replacement therapy is based on the fact that human normal immunoglobulin contains a broad spectrum of opsonising and neutralizing IgG antibodies against infectious agents that are present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Thus, adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range and thus allow the patient to combat a wide array of infections he would otherwise be susceptible to.

A measure of the beneficial effect of restoring IgG is the reduction of the incidence of serious bacterial infections ((SBIs) such as bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess) to below one per patient per year. The efficacy studies provided for HyQvia have shown this to be the case. Clinical efficacy (rate of serious acute bacterial infections as well as rate of all infections) as observed in the proposed target population (adults ≥ 18) is comparable to other immunoglobulin preparations.

The beneficial effect of the SC route is the added quality of life seen primarily in the possibility of administration of immunoglobulins at home either in self-administration or by a caregiver. In the literature it is described that the SC route also leads to less systemic events compared to the IV route. Furthermore, a more even level of IgG is achieved, avoiding the peaks of IV treatment. In the pivotal study the beneficial effect of HyQvia as compared to IV administration was shown to be in the lower rate of infusions temporally associated with systemic AEs (0.204 vs 0.422).

The uncertainties regarding the long-term effects of rHuPH20 administration, the impact of anti-rHuPH20 antibodies on neurogenesis/neuronal repair and fertility have been addressed. The SmPC with the identified patient population and the treatment guidance reflects the findings; education material will be provided to healthcare professionals and patients. Additional data will be generated through a pregnancy registry and a post-authorisation safety study, as defined in the risk management plan.

4. Recommendations

Description of post-authorisation measure(s)
REC
1. Improvement of the RP-HPLC assay to allow separate specifications to be set for the product-related impurities. The Applicant commits to establish these impurity acceptance limits after collecting data from the first 20 commercial lots. (REC)

Description of post-authorisation measure(s)
2. User Testing: As the initial readability test was performed on the preliminary package leaflet (without pictograms and other key changes made by CHMP) a further reduced user testing was considered advisable. The applicant committed to perform a reduced user testing upon finalization of the package leaflet with special focus on the pictograms. The applicant should specify the competence, expertise, and skills of the participants in order to allow a more in-depth analysis of their level of knowledge/education. The applicant has committed to submit the final report as soon as it becomes available (post-approval).

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of HyQvia in the

Replacement therapy in adults (≥ 18 years) in primary immunodeficiency syndromes such as:

- *congenital agammaglobulinaemia and hypogammaglobulinaemia*
- *common variable immunodeficiency*
- *severe combined immunodeficiency*
- *IgG subclass deficiencies with recurrent infections.*

Replacement therapy in adults (≥ 18 years) in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections,

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.
(See Annex I: Summary of Product Characteristics, section 4.2).

- ***Official batch release***

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the

requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe HyQvia are provided with an Educational pack.

The educational pack should contain the following:

1. Summary of Product Characteristics and Patient Information Leaflets

2. Patient information cards

3. Text statement for the doctor to be mentioned on the educational pack:

- a patient information leaflet and a patient information card should be given to the patient before treatment with HyQvia is initiated
- should any woman become pregnant whilst on treatment with HyQvia, HyQvia should be discontinued and treatment switched to an alternative IgG treatment which does not contain recombinant hyaluronidase. In addition, the patient should be encouraged to participate in the pregnancy registry.
- Information on the availability of a pregnancy registry and on how to enrol patients in it.

- The Patient information card should include information on the following key elements:

- <u>Information on antibodies against recombinant hyaluronidase</u>

- HyQvia contains recombinant human hyaluronidase that facilitates the dispersion and absorption of Immunoglobulin G and some patients receiving HyQvia may develop antibodies against it.
- In clinical trials up to 18 % of patients receiving HyQvia developed antibodies against recombinant human hyaluronidase.
- These antibodies may potentially react against the hyaluronidase that is naturally present in most tissue of the human body but it is unknown if it has any clinical consequences.
- In clinical trials no adverse reactions were observed that were considered related to the presence of antibodies against recombinant human hyaluronidase but the duration of treatment was limited up to 36 months and the potential for long term effects is unknown.
- Their effect on human fertility and the potential for adverse effects on conception is unknown.

Information on fertility

- Reversible contraceptive effects have been reported in male and female guinea pigs immunised to produce antibodies to hyaluronidase. However, antibodies to 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 unknown.

Information on pregnancy:

- Antibodies against recombinant human hyaluronidase may cross the placenta.
- Animal studies reveal no special hazard for humans based on conventional studies of developmental toxicity.
- No clinical studies have been conducted with HyQvia in pregnant women. The potential impact of antibodies against recombinant hyaluronidase on human embryo or foetal development is currently unknown.
- HyQvia should not be used by women who are pregnant or are planning to become pregnant. An alternative treatment that does not contain recombinant hyaluronidase should be considered.
- In the event a woman nevertheless becomes pregnant while being treated with HyQvia, treatment with HyQvia should be stopped and an alternate IgG treatment that does not contain recombinant hyaluronidase should be discussed with the treating doctor.
- It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy during HyQvia treatment.

Paediatric Data

The completion of the paediatric investigation plan P/306/2010 provided is deferred, therefore no statement regarding compliance is included.