28 April 2016
EMA/CHMP/37582/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

HyQvia

International non-proprietary name: human normal immunoglobulin

Procedure No. EMEA/H/C/002491/II/0021

Note

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

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Baxalta Innovations GmbH submitted to the European Medicines Agency on 13 October 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include paediatric population for all authorised indications; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0186/2015 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0186/2015 was completed. The PDCO issued an opinion on compliance for the PIP P/0186/2015.

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 did not seek Scientific Advice at the CHMP.

1.2. 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

Timetable	Actual dates
Submission date	13 October 2015
Start of procedure:	31 October 2015
CHMP Co-Rapporteur Assessment Report	23 December 2015
CHMP Rapporteur Assessment Report	23 December 2015
PRAC Rapporteur Assessment Report	4 January 2016
PRAC members comments	6 January 2016
Updated PRAC Rapporteur Assessment Report	7 January 2016
PRAC Outcome	14 January 2016
CHMP members comments	18 January 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2016
Request for supplementary information	28 January 2016
Joint Rapporteurs Response Assessment Report	12 April 2016
CHMP members comments	18 April 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	N/A
Opinion	28 April 2016

2. Scientific discussion

2.1. Introduction

Baxalta's combination product immune globulin (IG) infusion 10% with recombinant human hyaluronidase (rHuPH20) has been developed to enable the subcutaneous (SC) administration of large volumes of IgG, thus addressing the major disadvantage of SC IgG replacement therapy for patients with primary immunodeficiency diseases. Immune globulin 10% and rHuPH20 allows administration of IgG SC every 3 or 4 weeks as an alternative to intravenous administration or more frequent SC administration in patients with PIDD. The function of rHuPH20 in the product combination is to promote the dispersion and absorption of IG 10% by temporarily increasing the permeability of the SC tissue. Administration of the combination product is a 2-step process that comprises injection of rHuPH20 followed by infusion of IG 10% into a single SC site through the same needle/infusion set. IG 10 % is marketed as GAMMAGARD LIQUID in the US and KIOVIG in Europe. rHuPH20 is a highly purified, neutral pH-active, human hyaluronidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a deoxyribonucleic acid (DNA) plasmid encoding for a soluble fragment of human hyaluronidase (PH20).

rHuPH20 modifies the permeability of the connective tissue through the hydrolysis of hyaluronan and temporarily decreases the viscosity of the extracellular matrix and promotes dispersion of injected fluids, thus facilitating their absorption.

At the time of the initial MAA, efficacy in children and adolescents was considered established and the available clinical safety data did not reveal any specific concern in any age group. However, CHMP expressed a theoretical concern that anti-rHuPH20 antibodies, that were observed in some patients treated with HyQvia, could cross-react with endogenous PH20 and potentially effect fertilization, pregnancy or neurogenesis/ neuronal repair, thus leading to an exclusion of children from the indication. In the present variation application, the MAH presents newly generated clinical data and applies for an extension of the indication to the paediatric population.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Post-approval, Baxter has completed a package of additional nonclinical studies that substantially expands the available safety information to address theoretical concerns regarding fertility, pregnancy, neurogenesis and neuronal repair. These data were assessed during variation EMEA/H/C/002491/II/0013, which received a positive opinion on June 25, 2015 (Update of sections 4.2, 4.4, 4.6 and 5.3 of the SmPC in order to update the safety information regarding pregnancy, fertility and lactation following new additional preclinical data. Furthermore, the Annex II has been revised to remove educational material based on the availability of additional new data).

These data are summarized below:

1. Two dedicated Good Laboratory Practice (GLP) rabbit studies designed to evaluate potential effects of anti-rHuPH20 antibodies on male and female fertility and embryo-foetal development with a postnatal (juvenile) extension were ongoing during the HyQvia review cycle. These studies, now completed, demonstrate that anti-rHuPH20 antibodies had no observed adverse effects on male or female fertility, pregnancy, or offspring development from conception through adulthood. In addition, there were no adverse effects on sexual maturation or mating outcome of offspring persistently exposed to anti rHuPH20 antibodies during embryo-foetal and juvenile development (Halozyme Reports 12208 and 12195).

2. In vitro expression profiling studies have been expanded to include use of RNASeq technology. RNA-Seq is a sensitive, quantitative method that provides a more precise measurement of transcript levels than other methods (Wang 2009). RNA-Seq data from human, rabbit, and mouse demonstrate that PH20 expression is limited to reproductive tract tissues of the sexually mature male. There was no evidence of PH20 expression in foetal tissues and no detectable expression in any neuronal tissues at any stage of development. In contrast to the Preston publication, there was no evidence for PH20 expression under conditions of damage and repair in the Myelin Oligodendrocyte Glycoprotein (MOG) model of Experimental Autoimmune Encephalomyelitis (EAE) by histochemistry or RNA-Seq, despite the presence of oligodendrocyte precursor cells in the EAE lesions.

3. The reported effect of PH20 on oligodendrocyte precursor cell (OPC) differentiation was demonstrated to be due to a contamination (basic fibroblast growth factor (bFGF)) of the bovine testicular hyaluronidase (BTH) preparation used by Preston (Halozyme Report 13119). There was no effect of rHuPH20 on OPC differentiation. Furthermore, the effects of BTH on OPC differentiation were eliminated by inhibition of bFGF or depletion of bFGF from the BTH preparation.

4. Genetically engineered gene knockout mice (KO) provide another valuable tool to examine the potential impact of loss of function for that gene product. PH20 gene knockout mice were previously reported to be normal and fertile (Baba 2002). Further evaluation of PH20 KO mice was conducted to determine whether absence of PH20 has any consequence on brain histology, behavior, or neurological function. There were no changes in brain histology, myelination, or sensitive assessments of neuronal function. There also were no neurobehavioral differences between PH20 knockout mice and wild-type litter mates or normal controls, even under conditions of enhanced neurogenesis (Halozyme Report 13122). The absence of any observed effect in animals with complete loss of PH20 function further supports the conclusion that PH20 is not involved in neuronal progenitor cell proliferation or differentiation, overall brain development, or neurological function.

2.2.1. Ecotoxicity / environmental risk assessment

The MAH provided a justification for not submitting ERA studies, as due to their nature neither the active substance (human immunoglobulin) nor the excipient (rhuPH20, a recombinant protein) are likely to result in a significant risk to the environment. In addition, the extension of the indication to the paediatric population is not expected to produce a significant increase of use of the product. This is acceptable to the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The clinical investigation of HyQvia included children and adolescents in a sufficient number to fulfil guideline requirements, and the agreed PIP for HyQvia in PID (EMEA-000872-PIP01-10-M03, Decision number P/0186/2015). All studies included in the agreed PIP are completed and final clinical study reports have been submitted with previous applications.

At the time of initial marketing authorisation evaluation, efficacy in the paediatric patient population was confirmed. Clinical safety for the paediatric population in study 160603 was similar to the overall study population and there were no unique safety issues associated with the paediatric population. However, some areas of uncertainty regarding potential effects of anti-rHuPH20 antibodies cross-reacting with endogenous PH20 were raised as concerns at the time. Some of these theoretical concerns have been addressed by additional dedicated developmental and reproductive toxicology (DART) studies generated post-approval (variation EMEA/H/C/2491/II/0013, positive outcome).

The results from this study 160902 were submitted in frame of the Paediatric Article 46 Follow-Up Measure 008. Summary from this already approved procedure (29 July 2014) is given in the safety section below.

With the present variation, the MAH proposes to extend the current indication of the approved HyQvia Product Information (PI) to the paediatric population based on available clinical data in the paediatric population covering 3.3 years of exposure with HyQvia.

The MAH also proposes to perform a phase IV, Post-Authorization Study to collect additional data on the safety, tolerability and immunogenicity of HyQvia in paediatric patients (⩽18 years). The final protocol for this study will be subject to approval.

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.

- Tabular overview of all clinical studies/post-marketing/planned studies related to Hyqvia

Study	Description	Countries	Design	No. of pts.	FU	Final Report	Comment
160601	Tolerability and PK Comparison of IGIV, 10%) administered IV or SC		Phase 2/3 Prospective, open-label, nonrandomized, multi-center study	49PID	IGI, 10%: 12 weeks IGSC, 10% 29-53 weeks	Final report with MAA	rHuPH20 **was not** administered in this study 18 children 14 patients were 2 to <12 4 patients were 12 to <16 years old. PK data (IgG trough) were comparable to adults
160602	Determination of dose of rHuPH20 enabling up to 600 mg/kg BW of IGI, 10% administered SC in a single infusion site		Phase 1/2 prospective, open-label, nonrandomized, 2-arm multicenter study	11 PID	Arm 1 8-65 days Arm 2 133-165 days	Final report with MAA	No children

160603	Efficacy, Tolerability and PK Comparison GAMMAGARD LIQUID/KIOVIG iv, or sc following rHuPH20	US Canada	Phase 3 prospective, open-label, non-randomised, multi-center study	83 PID (68 completed)	1 day or more IGI 10%: 91 days IGSC with rHUPH20 ramp-up: 366 days	Final report with MAA	**24 children** (< 18y)
170901 Part 4	A Phase 1 Study SCIG Administered Either Alone or in Combination with rHuPH20 for the Evaluation of Safety, Tolerability, and Optimal rHuPH20-to-SCIG Dose Ratio	US	Phase 1 randomised, double blind, controlled study Discontinued	12 Healthy subjects	On 31 October 2009, the study was terminated by the company as a result of two cases of hemolytic anaemia. Investigation of cause of cases completed	Final report (Part 4): with MAA	No children
161001	A Phase 1 Study for the Evaluation of the Effectiveness rHuPH20 in Enhancing the SC of SCIG, 10% Solution	US	Phase 1 prospective, randomised, within-subject/ between subjects, placebo-controlled, single-center study	53 Healthy subjects	21(± 3) days	Final report with MAA	No children
160902	Long-Term Tolerability and Safety SCIG Solution administered SC Following rHuPH20 in Subjects (Art 46)	US	Phase 3, prospective, open-label, non-controlled, multi-center study **extension of 160603**	66 PID	During Safety Follow-up: For subjects with anti-rHuPH20 antibody titers <160 at last measurement, 24 weeks. For subjects with anti-rHuPH20 antibody titers ≥160 at last	Final Report: 03 Feb 2014 Variation application (Art 46) EMEA/H/C/2491/P46-008 Approved on 29 July 2014	3y OLE: 28.7.2010 -06.8. 2013 **13 patients** were < 18 y (thereof **11 completed**)

					measurement, 48 weeks		
161101	Tolerability, Safety and Administration Mode Evaluation of rHuPH20 Facilitated SC treatment With IG 10%	US	Phase 2/3, prospective, non-controlled, non-randomised, multicenter study	37 PID	3-5 days after infusion	LSO: 4 Jan 2013 Final CSR: 17 May 2013	FDA terminated US Study prematurely on July 2012 based on theoretical risks of exposure to anti-rHuPH20 antibodies. Subjects went directly into a safety follow-up epoch (Epoch 3) and were treated with Gammagard Liquid (IGIV:Arm 1 or IGSC: Arm 2) If any subject had anti-rHuPH20 antibodies with a titer $\geqslant$ 160 at the last measurement in Epoch 2, then this subject(s) would remain in Epoch 3 for 12 months. Subjects who had anti-rHuPH20 binding antibody titers <160 at all measurements during study Epoch 1 or 2, would remain in Epoch 3, until their treatment duration in Epoch 2 plus Epoch 3 was 24 weeks. **9 children** aged 6-<12 y
Post-marketing							
	PSURs	As of September				Since first licensure of HYQVIA on 16 May 2013,	Since MA, 2 additional post-marketing adverse

		2015, HYQVIA in 14 countries worldwide: AT, CZ, DK, FI, DE, EL, EI, IT, NL, NO, SE, UK and USA and Puerto Rico.				total of 496.278 grams of HYQVIA have been distributed globally, and an estimated 2.140 patients have been exposed to HyQvia (source: HYQVIA PSUR / PBRER interval 01 June 2014 -31 May 2015).	reactions have been identified: Hypersensitivity and Influenza like illness As of 31 May 2015, no new safety information has been received from postmarketing surveillance that would change the positive benefit-risk balance of HyQvia as determined previously.
161301	Registry Study to Collect Long-term Safety Data from Women Treated with HyQvia (Immune Globulin (Human) 10% and rHuPH20)	European Economic Area, North America, and other countries, where the product is licensed, as needed	non-interventional, prospective, uncontrolled, open-label, multicenter, post-authorisation registry.	All patients ever treated with HyQvia who become pregnant will be requested to participate in the registry by the MAH.	After delivery/end of pregnancy data on the outcome of the pregnancy will be collected, if available. The infant will be followed up for two years to collect safety data. Approximately every 6 ±2 months	Started; final preliminary study report to be included in each PSUR upon completion Final report: Q1 2020	Two pregnancies have been reported so far, but no patient is yet enrolled in the Registry as of October 1, 2015.
161302	Non-Interventional PASS on the Long-Term Safety of HyQvia in Subjects treated with HyQvia	EU	Non-Interventional PASS	80-120	12 months	Started Interim report: once 50 patients are enrolled) Final Report Q1 2020	Not yet available
Planned:							
161406	Non-Interventional PASS on the	USA	PASS			Final CSR estimated for completion in 2021	

	Long-Term Safety of HYQVIA (Global) category 3						
161504	PASS Phase IV from 2016 - 2021		PASS	40 PID		2021	40 children
Supportive:							
12222	anti rPH20 antibodies in the general population		A prospective clinical trial of 1,000 healthy individuals without prior exposure to hyaluronidase to assess effect of anti rPH20 antibodies on fertility and AI	general population in 767 subjects		Interim report 12.5.2014 (within Art 46 as a response to a question) Final report with this Variation submission	40/767 (5.2%) had rHuPH20-reactive antibodies. Antibody positivity increased with age and was3x more prevalent in males. **129 children** (12-<18) Thereof 2 subjects (both males) rHuPH20-reactive antibody positive No clear correlation between infertility or AI and the appearance of rHuPH20-reactive antibodies.
Study 1838-003	INFUSE-Pediatric Rehydration Study I		Children requiring re-hydration; Pre-adminstration of hylenex			Initial MAA	51 children; 0.3 - 9.8 years
Study HZ2-08-03	INFUSE-Pediatric Rehydration Study II (IV vs SC)		ditto			Initial MAA	148 children (75 with rHuPH20-facilitated SC); 0.2 - 9.8 years

The number of total subjects in completed studies by age group and gender is presented in the table below.

Age Group	Persons			Person Time		
	Male	Female	Total	Male	Female	Total
<18 years	24	12	36	34.65	16.92	51.58
18 to <65 years	64	64	128	65.24	64.75	129.99
65 to <75 years	3	9	12	4.44	12.97	17.41
75 or more years	0	1	1	0.00	3.79	3.79
Total Persons			**177**	**Total Person Time**		**202.77**

A total of 24 children ≤18 years of age in the pivotal study 160603 and in the extension study 160902, and another 12 in study 161101 which was prematurely ended. This latter group (12) was not included in the safety evaluation. At the time of the MAA, the requested interim analysis covered the period from the patients' first exposure to Hyqvia during the ramp-up phase in Epoch 2 of Study 160603 through to the interim analysis cut-off date (6 April 2012) in then still ongoing extension Study 160902. The median duration was 14.1 and 18.8 patient-years in the 2 to <12 year group and in the 12 to <16 year group, respectively. This has since been complemented by more data from Study 160902 so that the overall combined exposure of PID patients in both studies is ~ 188 patient-years. As described in the SmPC, the longest exposure for adults was 3.8 years and 3.3 years for paediatric patients.

The following table presents the study participation of patients by age group in the 3 clinical studies.

Table 1: Clinical Study Participation By Study And Age Groups (Studies 160603, 160902 and 161101: Safety Analysis Set)

		Subjects Treated with SC+rHuPH20				
Study	Age Group[a]	Number of Treated Subjects n	Number of Completed Subjects[b] n	Average IG Dose [g]	Median Duration of Sc+rHuPH20 Treatment (Median Duration of Follow-Up Treatment[c]) days (days)	Number of Subjects in Safety Evaluation n
160603	2-<12 years	13	8	13.95	379 (0)	14
	12-<18 years	11	11	30.06	383 (0)	12
	18 years and older	59	49	37.56	407 (0)	61
	Total	83	68	32.87	403 (0)	87
160902	2-<12 years	5	5	24.11	681 (169)	5
	12-<18 years	10	7	37.07	646 (170)	10
	18 years and older	48	38	36.65	664 (169)	51
	Total	63	50	35.72	669 (169)	66
161101	2-<12 years	9	6	11.97	96 (59)	9
	12-<18 years	3	2	24.10	96 (63)	3
	18 years and older	25	17	25.78	105 (58)	25
	Total	37	25	22.28	104 (59)	37

		Subjects Treated with SC+rHuPH20				
Study	Age Group[a]	Number of Treated Subjects n	Number of Completed Subjects[b] n	Average IG Dose [g]	Median Duration of Sc+rHuPH20 Treatment (Median Duration of Follow-Up Treatment[c]) days (days)	Number of Subjects in Safety Evaluation n
Total	2-<12 years	22	14	13.65	170 (27)	23
	12-<18 years	14	10	30.95	901 (149)	15
	18 years and older	84	53	33.24	629 (126)	86
	Total	120	77	29.38	476 (112)	124

[a]All subjects participating in 160902 rolled over from 160603, therefore age at 160603 screening has been used for age categorization in both studies.
[b]Subjects who participated in 160603 and 160902 are considered completed if he/she completed both studies.
[c]Median duration of Follow-Up treatment has been calculated for subjects who received PH20 at least once.

Study 12222 (*Analysis of the baseline prevalence of recombinant human PH20-reactive antibodies in the general population (SeraTrials 12007 and 12010)*) is not a HyQvia study and was therefore removed.

In the 3 clinical studies (160603, 160902 and 161101), 36 unique paediatric patients participated: 24 in study 160603 and 160902 (15 rolled over from study 160603), and 12 in study 161101.

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) data of HyQvia infusion were evaluated during the initial MAA and it was concluded that PK parameters were comparable between the different age groups and that satisfactory trough levels could be achieved. In addition, it was concluded that PK parameters of SC infusion of IG 10% after facilitation with rHuPH20 (in trial 160603) are similar to those achieved after IV infusion of IG 10% (in trial 160601) and thus could support the feasibility of infusing 3- or 4-week doses of IG 10% subcutaneously in patients. In the pivotal study 160603, trough levels were compared at the end of Epoch 1 (= after 3 months of IVIG treatment) with the levels at the end of Epoch 2 (= 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 guideline PK requirements were exceeded. Furthermore, for subjects aged 12 or older, bioequivalence with respect to AUC_{0-T} for IG 10% administered IV or SC at an adapted dose was shown.

In addition, for subjects aged 12 years or older, IgG subclass distribution, levels of specific antibodies, AUC, C_{max}, T_{max}, 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 IgG 10% infused after rHuPH20 facilitation in comparison to IgG 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.

2.4. Clinical efficacy

2.4.1. Main studies: 160603 and 160902

The initial submission for HyQvia was based on the pivotal Phase III study 160603; however, subjects enrolled in study 160603 were eligible to enter a long term follow up study (160902) in order to evaluate long term safety and efficacy. Sixty six of the 68 subjects who completed study 160603 enrolled in the extension study. In the pivotal study 160603, there was no significant difference in infection rates or rates of adverse events between those subjects less than or greater than 18 years of age and this continued to be the same in the extension study as well as in the overall combined analysis. Eighty three (83) subjects were exposed to HyQvia in the pivotal efficacy trial 160603; out of 83 subjects, 24 were younger than 18 years of age.

Validated acute serious bacterial infections

The annual rate of validated acute serious bacterial infections during HyQvia treatment in studies 160603 and 160902 were 0.025 and 0.020 per patient-year respectively. These were significantly lower than the primary endpoint of 1 infection per subject per year ($p < 0.0001$). Of the 3 validated acute serious bacterial infections that occurred in subjects < 18 years of age, 2 were treated as outpatients with oral antibiotics and the other one occurred in a patient with Hyper-IgE syndrome. Hyper-IgE patients are prone to Staphylococcal pneumonia due to a defect in the signal transducer and activator of transcription 3 (STAT3) or dedicator of cytokinesis 8 (DOCK8) inflammatory pathways, defects which are in addition to the antibody production defect.

All infections

An additional analysis of rates of infections in subjects in study 160603, and combined for studies 160603 and 160902, stratified by age of subjects (18+ years and <18 years) was conducted. The annual rate of all infections in study 160603 was similar for subjects less than 18 years of age and those 18 or older; see table below.

Overall Rate of Infections by Age Groups while on HyQvia Treatment Study 160603

Age Group	Number of Subjects	Rate of Infections/Year	
		Point Estimate	95% CI
18+ years	59	3.13	2.59 to 3.74
<18 years	24	3.11	2.15 to 4.32

The overall rate of infections in the combined 160603/160902 studies was also similar for subjects less than 18 years of age and those 18 or older; see table below.

Overall Rate of Infections by Age Groups while on HyQvia Treatment in Studies 160603/160902

Age Group	Number of Subjects	Rate of Infections/Year	
		Point Estimate	95% CI
18+ years	59	2.98	2.56 to 3.44
<18 years	24	3.02	2.15 to 4.10

The CHMP noted that the submitted combined analyses of infection rates from both the pivotal study 160603 and the extension study 160902 demonstrate that observed rates are comparable to those achieved in trials for licensed IG products and that they remain stable over time. The median number of

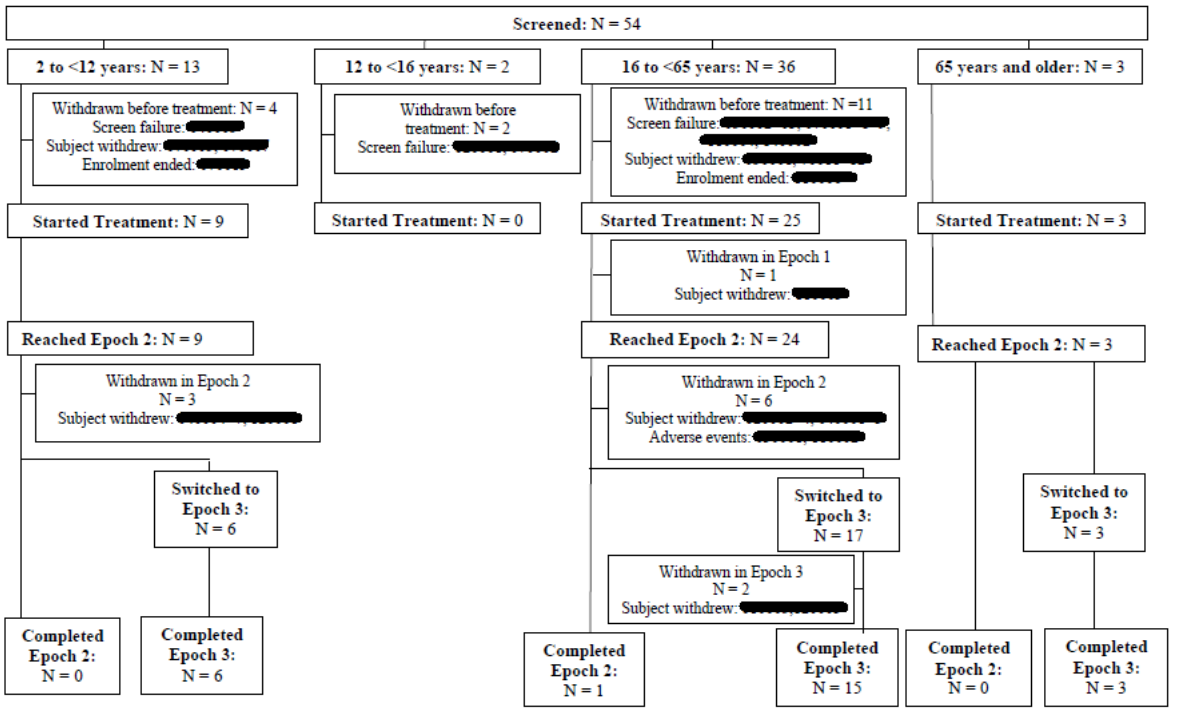
infusion sites per month was 1.09 for SC administration with rHuPH20, and 1.34 for IV administration. Subgroup analyses for all efficacy endpoints of trial 160603 by age and including the ramp-up period were provided during the initial MAA evaluation; due to the low number of subjects in some categories and the resulting wide confidence intervals, exact interpretation is difficult, however, all available data point in the same direction.

A total of three validated acute serious bacterial infections (VASBIs), all of them pneumonia, occurred during the study: 2 in SC-experienced subjects ages 6 and 11 years which occurred after the ramp-up and 1 in a SC-naïve subject of age 14 which occurred during the ramp-up period. No other subjects had VASBIs. The MAH concluded that due to the low number of events and the low number of subjects of ages below 16, subgroup analyses of VASBIs by age group or SC-naïve status were not considered to be meaningful, which can be agreed by the CHMP.

2.4.2. Supportive study 161101

This was a Phase 2/3, prospective, non-controlled, multi-center study conducted in the US to evaluate tolerability and safety and other parameters of subcutaneous treatment using IGI, 10% with rHuPH20 in PIDD subjects. The study comprised 3 epochs. In Epoch 1, subjects were treated with IGI, 10% and rHuPH20 subcutaneously with a dose/interval ramp-up of 3 weeks at the study site. In Epoch 2, subjects received subcutaneous IGI, 10% with rHuPH20 treatment for up to 6 months. The first infusions of Epoch 2 were administered at the study site; subsequent infusions were preferred to be performed at home (or equivalent site), by the trained subject/caregiver, if in the opinion of the investigator such treatment was safe and appropriate. The last infusion of Epoch 2 was also performed at the study site, so that the investigator could re-assess the proficiency of self-treatment. Following a discussion with the FDA at the end of July 2012, all subjects still active in the study stopped rHuPH20 drug product treatment. They went into a safety follow-up period (Epoch 3) and were treated with IGI, 10% (Gammagard Liquid) via either the intravenous route (IGIV) or the subcutaneous route (IGSC), at the discretion of the investigator and the subject. Out of the 54 subjects (9 children) that were screened for the study, 17 patients did not commence treatment and 37 started treatment (Safety Analysis Set, SADS). All but one of the subjects in the SADS reached Epoch 2 (Epoch 2 Analysis Set, E2DS; N=36). During Epoch 2, 9 subjects withdrew. At the time when rHuPH20 was stopped, 1 subject had completed Epoch 2. The remaining 26 were switched to Epoch 3. During Epoch 3, 2 subjects withdrew, 24 completed Epoch 3. Thus, 25 subjects completed the study (thereof 6 children). On average, 9 children were treated a similar length of time compared to the 36 adults. Their exposure to Hyqvia in Epoch 1 + 2 lasted a median of 97 days.

Figure 1
Disposition of Subjects (Study 161101)



Primary Efficacy Outcome: Trough levels of total IgG at the end of Epoch 2 (9.21 g/L [95%CI: 8.28-10.25]) were comparable to the levels measured at screening (median 10.53 g/L [95%CI: 9.46-11.73]), with a geometric mean ratio of the log-transformed IgG trough level at end of Epoch 2 versus IgG trough level at screening of 87.9% (95%CI: 79.7-96.8).

Secondary Efficacy Outcomes:

- No serious bacterial infections were reported in any subject throughout the study.
- The point estimate for the rate of all infections per year was 2.45 (95% CI: 1.55-3.66) for Epoch 1 and Epoch 2 combined.
- The point estimate for the rate per month of days off either, work, school or daily activity was less than 1 day/month. The rate of days on antibiotics was less than 3 days /month. No subjects were hospitalized during the study period and the rate of acute physician visit due to infection or other illness was less than 1 visit/month.
- Analysis of the mode of infusion was inconclusive due to the premature stop of subject enrollment and early termination of Epoch 2, however the following results were observed:
  - Median number of infusions per month: 2.90 in Epoch1; 1.09 in Epoch2.
  - Median number of infusion sites (needle sticks) per infusion/month: 2.90 in Epoch 1; 1.12 in Epoch 2.
  - Median duration of infusion less than 2h.
  - Median maximum infusion rate: 240mL/h in Epoch 1; 300mL/h in Epoch 2.
  - Median number of weeks to reach final dose interval (3 weeks or 4 weeks): 3 weeks.
  - No significant differences in the mode of administration characteristics were observed between age groups.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

At the time of the initial MAA, the design of the pivotal study 160603 (open-label, non-controlled multi-centre study) was considered adequate to fulfil guideline requirements for subcutaneous immunoglobulin. 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 sufficient numbers to fulfil PIP and relevant guideline requirements. 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 SC IG plus rHuPH20 (following an SC ramp-up phase of approximately 6 weeks) treatment exceeded guideline requirements for new SCIG (6 months), but in light of the new facilitation principle, this is considered adequate for the evaluation of efficacy. In addition, the extension study 160902 provides data on the effects of long-term treatment with HyQvia, and outcomes remained stable over time.

Efficacy data and additional analyses

Observed data provide reassurance that IG infused with rhuPH20 facilitation achieves trough levels and infection rates comparable to those of other licensed IG products. Furthermore, 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 who received SC infusions without rHuPH20 had a median of 21.43 sites per month. This underlines the main advantage of facilitated SC infusion, namely providing the opportunity of infusion intervals comparable to IV administration combined with the possibility for home treatment as for conventional SC infusions.

The CHMP noted that efficacy results of trial 161101 are comparable to those observed for the pivotal trial in the initial dossier. However, since study 161101 with HyQvia was discontinued following a discussion with the FDA, it only provided supportive data for this application, in the interest of full transparency. No paediatric data from this study were included in the submitted paediatric safety/efficacy analysis.

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy of HyQvia has already been assessed during the initial marketing authorisation application and was found as satisfactory for all age groups. During this type II variation, a reassessment of data provided at the time of the MAA in addition to the data provided for this variation reconfirmed this conclusion.

2.5. Clinical safety

At the time of the marketing authorisation application some of the preclinical data (fertility in guinea pigs, but not in other species examined) and theoretical safety considerations on long-term use of hyaluronidase and subsequent antibody development led to a cautionary approach that restricted the use of Hyqvia to adults. These theoretical concerns were partially addressed by additional dedicated developmental and reproductive toxicology (DART) studies generated post-approval (variation EMEA/H/C/2491/II/0013 which received a positive opinion on 25 June 2015). In addition, it could be shown that the finding of a possible inhibition of the myelination of oligodendrocyte precursor cells in the paper by Preston M (Ann Neurol. 2013) was due to contamination with basic fibroblast growth factor (bFGF).

This variation requests the extension of the indication to encompass children based on the previously

assessed study 160902 data, the safety data of study 161101 (although terminated), and safety results of study 12222 in the general population. Furthermore the applicant argued that to perform a long-term study in children, it would be necessary to have the approved indication, as otherwise recruitment would be difficult.

Study 160603

Patient exposure

The initial submission for HyQvia was based on the pivotal Phase III study 160603 (24/83 subjects were younger than 18 years of age); however, subjects enrolled in study 160603 were eligible to enter a long term follow up study (160902) in order to evaluate long term safety and efficacy. 66 of the 68 subjects who completed study 160603 enrolled in the extension study. Safety data from both studies underwent the standard analyses and showed rates of adverse event consistent with other studies of immunoglobulin products. In the pivotal study 160603 there was no significant difference in infection rates or rates of adverse events between those subjects less than or greater than 18 years of age and that continued to be true in the extension study as well as in the overall combined analysis.

Exposure for all patients in the combined studies was 187.69 patient-years and 48.66 patient-years for paediatric subjects <18 years of age. The longest exposure was approximately 3.8 years (198 weeks) for all subjects and 3.3 years (174 weeks) for the paediatric population.

Fifteen (15) subjects withdrew or were discontinued from study 160603; 5 of them were <18 years of age. Of the 6 subjects who withdrew due to HyQvia-related adverse events, 2 subjects were <18 years of age. Three (3) subjects <18 years old withdrew due to geographic factors (N=2) and fear of needle sticks (N=1).

Adverse events

Systemic Adverse Events

The rates of adverse events were analysed for the entire period of exposure to HyQvia in both studies combined; see table below. Rates of overall and related systemic adverse events were 8.03 and 1.75 per subject year respectively.

Overall Rate of Systemic AEs (Excluding Infections) per Subject-Year while on HyQvia Treatment in Studies 160603/160902

Total number of subject-years under treatment	Systemic AEs	
	Total	Related
	Number and rate of AEs	Number and rate of AEs
187.69	1507 (8.03)	329 (1.75)

An additional analysis of rates of systemic adverse reactions in studies 160603 and 160902 combined, stratified by age of subjects (18+ years and <18 years) was conducted. The rate of all systemic as well as causally related systemic adverse reactions was lower for the subjects less than 18 years of age; see table below. There were no severe or serious adverse reactions in the patients less than 18 years of age.

Overall Rate of Systemic AEs (Excluding Infections) per Subject-Year by Age Groups (less than 18, 18+) while on HyQvia in Studies 160603/160902			
		Systemic AEs	
		Total	Related[c]
Age Group	Total number of subject-years under treatment[a]	Number and rate[b] of AEs	Number and rate[b] of AEs
18+ years	139.04	1200 (8.63)	259 (1.86)
<18 years	48.66	307 (6.31)	70 (1.44)

[a] Subject-years under treatment = Cumulative exposure (in years) of all subjects to HyQvia

[b] Total number of AEs divided by the total number of subject-years while on HyQvia

Local adverse events

The overall rate per subject-year of local AEs while on HyQvia treatment in studies 160603/160902 is depicted below. None of these AEs were considered serious.

Overall Rate of Local AEs (Excluding Infections) per Subject-Year while on HyQvia Treatment in Studies 160603/160902		
Total number of subject-years under treatment[a]	Total	Related[c]
	Number and rate[b] of AEs	Number and rate[b] of AEs
187.69	498 (2.65)	488 (2.60)

[a] Subject-years under treatment = Cumulative exposure (in years) of all subjects to HyQvia

[b] Total number of AEs divided by the total number of subject-years while on HyQvia

An additional analysis of rates of local adverse events in studies 160603 and 160902 combined, stratified by age of subjects (18+ years and <18 years) was conducted. The rate of all local adverse events per patient year for the patients less than 18 years of age, as well as the causally related events, was less than half that of the patients 18 years and older, as stated in the table.

Overall Rate of Local AEs (Excluding Infections) per Subject-Year by Age Groups (less than 18, 18+) while on HyQvia Treatment in Studies 160603/160902			
		Total	Related[c]
Age Group	Total number of subject-years under treatment[a]	Number and rate[b] of AEs	Number and rate[b] of AEs
18+ years	139.04	429 (3.09)	421 (3.03)
<18 years	48.66	69 (1.42)	67 (1.38)

[a] Subject-years under treatment = Cumulative exposure (in years) of all subjects to HyQvia

[b] Total number of AEs divided by the total number of subject-years while on HyQvia treatment

Over 97% of HyQvia infusions (excluding ramp-up) were completed without the need to slow, interrupt, or discontinue the infusion due to an adverse event, demonstrating that HyQvia was well tolerated. There was no difference between the two age groups.

The CHMP was of the opinion that the combined analyses of safety data from both the pivotal study 160603 and the extension study 160902 demonstrate that for rates of both systemic and local adverse events are comparable for paediatric and adult subjects. A trend towards a lower incidence of AEs in the paediatric age group can be observed, but due to the low subject numbers this is difficult to interpret.

Study 160902

The results from this study were submitted in frame of the Paediatric Article 46 Follow-Up Measure 008.

Summary adapted wording from previously approved procedure (29 July 2014):

Data from the predecessor Study 160603 covered safety parameters for approximately the first 1.5 years of IG 10% with rHuPH20 SC treatment. Data from the extension Study 160902 show these parameters for the ensuing period of approximately 1.5 to 2 years. Eleven children were followed approx. 686 days.

Exposure:

Duration of Treatment [days] with SC and rHuPH20 (Study 160902: Safety Analysis Set)

Age Group	N	Mean	SD	Min	Q1	Median	Q3	Max
Subjects aged 2 to <12 years	4	681.3	9.3	672	675.0	679.5	687.5	694
Subjects aged 12 to <16 years	7	679.7	34.1	645	645.0	694.0	700.0	729
Subjects aged 16 to <65 years	44	524.4	238.8	60	289.5	664.0	695.0	728
Subjects aged 65 years and older	8	636.6	93.8	414	643.5	652.5	686.0	715
Total	63	565.9	211.8	60	643.0	669.0	696.0	729

Safety evaluation encompassed SAEs, infusions requiring adjustment, severity of AEs, antibodies to rHuPH20, rates of AEs by subject, by infusion, by relationship, by temporal association. Dosing of the Ig 10% was every 2, 3, or 4 weeks SC preceded by rHuPH20 at 75U/gram Ig. The safety follow-up was either after SC or IV administration. 62.1%of patients (41/66) applied a 4 week-infusion interval, 15/66 (22.7%) subjects, a 2 week-infusion interval and 7/66 (10.6%) a 3-week infusion interval. Across all age groups and infusion intervals, a median number of 1.09 infusions/month (range: 0.3-2.1) was administered.

Throughout the study and across all age groups, 1651 AEs were reported, of which 1188 AEs were mild in severity, 438 were moderate and 25 were severe. Out of the 1651 total AEs, 1244 AEs occurred under IGSC, 10% with rHuPH20 treatment, and 407 during the Safety Follow-up. Throughout the study across all age groups, 18 SAEs were reported for a total of 2198 infusions (rate per infusion: 0.0082). All SAEs were deemed unrelated to IP by the investigator; none occurred in subjects aged 2 to <12 years.

During SCIG 10% and rHuPH20 treatment, the rates of all related AEs and of total (related and unrelated) AEs (excluding infections) per subject per year were 4.35 and 10.68, respectively.

The median rates of temporally associated AEs per infusion were comparable for both, the predecessor study 160603 and 160902 as well as the Safety Follow-up study, namely 0.21 (95% CI: 0.13; 0.31) and 0.28/0.25, respectively. A numerical discrepancy became evident between the rates of AEs concerning the different age groups; collected data show more adverse events in elderly subjects. Amongst other factors, this might be caused by special physical conditions of elderly individuals, especially related to their medical history. No increase in the rate of local AEs was observed after long-term rHuPH20-facilitated IGSC, 10% treatment.

The rate of all adverse reactions by subject was also stable or decreased over time (3.317 during rHuPH20-fascilitated IGSC, 10% treatment vs. 2.588 during the Safety Follow-up period). In particular, the rates of local adverse reactions by infusion declined (from 8.8% to 3.7%), as is commonly seen with conventional subcutaneous therapy. During rHuPH20-facilitated IGSC, 10% treatment, the rate of all AEs related to rHuPH20, by subject, was 0.365 and the rate of all AEs related to both IGI, 10% and rHuPH20 by subject, was 1.444. Analysis of immunogenicity with respect to neutralizing antibodies against rHuPH20 did not raise any safety concerns with respect to SC administration of HyQvia. 13/66 patients (19.6%) had antibodies, however, no subject developed neutralizing antibodies against rHUPH20 during

Study 160603 and Study 160902 and anti-rHuPH20 antibody titers declined during IGSC, 10% with rHuPH20 treatment and during the Safety Follow-up period.

The results indicate that HyQvia is an effective treatment for adult and paediatric patients. No new safety signals were detected, the majority of AEs was mild, manageable and patients recovered after administration of a supportive therapy. One subject experienced a severe anaphylactic reaction during the Safety Follow-up period which was considered treatment-related to IGI, 10% and hence, was discontinued. Even if true hypersensitivity reactions are rare, this type of Adverse Drug Reaction is a potential complication with administration of human normal immunoglobulins. There were no relevant differences concerning the types of AE between adult and paediatric patients, the rate of total AEs tended to be lower in children than in adults. However, the younger patient population (2 y-16y =11 subjects) constitutes a fifth of the patient population aged 16->65 years (55 subjects), so a comparison of these rates is of limited validity.

AEs by age group:

Age group (years)	Serious	Total	Moderate	Mild
2-12 (N=4)	No	0.5433	0.0551	0.4882
12-16 (N=7)	No	0.6402	0.2275	0.4074
	Yes	0.0053	0.0053	0.0053
16-65 (N=47)	No	0.8078	0.1989	0.6023
	Yes	0.0057	0.0010	0.0010
>65 (N=8)	No	0.8151	0.2689	0.5336
	Yes	0.0094	0.0044	0.0044

Preference of treatment:

Scores for treatment preference showed that 21 subjects liked the ability to self-administer, 14 subjects disliked it, and 12 had no preference.

Conclusion on study 160902

Overall, extension study 160902 as well as the safety follow-up study (total duration 3 – 3.5 years) showed results that are consistent with the collected data of the predecessor study 160603. They confirmed an acceptable safety and efficacy profile with HyQvia when administered as 2-, 3- or 4-weekly scheme in patients with PID. Concerning efficacy results, a 4-weekly treatment schedule is reasonable with regard to sufficient IgG (trough) levels and an adequate clinical benefit as defined by protection against bacterial infections is provided.

Study 161101 (undertaken in the US, terminated early after discussion with the FDA)

Primary Safety Outcome:

During Epoch 1 and Epoch 2 combined, 59 related systemic AEs occurred. The rate of related systemic AEs/infusion, excluding infections (primary outcome) was 0.326 (95%CI: 0.186-0.522) and the rate per number of subjects was 37.8% (14/37), for Epochs 1 and 2 combined.

Secondary Safety Outcomes:

Tolerability and Safety:

- Proportion of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2.

  In the Epoch 2, 6/36 subjects achieved a treatment interval of 3 weeks and the remaining 30

subjects achieved a treatment interval of 4 weeks.

- Proportion of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2 for 24 weeks.

  Out of the 36 subjects that reached Epoch 2, 9 withdrew in Epoch 2 and, hence, did not maintain a 3-4 week treatment interval and 1 subject completed Epoch 2 maintaining the 3-4 week treatment interval. The remaining 26 subjects were switched to Epoch 3 before the end of Epoch 2 according to protocol amendment 2.

- Number and rate per infusion (excluding infections) of related local AEs.

  A total of 153 related local AEs occurred during Epoch 1 and Epoch 2 combined, in 27 out of 37 (73.0 %) subjects. In the E2DS the point estimate of the rate of related local AEs per infusion was 0.84 (95%CI: 0.582-1.164) in Epoch 1 and Epoch 2 combined.

- Number and rate per infusion (excluding infections) of all AEs.

  A total of 212 related AEs occurred during Epoch 1 and Epoch 2 combined, in 28 out of 37 (75.7%) subjects. When considering all related AEs other than infections, in the E2DS the point estimate of the rate of all related AEs per infusion was 1.646 (95%CI:1.232- 2.145) in Epoch 1 and Epoch 2 combined..

- Number of subjects who develop neutralizing antibodies to rHuPH20

  None of the 37 treated subjects develop neutralizing antibodies to rHuPH20 in the course of the study. In addition, no subject developed a positive antibody titer capable of binding to rHuPH20, which was defined as a titer ⩾160. Titers < 1:160 were considered to be either background fluctuation in the assay or consistent with passive transfer of antibody from the IGI, 10%, which has been shown to contain such binding antibodies.

25 participants filled in the SF-36 questionnaire after the study (20 were > 14 years of age and 5 were parents of children < 13 years of age) in order to express their treatment preference.

The table below presents the numbers of adverse events (AEs) and related adverse events (ADRs), including infections, for all subjects of all ages who participated in study 161101.

Number of AEs and ADRs of study 161101

	AEs	AEs Related to HyQvia	Systemic AEs	Local AEs
Epoch 1	130	86	50 (related 19)	80 (related 67)
Epoch 2	193	126	105 (related 40)	88 (related 86)
Total	323	212	155 (related 59)	168 (related 153)

Serious adverse event / deaths / other significant events

Study 161101

One SAE occurred in Epoch 3 of the study concerning hypoglycemia in a 53 year old white female PID patient 6 days after the infusion of Gammagard Liquid (no rHuPH20). The narrative was provided. The SAE had resolved at the time of study completion.

Laboratory findings

Study 161101

Haemolysis: Out of 28 subjects, 4 (14.3%) experienced a potential haemolysis, as assessed by a decline

in haemoglobin of more than 2.0 g/dL (Subjects). Further analysis showed a positive urine hemosiderin for subject during the ramp-up period and for subject during the full infusion as well as free haemoglobin concentration >600mg/L for Subject during the ramp-up period. This was considered to be an artefact since none of the other parameters of haemolysis were positive. At no time was there a concordance of positive tests confirming a diagnosis of haemolysis. None of the incidences of fall in haemoglobin were confirmed to be due to a haemolytic reaction; however, a firm conclusion cannot be made based on this study.

Haematology parameters: In the SADS (N=37), 17 clinically significant abnormal results at the assessment of the last value in Epoch 2 were reported in subjects who had a normal baseline result for that parameter: 1 shift in haematocrit; 1 shift in leukocyte counts; 2 shifts in neutrophil counts; 6 shifts in eosinophil counts, 5 shifts in monocyte counts, and 2 shifts in platelet counts. There were no clinically significant shifts from normal to abnormal results for the remaining haematology parameters assessed: haemoglobin concentration, erythrocyte, basophil and lymphocyte counts.

Clinical chemistry parameters: Twenty four clinically significant changes from normal to abnormal values were reported at the assessment of the last value in Epoch 2 for the following serum clinical chemistry parameters: 1 shift in albumin; 1 shift in aldolase; 2 shifts in ALT; 3 shifts in AST; 5 shifts in bicarbonate; 1 shift in BUN; 1shift in creatinine; 3 shifts in CPK; 3 shifts in glucose; 1 shift in LDH; 2 shifts in potassium and 1 shift in protein concentrations. No clinically significant shifts from normal to abnormal results were documented for the remaining clinical chemistry parameters assessed: alkaline phosphatase, amylase, serum bilirubin, chloride and sodium concentrations.

Urinalysis: At the assessment of the last value in Epoch 2, 3 clinically significant changes from normal to abnormal values were reported: 1 shift in urine protein; 1 shift in urine blood; 1 shift to abnormal specific gravity. There were no clinically significant changes from baseline to the assessment of last value in Epoch 2 for the remaining parameters: urine glucose, bilirubin, urobilinogen and pH.

Preference of administration route: 25 participants filled in the SF-36 questionnaire after the study (20 were > 14 years of age and 5 were parents of children < 13 years of age). For the “overall treatment preference” Hyqvia was preferred in 13 cases and 12 stated that they had no preference or preferred the former treatment (be it SCIG or IVIG). All 5 parents preferred Hyqvia; this may have to be viewed with caution, as parents will want to spare their children (and themselves) the needle sticks. The results are in keeping with those of study 160902, where approximately half of the patients preferred Hyqvia.

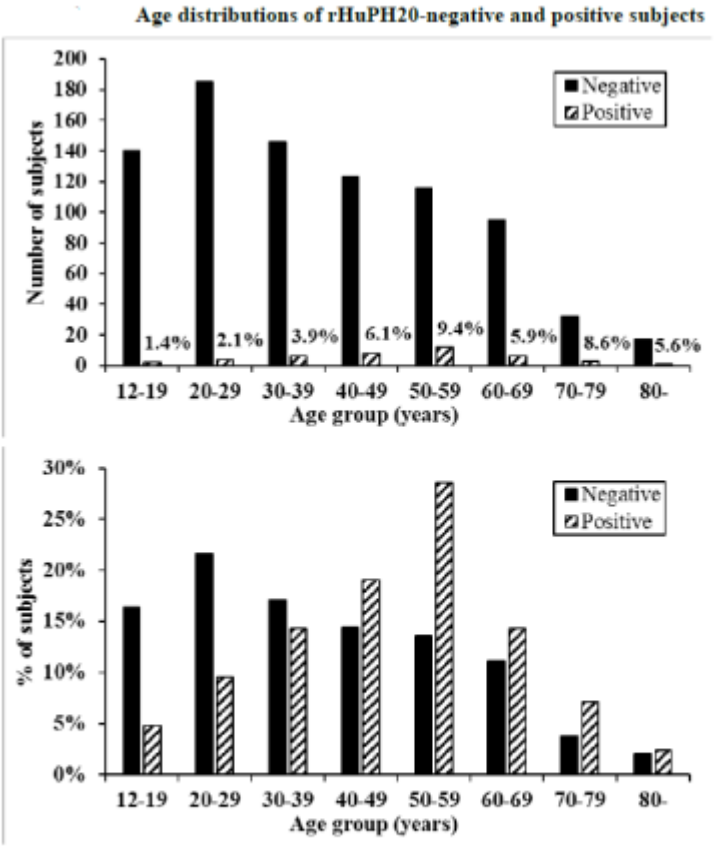
Discontinuation due to adverse events

Of the 9 discontinuation is study 161101 that occurred in Epoch 2, 3 were caused by related AEs on IGI.

Study 12222 (anti-rHuPH20 antibodies in normal population)

Study 12222 was a blood sample collection study in volunteers and was designed to determine the prevalence of rHuPH20-reactive antibodies in a normal population that was geographically, ethnically, and age diverse. Furthermore, this study was intended to explore potential factors predisposing for development of such antibodies, and possible consequences to fertility and offspring. An interim analysis of 692 patients has been previously submitted (data cut-off Apr 2014). Meanwhile, the study was finalised and the final Report 12222 is provided with this submission. Approximately 5% of the general adult population tested positive for anti-rHuPH20 antibodies. Separate clinical protocols were established for the adult and paediatric portion of this study. The adult protocol (SeraTrials 12007) had a target enrolment of at least 800 male and female volunteers, whereas the paediatric protocol (SeraTrials 12010) had a target enrolment of at least 200 subjects 12 to 17 years of age. However, due to difficulties in

recruiting certain demographic/age groups, such as children and subjects of advanced age, enrolment was terminated and the analysis limited to the samples obtained for the study period August 2012 through December 2014. Accordingly, the presence or absence of rHuPH20-reactive antibodies, and their titers if present, was determined in plasma from samples obtained from 767 normal adult subjects, 381 men and 386 women, along with 129 subjects age 12-17, 70 boys and 59 girls.



Data are shown as number of subjects (upper panel) and frequency distributions (lower panel) for rHuPH20-reactive negative (n = 854) and positive (n = 42) subject populations. Wilcoxon's rank-sum test p = 0.0006.

Forty adults and two subjects age 12-17 (both males) were confirmed positive for rHuPH20-reactive antibodies, yielding adult and paediatric positivity rates of 5.2% and 1.6%, respectively. The age distributions of subjects from pooled adult and paediatric populations that were positive and negative for rHuPH20-reactive antibodies were significantly different (Wilcoxon's rank-sum p = 0.0006) indicating that antibody positivity increased with age. In pooled adult and paediatric subjects, antibody positivity was significantly more prevalent in male versus female subjects (Fisher's exact p = 0.0007), see table below. This was also true if only the adult population was considered (odds ratio 3.21 with range 1.55 – 6.67, Fisher's exact p = 0.0010). In adults the prevalence across groups of different race/ethnicity was not significantly different (likelihood chi-square p = 0.24). The rHuPH20-reactive antibody titers ranged from 5 to 2560. Some form of autoimmune or inflammatory disease was identified in 25 subjects. There was no significant overall association between the presence of antibodies and autoimmune/inflammatory disease.

Prevalence of rHuPH20-reactive antibodies in male vs female subjects

	Men	Women
Antibody positive	32	10
Antibody negative	419	435
Odds ratio, men vs women (95% confidence range)	3.32 (1.61 – 6.84)	
Fisher's exact p	0.0007 [1]	

[1] Statistically significant at the $p < 0.05$ level

Associations between fertility/pregnancy outcomes and rHuPH20-reactive antibody positivity (in all adult subjects

Of the 381 participating men, two subjects reported ever visiting a specialist in infertility, and one of those two subjects reported being diagnosed with infertility; however, neither was positive for rHuPH20-reactive antibodies. Of the 123 male subjects that reported having fathered children, 17 tested positive for rHuPH20- reactive antibodies. This constituted a higher ratio than that observed in male subjects who did not father children (Fisher's exact p = 0.0036). Thirty-four men reported having undergone vasectomy; of these subjects, 5 tested positive for rHuPH20-reactive antibodies, whereas 25 of 347 non-vasectomized men tested positive (Fisher's exact p = 0.17). None of the 30 antibody-positive adult male subjects reported having had testicular surgery, injury/trauma, inflammation, or testicular mumps; nor any episodes of recurring urinary tract infections. Of the 386 participating women, two subjects had visited an infertility specialist, and four reported being diagnosed with infertility (including the two that had visited an infertility specialist); however, all were negative for rHuPH20-reactive antibodies. Eight female subjects testing positive for rHuPH20-reactive antibodies had borne at least one child, and none of them reported having any miscarriages. The rate of childbearing was not statistically different between antibody-positive and antibody-negative women. One antibody-positive subject and three antibody-negative subjects reported a premature birth (prior to 37 weeks of gestation), and these rates were not significantly different from each other (Fisher's exact p = 0.14). None of the ten female antibody-positive subjects reported experiencing recurring urinary tract infections or other infections or inflammatory disease of the pelvic area.

Prevalence of rHuPH20-reactive antibodies

An analysis of the prevalence of rHuPH20-reactive antibodies in various subgroups of the general population was conducted. Antibody-positive individuals were on the average significantly older than antibody-negative subjects (p = 0.0006), although there was considerable overlap in age between the two populations. Of note, male subjects had approximately 3-fold higher rates of rHuPH20 antibody positivity than female subjects, a finding which was statistically significant (p = 0.0007). However, no evidence for a negative effect on fertility in rHuPH20-reactive antibody-positive subjects could be discerned in either gender. Finally, no association was observed between rHuPH20-reactive antibody positivity and autoimmune/inflammatory conditions.

The CHMP discussed the results in adults and adolescents that had the objective to determine the prevalence of anti-PH20 antibodies in healthy male and female subjects. 42 out of 896 subjects tested as antibody positive (40/767 adults and 2/129 adolescents), at relatively low titers. Further analyses could establish no association with autoimmune disorders or fertility problems in those subjects. The data from these two trials underline the fact that anti-PH20 antibodies are present in a proportion of healthy subjects (about 4.6% in these trials) without any discernible clinical significance. Consequently, it can be concluded that anti-PH20 antibodies are present in plasma donations and therefore possibly in other human normal immunoglobulin preparations. Nevertheless, the CHMP requested a clarification whether the antibody positivity (which increased with age) could have occurred after the adults had already

reproduced. Based on MAH's response, it was acknowledge that the study design was not intended to clarify any causal relationship between anti-rHuPH20 antibodies and impaired fertility and the CHNP concurs that study 12222 contributes to the comprehensive evaluation of anti-PH20 antibodies.

Fifteen (15) of the 83 subjects exposed to HyQvia during Studies 160603 and 160902 developed at least a single positive titer (160) of antibodies capable of binding to rHuPH20. Three (3) of the 15 subjects were <18 years old. In one subject <18 years old, the titer ranged from negative to 160 (single positive titer) and declined to 10 at the end of the study. In the second subject <18 years old, the titer ranged from negative to 1280 (highest titer) and declined to 40 at the end of the study. In the third subject <18 years old, the titer ranged from negative to 10240 (highest titer) and declined to 320 at the end of the study. For all three subjects, titers declined to baseline or to titer levels observed in PH20-naïve subjects despite continued exposure to HyQvia.

Post-marketing experience

The latest PSUR was assessed in PSUSA EMEA/H/C/PSUSA/00001633/201505, which covered the period from 01 June 2014 – 31 May 2015. The procedure finalised on 14th January 2016 with the outcome of maintenance of the MA.

Since granting of the marketing authorisation in 2013, cumulatively 496.278 g have been sold. Two (2) additional post-marketing adverse reactions have been identified: Hypersensitivity and Influenza like illness and are added to the PI.

Long-term follow-up: Two non-interventional long-term follow-up safety studies (161301 and 161302) with HyQvia were ongoing during the reporting interval.

Study 161301 (Global Baxalta Pregnancy Registry). Current status: No subject was enrolled during the reporting period. Preparation for Registry implementation is ongoing (ethic committee approvals, site initiation, and notification letters to physicians)

Study 161302 (Baxalta HyQvia PASS EU). Current status: As of 31 May 2015, 10 sites open in total, (4 in Germany, 4 in the Netherlands and 2 in Denmark) and and a total of 30 subjects were enrolled in the study. First Irish Ethic Committee approval took place on 17DEC2014. New countries are planned to be on-board (Italy and United Kingdom).

2.5.1. Discussion on clinical safety

Study 160902 (P46 procedure) and its safety follow-up study (total duration 3 - 3.5 years) encompassing 66 PID patients (thereof 11 children) showed results that were consistent with the collected data of the predecessor study 160603. They confirmed an acceptable safety and efficacy profile with HyQvia when administered as 2-, 3- or 4-weekly scheme in patients with PID. There were no relevant differences concerning the types of AEs between adult and paediatric patients, the rate of total AEs tended to be lower in children than in adults. Nevertheless, at the end of the procedure, the conclusion was that although the data did not show any grave concerns for children (compared to adults), it did not alter the regulatory approach of the use of this product in children, as the number of paediatric patients (11) was not sufficient to draw any clear conclusions and could provide sufficient reassurance as to any possible long term effects of the product. Therefore, the caution of excluding children from the indication in the SmPC was upheld along with the statements concerning pregnancy. However, the conclusion regarding the warning statements concerning pregnancy is superseded by the outcome of variation II/13, where these warning statements were removed from the SmPC.

In general, the data from study 161101 encompassing 37 PID patients (thereof 9 children) do not show any untoward concerns regarding SAEs and neutralizing antibody development (there were no related SAEs and no subject developed neutralizing anti-rHuPH20 antibodies). Related local reactions were seen in 73% of the patients, which is not unusual for an SCIG application (e.g. for a SCIG EU study within a MAA local reactions were seen in 49%, yet in an equivalent US study local reactions were seen in all patients (100%)).
The rate of subjects with systemic related AEs seemed to be rather high (38%) and more in tune with that of IVIGs thereby reducing the beneficial effect normally associated with SCIGs. Furthermore, in Epoch 3 (i.e. SC w/o rHuPH20 or IVIG) the rate of patients with systemic ADRs was 15.4%.
Moreover, the study is considered only supportive as the assessment is limited due to:

- The study protocol was amended due to the aforesaid theoretical considerations of long-term effects on fertility. Therefore the actual 6 month data with Hyqvia was reduced to approx. 2.5 months and 26/36 patients were switched to a treatment without rHuPH20.
- The number of children is very small (9) and no separate evaluation was performed.
- The number of protocol violations is exceedingly large for such a short trial. In particular this affects the evaluation of haemolysis.
- There is an overlap of treatment effects from the previous treatment; 15 patients (41%) received IVIG on a 3-4 weekly basis, (the remainder received SCIG on a weekly basis). Given the half-life of IVIGs at ~ 18-30 days and a virtual wash-out of 5-6 half-lives (min: ~90 days), then a considerable amount of the data in Epoch 1 + 2 cannot be properly evaluated.
- The study was early terminated on request of the FDA.

Study 12222 was conducted in rHuPH20 exposure naïve subjects to determine the prevalence of anti-rHuPH20 antibodies in normal population. Samples were obtained from 767 normal adult subjects, 381 men and 386 women, along with 129 subjects age 12-17, 70 boys and 59 girls. The analysis showed that males had ~3-fold higher rates of rHuPH20 antibody positivity than females and there were higher rates in adults compared to children (5.2% and 1.6%, respectively). There was no evidence for a direct negative effect on fertility in rHuPH20-reactive antibody-positive subjects (in either gender) and no direct association was observed between rHuPH20-reactive antibody positivity and autoimmune/inflammatory conditions.

The Product Information of HyQvia has been adequately updated with the safety information from the conducted trials.

2.5.2. Conclusions on clinical safety

All available safety data of HyQvia in healthy volunteers as well as primary immunodeficiency patients show an acceptable safety profile across all investigated age groups. However, due to theoretical concerns for potential effects of anti-rhuPH20 antibodies (at least transient titres developed in 15/83 subjects in the pivotal study 160603) on fertility, pregnancy and neuronal regeneration, paediatric patients were excluded from the indication at the initial evaluation for marketing authorisation.

For this variation procedure clinical trials previously or partially assessed (Study 160902 and Study 12222) and some new clinical data (Study 161101) were submitted – overall these data did not contribute significantly to further elucidation of the theoretical concern of long-term effects in children. The MAH also addressed the remaining concerns through additional non-clinical and serological studies, which were evaluated in previous variation procedure. Furthermore, the MAH also proposed to conduct an additional post authorisation safety study in paediatric subjects. In particular, the MAH proposed a post authorisation, prospective, non-controlled, multicentre study to evaluate safety, tolerability and other

parameters of subcutaneous treatment using HyQvia in paediatric subjects with PIDD who have received prior immunoglobulin therapy.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 31 May 2016.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.0 is acceptable. Minor revisions were recommended to be taken into account with the next RMP update relating to the categorisation of the study *Proposed Post-authorization Study on Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Paediatric Subjects with PID* in section III of the RMP. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 8.0 with the following content:

Safety concerns

Important identified risks	Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency
	Altered immune response: Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella • Interference with serological testing after infusion of immunoglobulin
	Infusion site reactions (including discomfort/pain, erythema, swelling/edema, pruritus, infusion site mass, nodule, infusion site warmth, infusion site hematoma, and infusion site haemorrhage)
	TEEs (previously: thromboembolic events)
	Hemolysis/Hemolytic anaemia
Important potential risks	Transmissible infectious agents
	Spread of localised infection
	Renal dysfunction/failure
	AMS (previously: aseptic meningitis syndrome)
	Drug administration error: incorrect sequence of administration of products
Missing information	Lack of information on safety in pregnant and lactating women
	Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years
	Limited information on safety in geriatric populations
	Limited clinical data on treatment in patients with myeloma

	Limited clinical data on the influence of the type of PID on the immunogenicity of recombinant human hyaluronidase
	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against recombinant human hyaluronidase
	Limited clinical data on patients with serum creatinine levels greater than 1.5 times the ULN for age and gender.

Pharmacovigilance plan

Study / Activity Type, Title and Category (1- 3)	**Objectives**	**Safety Concerns Addressed**	**Status (planned, started)**	**Date Of Interim Or Final Reports (planned or actual)**
Study 161302 PASS: Non-Interventional PASS on the Long-Term Safety of HyQvia in Subjects treated with HyQvia category 1	To obtain data on the potential for long-term local and systemic reactions related to the development of antibodies to recombinant human hyaluronidase	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	Started	Final Clinical Study Report (CSR) estimated for completion in Q1 2020 (Interim report: once 50 patients are enrolled)
Study 161301: Registry Study to Collect Long- Term Safety Data from Women Treated with HyQvia (Immune Globulin (Human) 10% with rHuPH20) category 3	To obtain long-term safety data on both mother and child in the event of pregnancy exposure to HyQvia	Lack of information on safety in pregnant and lactating women	Started	Preliminary study report to be included in each PSUR upon completion; final Clinical Study Report (CSR) estimated for completion in Q1 2020
Study 161406: Non-Interventional PASS on the Long-Term Safety of HYQVIA (Global) category 3	To evaluate safety data in patients with PID. This study is a post market commitment to the FDA. (US only)	Limited clinical data on the potential for long-term local and systemic reactions	Planned in the US only	2021

Study / Activity Type, Title and Category (1- 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date Of Interim Or Final Reports (planned or actual)
Proposed Post-authorization Study on Safety, Tolerability, and Immunogenicity Evaluation of HyQvia in Paediatric Subjects with PID	Phase 4, post authorization, prospective, non-controlled, multicenter study to evaluate safety, tolerability, and other parameters of subcutaneous treatment using HyQvia in pediatric subjects with PIDD who have received prior immunoglobulin therapy	Limited information on long-term treatment in patients under the age of 18 years	Planned	2021

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	Discussed in SmPC Sections 4.3 and 4.4.	None
Altered immune response: Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella • Interference with serological testing after infusion of immunoglobulin	Discussed in SmPC Sections 4.4 and 4.5.	None
Infusion site reactions (including discomfort/pain, erythema, swelling/edema, pruritus, infusion site mass, nodule, infusion site warmth, infusion site hematoma, and infusion site haemorrhage).	Discussed in SmPC Sections 4.4 and 4.8	None
TEEs	Discussed in SmPC	None
Hemolysis/Hemolytic anaemia	Discussed in SmPC Section 4.4.	None
Transmissible infectious agents	Discussed in SmPC Section 4.2/4.4.	None
Spread of localised infection	Discussed in SmPC Section 4.2/4.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal dysfunction/failure	Discussed in SmPC Section 4.4.	None
AMS	Discussed in SmPC Section 4.4.	None
Drug administration error: incorrect sequence of administration of products	Discussed in SmPC Sections 4.2.	None
Lack of information on safety in pregnant and lactating women	Discussed in SmPC Sections 4.6.	None
Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	Discussed in SmPC Sections 4.2, 4.8, and 5.1.	None
Limited information on safety in geriatric populations	Discussed in SmPC Section 4.4.	None
Limited clinical data on treatment in patients with myeloma	None	None
Limited clinical data on the influence of the type of PID on the immunogenicity of recombinant human hyaluronidase	None	None
Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against recombinant human hyaluronidase	Discussed in SmPC Section 4.8.	None
Limited clinical data on patients with serum creatinine levels greater than 1.5 times the ULN for age and gender	Discussed in SmPC Section 4.8.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The changes in the PI are presented in Attachment 1.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefits of immunoglobulin replacement therapy with HyQvia in the paediatric population are the same as those for the adult population, namely the prevention of serious bacterial infections, a reduced incidence of infections, less use of antibiotics, less days absent from work/school. The efficacy of HyQvia with regard to these clinically relevant outcomes has already been established at the initial evaluation for marketing authorisation in a population including children, adolescents and adult PID patients.

One of the main advantages of the facilitated SC infusion is the increased infusion interval and the reduced need for needle sticks compared to conventional SC infusion. The median number of infusion sites per month was 1.09 for SC administration with rHuPH20 and 1.34 for IV administration, in contrast to a median of 21.43 sites per month for subjects who received SC infusions without rHuPH20.

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome.

Uncertainty in the knowledge about the beneficial effects

There is no real uncertainty as to the benefit of IgG replacement in PID patients. As to the benefit of SCIG + rHuPH20, it seems to be preferred by approximately half of the patients who completed preference questionnaires in study 161101). The results are in keeping with those of Study 160902, where approximately half of the patients preferred Hyqvia and this is reassuring. The uncertainty is this regard is particularly large with children as their caregivers could be more in favour of SCIG + rHuPH20 than adult PID patients would be. This may be addressed in the planned PASS, as stated in the agreed RMP.

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. Interestingly, the rate of patients with systemic ADRs is reminiscent of rates seen with some IVIGs. This would partially counterbalance the habitually lower systemic ADRs seen with normal SCIGs. Safety data at the time of the initial marketing authorisation revealed an expected increase of local adverse events and a reduction of systemic adverse events in comparison to IV administration of human normal immunoglobulin. The observed safety profile was comparable to other licensed immunoglobulin products and did not reveal any specific safety signals in any age group.

Uncertainty in the knowledge about the unfavourable effects

The uncertainty regarding the possible impact of anti-PH20 antibodies on fertility have been addressed by preclinical data in several different animal species, submitted as part of a previous variation and the PI was amended accordingly. The majority of these studies did not indicate a safety signal. The human study in the general population seems to confirm this. Nevertheless, complete satisfaction as to any potential risk of anti-PH20 antibodies especially in children/adolescents on their future fertility cannot be fully answered. The post-authorisation safety study concerning tolerability and immunogenicity evaluation of HyQvia in
Paediatric Subjects with PID, as suggested by the MAH, can only look at a limited window in the development of the children.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The similar safety profile of the paediatric and adult patients is considered important in order to extend the indication of HyQvia to children. However, long-term safety follow up will be conducted by the MAH in the post authorisation safety study.

Benefit-risk balance

The MAH addressed some of these theoretical concerns with additional dedicated developmental and reproductive toxicology (DART) studies generated post-approval. The variation EA/H/C/2491/II/0013 which received positive opinion on 25 June 2015 led to the editing of the wording in the HyQvia SmPC concerning fertility, pregnancy and breast-feeding and the Annex II has been revised to remove educational material.

However, 15 of 83 patients exposed to HyQvia developed at least transient titres of anti-rhuPH20 antibodies. Theoretical concerns regarding the potential effects of such antibodies cross-reacting with endogenous PH20 on fertility, pregnancy and neurogenesis led to the exclusion of children from the indication, as paediatric patients cannot provide informed consent to a treatment after weighing its benefits and risks.

In addition to these already assessed data, the final study reports from SeraTrials 12007 (adult protocol) and SeraTrials 12010 (adolescent protocol) of the 12222 trial were submitted and evaluated. These trials established a prevalence of anti-PH20 antibodies in about 5% of healthy subjects, with no correlation to autoimmune diseases or fertility problems. These data look reassuring. A comparison of subgroup analyses of efficacy and safety data from clinical trials 160603 and 160902 in PID patients demonstrated comparable outcomes in the adult and paediatric population.

Discussion on the Benefit-Risk Balance

The beneficial effects of an IG substitution with HyQvia, allowing infusion intervals and numbers of needle sticks comparable to the IV administration of immunoglobulin as well as self-administration or administration by parents or care-givers for younger patients, are acknowledged. The amount of pre-clinical and clinical data to date seems reassuring with regard to the risks of rhuPH20 antibodies. The future data from the proposed study paediatric PID Phase IV study 161504 may provide more (long-term) clarity in this issue and it is therefore considered acceptable to initiate this trial.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include paediatric population for all authorised indications: as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0186/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include paediatric population for all authorised indications: as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the Scientific Discussion HyQvia-H-C-2491-II-021.