27 October 2022
EMA/885669/2022
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/0078

Note

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

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Assessment Timetable/Steps taken for the assessment

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	10 May 2022	10 May 2022	☐
☐	PRAC and CHMP Rapporteur Joint Assessment Report	20 Jun 2022	21 Jun 2022	☐
☐	PRAC members comments	24 Jun 2022	24 Jun 2022	☐
☐	CHMP members comments	27 Jun 2022	27 Jun 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	28 Jun 2022	28 Jun 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	30 Jun 2022	28 Jun 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	05 Jul 2022	05 Jul 2022	☐
☐	Start of written procedure	05 Jul 2022	05 Jul 2022	☐
☐	Request for supplementary information	07 Jul 2022	07 Jul 2022	☐
☐	Submission of MAH responses	29 Aug 2022	12 Aug 2022	☐
☐	Re-start of procedure	30 Aug 2022	30 Aug 2022	☐
☐	PRAC and CHMP Rapporteur Joint Assessment Report	03 Oct 2022	04 Oct 2022	☐
☐	PRAC members comments	14 Oct 2022	n/a	☐
☐	CHMP members comments	17 Oct 2022	n/a	☐
☐	Updated PRAC and CHMP Rapporteur Joint Assessment Report	18 Oct 2022	n/a	☐
☐	Start of written procedure	25 Oct 2022	25 Oct 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	25 Oct 2022	25 Oct 2022	☐
☒	Opinion	27 Oct 2022	27 Oct 2022	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Baxalta Innovations GmbH submitted to the European Medicines Agency on 31 March 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and II

Update of section 4.8 and 5.1 of the SmPC in order to update safety data in paediatric population based on final results from study 161504 – Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects With Primary Immunodeficiency Diseases, listed as a category 3 study in the RMP. This is a paediatric interventional Phase 4 study performed to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age two to <18 years) patients with Primary Immunodeficiency Diseases (PIDD).
In addition, the MAH is taking this opportunity to update Annex II-D of the PI following procedure EMEA/H/C/002491/II/0070/G.
The RMP version 13.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics (SmPC) and Annex II and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The MAH submitted the results of the PASS 161504 (category 3 study), which collected additional data on safety, tolerability, and immunogenicity of HyQvia in paediatric (age 2 to <18 years) subjects with PIDD. Resulting from this data, the RMP has been updated.

Information on the PASS have been included in the RMP and the study has been removed from the pharmacovigilance plan and from additional pharmacovigilance activities. In addition, amendments to the RMP and the SmPC were proposed based on the previous variation II/70: the MAH provides detailed information on educational material for healthcare professionals and patients and includes a dairy for patients. The amendments of the RMP (version 13.1) and of Annex II-D of the SmPC are accepted by the CHMP.

In addition, pursuant to Article 23(3) of Regulation No (EU) 726/2004, HyQvia is removed from the additional monitoring list as the PASS 161302 is fulfilled. Therefore, the statement that this medicinal product is subject to additional monitoring is removed from the SmPC and Package leaflet. The main results of the PASS 161504 are described below:

The Phase 4, non-controlled, multicenter study 161504 provides additional data on safety, tolerability, and immunogenicity of HyQvia in paediatric subjects (age 2 to <18 years), who had received prior immunoglobulin therapy. Both HyQvia pre-treated and HyQvia new starters were enrolled in the study. For HyQvia new starters, intervals and doses in Epoch 1 were gradually increased in a ramp-up phase to an interval of 3 or 4 weeks (same interval that they had been treated IV before the study, or the interval selected at the investigator's discretion if pre-study treatment was SCIG). The HyQvia pre-treated subjects started directly into the Epoch 2 of the study and did not complete the Epoch 1 ramp-up.

Overall, the rate of reported AEs is low and reflects the expected, identified adverse reactions for

HyQvia. Two (2) severe TEAEs related to HyQvia treatment were reported (infusion site pain and emotional distress), both in the same subject, who discontinued the Epoch 2 of the study due to emotional distress.

Neutralizing antibodies were not assessed as no subject developed anti-rHuPH20 antibodies with a titer ≥160. The current study is in line with the findings of the PASS 161302 that confirmed rHuPH20-reactive binding antibodies to be rare and which did not detect any neutralizing antibodies in the subjects.

Stable and sufficiently protective IgG levels determined throughout the study and a low rate of ASBI occurrences among the paediatric subjects with PIDD (0.019 per subject-year) underline the efficacy of HyQvia treatment.

No new safety concerns were identified following HyQvia treatment in paediatric subjects with PIDD who had received immunoglobulin therapy prior to study enrolment. A summary of the safety data and a summary of the study have been included in section 4.8 and 5.1 of the SmPC, respectively.

The CHMP concluded that the benefit-risk balance of HyQvia remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of section 4.8 and 5.1 of the SmPC in order to update safety data in paediatric population based on final results from study 161504 – Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects With Primary Immunodeficiency Diseases, listed as a category 3 study in the RMP. This is a paediatric interventional Phase 4 study performed to acquire additional data on safety, tolerability and immunogenicity of HyQvia in paediatric (age two to <18 years) patients with Primary Immunodeficiency Diseases (PIDD).
In addition, the MAH is taking this opportunity to update Annex II-D of the PI following procedure EMEA/H/C/002491/II/0070/G, and to remove the statement that this medicinal product is subject to additional monitoring from the SmPC and Package leaflet following the fulfilment of the PASS 161302.
The RMP version 13.1 has also been adopted.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘HyQvia-H-C-002491-II-0078’

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

See Recommendation above

6. Clinical Efficacy aspects

N.a. This submission encompassed a PASS study

7. Clinical Safety aspects

Post-Authorisation Safety Study (PASS) results: Study 161504 "Post-Authorisation Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases".

7.1. Milestones

In the final study report, a table with milestones was not included. The Last Patient Out of the Study was on 15 January 2021 and therefore, considering that this is a pediatric study, the CSR should have been submitted 6 months afterwards. This delay was explained by the MAH with the challenges during the coronavirus pandemic. According to the last protocol amendment in 04 December 2019, the planned study period was as follows:

PLANNED STUDY PERIOD	
Initiation	2016
Primary Completion	2023
Study Completion	2023
Duration	Approximately seven years

The first patient was enrolled in May 2017. In earlier amendments of the protocol (October and March 2016), the primary and study completion dates were dated for 2021.

CHMP comment:

The PASS was finished earlier than stated in the last study protocol amendment, but as originally planned in the beginning of the study. As no subject reported an anti-rHuPH20 antibody titer of ≥160 at any timepoint during the study, the actual study participation duration was shorter for all subjects since no subject proceeded into Epoch 3 of the study due to the titer. One subject did go into Epoch 3.

The delay in the submission of the final study report after the last patient finished the study is acceptable due to the coronavirus pandemic.

7.2. Rationale and background

The rationale for the current HyQvia post-authorization (161504) study, was to collect additional data on safety, tolerability, and immunogenicity of HyQvia in pediatric (age 2 to <18 years) subjects with PIDD.

The MAH describes the usage of immunoglobulins (IG) as replacement therapy (0.3 to 0.6 g/kg body weight (BW) every 3 to 4 weeks) in primary immunodeficiencies (PIDD) to prevent or reduce severe infections.

HyQvia is a human immunoglobulin (mainly IgG) with rHuPH20 that is applied subcutaneously. It is manufactured from pooled human plasma from minimum 1,000 donations and reflects the IgG variety of the average population. The IGI 10% (Human) also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in the IGI 10% (Human) of HyQvia have not been fully elucidated.

HyQvia is licensed for the treatment of PIDD in adults in the US (Baxter Healthcare Corporation, 2014) and among adults and children in the EU (Baxalta Innovations GmbH, 2018). It is approved as a replacement therapy in adults, children and adolescents (0 to 18 years) in primary immunodeficiency syndromes with impaired antibody production and for secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF), or serum IgG level of <4 g/L. HyQvia is also indicated for treatment of but, not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

7.3. Research question and objectives

Study Purpose

The purpose of the study was to acquire additional data on safety, tolerability and immunogenicity of HyQvia in pediatric (age two to <18 years) subjects with Primary Immunodeficiency Diseases (PIDD). The study did not employ placebo or active controls.

Objectives:

Primary Objective

The primary objective of the study was to assess the safety of HyQvia treatment in pediatric subjects with primary immunodeficiency disease (PIDD) who had received immunoglobulin therapy prior to study enrolment.

Secondary Objectives

The secondary objectives of the study were further safety assessments (e.g. immunogenicity), tolerability, characteristics of product administration and efficacy (IgG trough levels).

Tertiary Objectives

The tertiary objectives were further safety and efficacy assessments.

7.4. Amendments and updates to the protocol

The MAH states that the original protocol dated 16 Mar 2016 was amended twice. The amendments of the study protocol did not have an impact on the validity of study results as initially planned in the first endorsed study protocol.

Besides others, the most relevant amendments were to clarify the reporting requirement for SUSARs and to match the requirements of the latest revision of the sponsor's protocol template and update the study inclusion criteria. Most amendments were editorial changes.

Impact of the COVID-19 Public Health Emergency on the Conduct of the Study

Study enrolment was completed before COVID-19 started, and therefore was not impacted. When the COVID-19 public health emergency started in March 2020, the scheduled visits of a total of 3 subjects were delayed (Epoch 2 Month 6, n=2 and Epoch 2 Month 12, n=1). The Epoch 2 Month 12 visits for the
2 subjects were conducted at a delayed date; however, the Epoch 2 Month 6 visit could not be arranged for the third subject prior to the next scheduled visit (Epoch 2 Month 9) due to the prolonged COVID-19 restrictions. Hence, the subject was treated at home between Epoch 2 Month 3 and Month 9.

With regards to the adjustments or mitigations of study visits or study procedures, the sponsor implemented contingency measures as appropriate to manage study conduct during disruption of the study as a result of COVID-19 control measures. Hence, there was no substantial impact of COVID-19 on the study.

A total of 3 protocol deviations (all minor) were considered related to COVID-19 pandemic situation. These 3 protocol deviations occurred in 3 subjects at 2 out of the 16 sites participating in the study. Subjects were unable to attend scheduled visits. However, no impact on key safety assessments were reported as a result of COVID-19 pandemic.

Changes in the Planned Analyses

- Given the primary objective of the study was to acquire additional data on safety of HyQvia treatment in pediatric subjects with PIDD who have received prior immunoglobulin therapy before enrolment into the study, the Per-Protocol Set was not used in this study. Therefore, the Per-Protocol Set definition was not provided in the SAP, neither was it considered for any data analysis.
- Clarification on the protocol endpoint "Number of infusion sites (needle sticks) per infusion/month" was made in the final SAP document (dated 25 May 2021). This endpoint was equivalent to "Number of infusion sites (needle sticks) per infusion" and "Number of infusion sites (needle sticks) per month".
- Additional endpoints and outcome measures for analysis were added for a more complete and robust analysis and for alignment with Study 161503, where applicable.

CHMP comment:

The changes in section "9.8.1 Changes in the Conduct of the Study" of the study protocol did not have an impact on the validity of study results as initially planned in the first endorsed study protocol.

7.5. Research methods

Study design

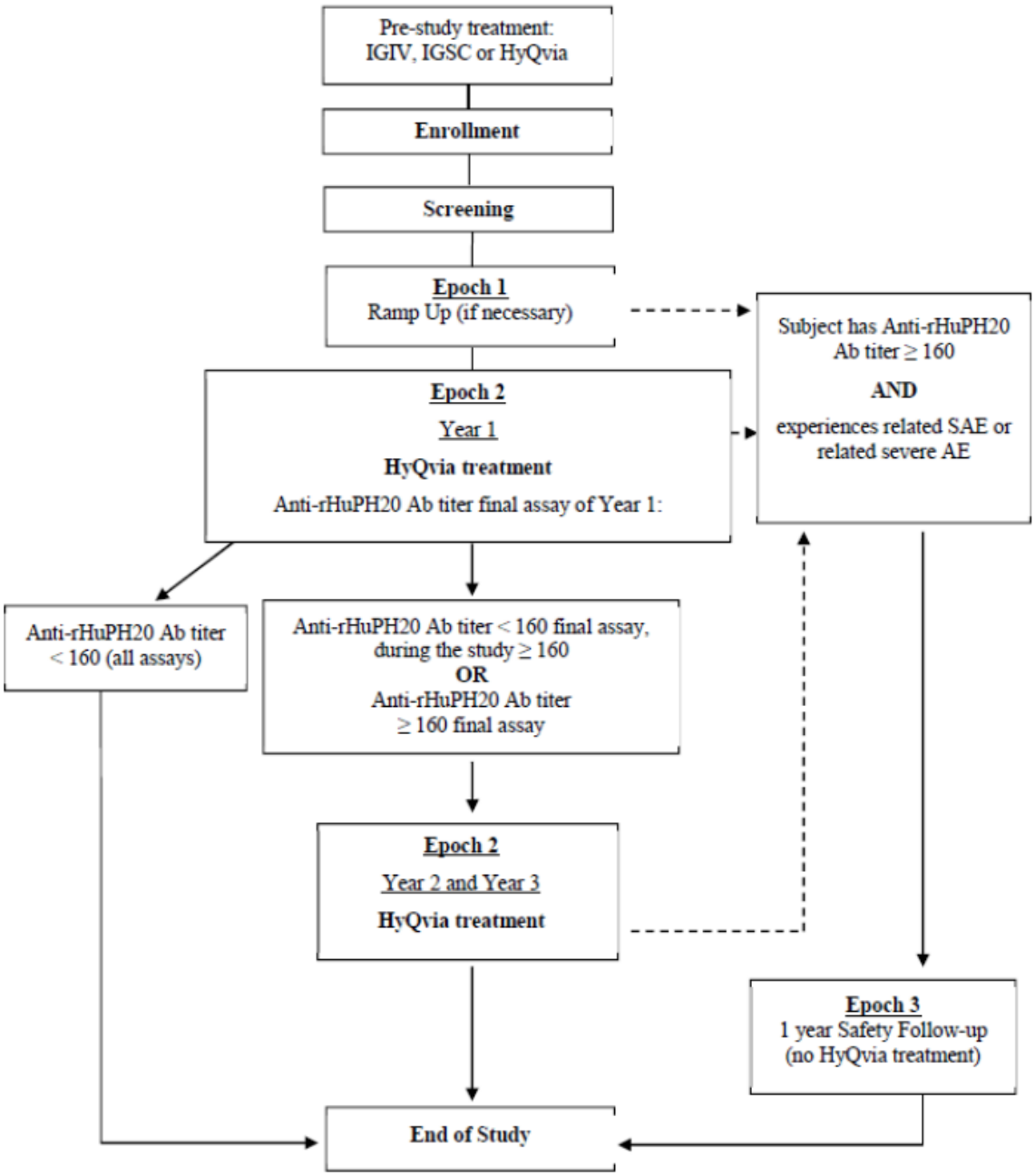
This was a Phase 4, post-authorization, prospective, non-controlled, multicenter study conducted in 16 study centers in the European Economic Area. The study comprised of 3 treatment periods: Epoch 1, Epoch 2, and a 1-year safety follow-up (Epoch 3), if needed. Pediatric subjects between 2 and <18 years at screening, who had a documented diagnosis of PIDD, had been receiving immunoglobulin therapy prior to study enrolment, and had parent or legally authorized representative's informed consent (and where applicable minor subject's assent), were to be assessed at baseline.

All subjects were tested regularly for binding anti-recombinant human hyaluronidase PH20 (rHuPH20) antibodies approximately every 3 months throughout the study. Testing for anti-rHuPH20 neutralizing antibodies was performed for subjects with an anti-rHuPH20 binding antibody titer ≥160.

Approximately 40 pediatric subjects already on IgG treatment prior to study were planned to be enrolled from around 20 study sites in the European Economic Area. Finally, 42 subjects were enrolled and analysed for the efficacy and safety of HyQvia (see section study size).

Initially, the overall duration of the study was expected to be approximately 6 years from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period was expected to be approximately 2 years. The maximum subject participation period was estimated to be approximately 4 years from enrolment to subject completion (participation in Epoch 1, Epoch 2, and Epoch 3). However, as no subject reported the anti-rHuPH20 antibody titer of ≥160 at any timepoint during the study, the actual study participation duration was shorter for all subjects.

Figure 1. Study Design Schematic



Abbreviations: Ab= antibody, AE=adverse event, IGIV=immune globulin intravenous (human), IGSC=Immune globulin subcutaneous (human), rHuPH20= recombinant human hyaluronidase PH20, SAE=serious adverse event.

Figure 1 Study design for Baxalta study 161504.

Epoch 1 (Treatment with HyQvia, Ramp-up for up to 6 weeks for HyQvia-naïve subjects):

Subjects with PIDD on non-HyQvia IV or SC treatment with immunoglobulin (IV-pre-treated, SC pre-treated) at the time of enrolment were treated with HyQvia SC with a dose or interval ramp-up period of up to 6 weeks, with all infusions administered at the study site.

Subjects already treated with HyQvia at the time of enrolment were enrolled directly into Epoch 2.

Epoch 2 (Treatment with HyQvia, final dosing for up to 3 years for all subjects):

The ramp-up (Epoch 1) was followed by Epoch 2 with HyQvia treatment at the following intervals:

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

For HyQvia pre-treated subjects, there was no change in frequency of administration. An alternative treatment interval, for example infusion every 2 weeks, was also considered for tolerability reasons at the discretion of the investigator, after informing the sponsor.

After 1 year in Epoch 2, the anti-rHuPH20 binding antibody assay results during that year were used to decide the next steps in the study:

- Subjects with anti-rHuPH20 antibody titer <160 at all timepoints during the study, performed the study completion visit at the next possible occasion.
- Subjects with anti-rHuPH20 antibody titer ≥160 during the study and/or at the last measurement were to continue in Epoch 2 for an additional 2 years of HyQvia treatment and observation.

In Epoch 2, the first 2 or 3 infusions had to be administered at the study site. Subsequent infusions were preferably to be performed at home (or equivalent site) by the subject or caregiver, following training by the investigator/designee if in the opinion of the investigator, such treatment was safe and appropriate.

Epoch 3 (Treatment with KIOVIG or Cuvitru; safety follow-up for up to 1 year):

Epoch 3 was approximately a 1-year safety follow-up, which was to be conducted if needed. Subjects with anti-rHuPH20 antibody titer ≥160 during Epoch 1 or Epoch 2 and who experienced either a related serious adverse event (SAE) or a related severe adverse event (AE) were followed accordingly.

In case that a subject in Epoch 1 or in Epoch 2 experienced a related SAE or severe AE without anti-rHuPH20 antibody titer ≥160, the subject was to be (at the discretion of the investigator and subject) (i) terminated from the study; or (ii) switched directly to Epoch 3; or (iii) continued in Epoch 1 or 2 with appropriate medical intervention such as decreasing the HyQvia infusion rate and/or premedication.

In Epoch 3, the subjects were treated with KIOVIG intravenously (IGIV 10%) or Cuvitru subcutaneously (IGSC 20%), at the discretion of the investigator and the subject. Infusions were administered at home or at the study site. Subjects with antibody titer of ≥160 entering Epoch 3 were to continue regular anti-rHuPH20 antibody testing (approximately every 3 months) for approximately 1 year.

CHMP comment:

Notably, in Epoch 3 of the study, treatment with KIOVIG or Cuvitru, but not with HyQvia, was planned. Epoch 3 was thought as a safety follow-up phase of the study. One subject from the HyQvia new starter group discontinued Epoch 2 and entered Epoch 3 due to a severe related TEAE of emotional distress. HyQvia treatment was withdrawn. An anti-rHuPH20 antibody titer ≥160 was detected in none of the patients.

Interim analysis

A prospectively planned interim analysis of data (cut-off date: 14 May 2020) was performed when 75% of all subjects enrolled in this study completed 12 months of participation (1-year observation period) in Epoch 2. The purpose of the analysis was to update the scientific community, on the interim safety, tolerability, and immunogenicity of HyQvia in pediatric subjects with PIDD. Only subjects enrolled in Epoch 1 and Epoch 2 were considered for this analysis. No change to the design, conduct or final analysis of the study occurred due to the interim analysis.

Outcome measures of the study

Primary Outcome Measure

1. Number and rate per infusion (excluding infections) of all severe related AEs

2. Number and rate per infusion (excluding infections) of related SAEs

Secondary Outcome Measures

Efficacy

1. Trough levels of IgG (for Study Epochs 1 and 2)

- IgG total trough levels
- IgG subclass trough levels
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae, and Hepatitis B Virus ([HBV])

Safety/Tolerability

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

2. Proportion of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2 for 12 months

3. Number and rate per infusion (excluding infections) of local and systemic AEs and adverse reactions (ARs), temporally associated AEs, related (causally) and/or temporally associated AEs and SAEs

4. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20

5. Additional safety outcome measures include:

- Clinical laboratory outcomes: raw (actual) values and change from baseline
- Vital signs: raw (actual) values and change from baseline

Mode of Product Administration (For Study Epoch 1 and Epoch 2):

1. Infusions

    a. Number of infusions per month

    b. Number of infusion sites (needle sticks) per infusion and per month

    c. Duration of infusion (defined as the time from the start of rHuPH20 infusion until the stop of the immunoglobulin infusion)

    d. Maximum infusion rate/site

    e. Infusion volume/site

f. Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE

2. Number of weeks to reach final dose interval (defined as 3 weeks or 4 weeks infusion interval)

Health-Related Quality of Life

1. Treatment Preference Questionnaire

2. Treatment Satisfaction Questionnaire for Medication: TSQM-9

3. Health-related Quality of Life (HRQoL) Questionnaire: Pediatric Quality of Life (Peds-QL), European Quality of Life 5 Dimension (EQ-5D)

Tertiary Outcome Measures/Other assessments

Infections

1. Number of acute serious bacterial infections (ASBI)

2. Number of all infections

Healthcare Resource Utilization Endpoints

1. Days not able to go to school or work or to perform normal daily activities due to infection or other illnesses

2. Days on antibiotics

3. Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized

4. Number of acute physician visits (office and emergency room) due to infection or other illnesses

Setting

According to the MAH, administration and duration of treatment throughout the study were as follows:

Administration

HyQvia:

Study Epoch 1 (Ramp-up)

- For subjects with a BW of <40 kg: 5 mL/h/site (at start) to 80 mL/h/site (maximum, if tolerated)
- For subjects with a BW of ≥40 kg: 10 mL/h/site (at start) to 240 mL/h/site (maximum, if tolerated)

Study Epoch 2 (Final dosing)

- For subjects with a BW of <40 kg: 10 mL/h/site (at start) to 160 mL/h/site (maximum, if tolerated)
- For subjects with a BW of ≥40 kg: 10 mL/h/site (at start) to 300 mL/h/site (maximum, if tolerated)

KIOVIG (IGI 10%, IGIV 10%) (Epoch 3):

If needed, subjects were to be treated with KIOVIG once every 3 or 4 weeks during Study Epoch 3 (Safety Follow-up). Administration was performed by IV route. The weekly dose was to be equivalent to 100% (±5%) of the dose in the previous study Epoch. The infusion rate and infusion volume per site were to follow the suggestions of the KIOVIG Summary of Product Characteristics.

Cuvitru (IGSC 20%) (Epoch 3):

If needed, subjects were to be treated with Cuvitru subcutaneously daily to once every 2 weeks at the investigator´s discretion, during Study Epoch 3 (Safety Follow-up). Administration was to be performed by SC route. The weekly dose was to be equivalent to 100% (±5%) of the dose in the previous study Epoch. The infusion rate and infusion volume per site were to follow the suggestions of the Cuvitru Summary of Product Characteristics, which is available in the countries where Cuvitru is registered. In countries where Cuvitru is not registered, an Investigator's Brochure was made available for the purpose of this study.

Duration of Treatment:

The recruitment period was expected to be approximately 2 years. The maximum subject participation period was estimated to be approximately 4 years from enrolment to subject completion (participation in Epoch 1, Epoch 2, and Epoch 3). Of note, the actual study participation duration was shorter for all subjects because no subject was reported with anti-rHuPH20 antibody titer of ≥160 at any timepoint during the study.

Subjects

Diagnosis and Criteria for Inclusion:

Each subject had to meet all of the following criteria to be eligible for the study:

1. Subject had to have a documented diagnosis of a form of primary humoral immunodeficiency involving a defect in antibody formation and required gammaglobulin replacement, as defined according to the IUIS (International Union of Immunological Societies) Scientific Committee 2015 (Picard et al., 2015) prior to enrolment. The diagnosis had to be confirmed by the sponsor´s Medical Director prior to first treatment with IP in the study.

2. Subject was at least 2 and below 18 years of age at the time of screening.

3. Subject had been receiving a consistent dose of IgG, administered in compliance with the respective product information for a period of at least 3 months prior to screening. The average minimum pre-study dose over that interval was equivalent to 300 mg/kg body weight (BW)/ 4 weeks and a maximum dose equivalent to 1000 mg/kg BW/4 weeks.

4. Subject had a serum trough level of IgG >5 g/L at screening.

5. If female of childbearing potential, the subject presented with a negative pregnancy test and agreed to employ adequate birth control measures for the duration of the study.

6. Subject/legally authorized representative was willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subject had a known history of or was positive at screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction for hepatitis C virus (HCV), polymerase chain reaction for human immunodeficiency virus (HIV) Type 1/2.

2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests could be repeated once to determine if they were persistent):

a. Persistent alanine aminotransferase and aspartate amino transferase>2.5 times the upper limit of normal for the testing laboratory

b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] ≤500/mm3)

3. Subject had anemia that would have precluded phlebotomy for laboratory studies, according to standard practice at the site.

4. Subject had an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IV immunoglobulin, SC immunoglobulin, and/or Immune Serum Globulin infusions.

5. Subject had severe immunoglobulin A (IgA) deficiency (less than 7.0 mg/dL) with known anti-IgA antibodies and a history of hypersensitivity.

6. Subject had a known allergy to hyaluronidase.

7. Subject had active infection and was receiving antibiotic therapy for the treatment of infection at the time of screening.

8. Subject had a bleeding disorder or a platelet count less than 20,000/µL, or who, in the opinion of the investigator, would have been at significant risk of increased bleeding or bruising as a result of SC therapy.

9. Subject had severe dermatitis that would have precluded adequate sites for safe product administration in the opinion of the investigator.

10. Subject had participated in another clinical study involving an IP or investigational device within 30 days prior to enrolment or was scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.

11. Subject was a family member or employee of the investigator.

12. If female, subject was pregnant or lactating at the time of enrolment.

CHMP comment:

The MAH adequately describes the design of the study, the drug treatment scheme administered throughout the study and exclusion and inclusion criteria for the subjects that were enrolled. There were no significant changes compared to the final approved study protocol.

Variables

According to the MAH, efficacy measurements were performed by measuring trough levels of IgG, analysis of questionnaires concerning treatment preference, treatment satisfaction for medication, HRQoL. Moreover, data on safety was collected (adverse events).

The subject's medical history, medication and non-drug therapy was documented and physical examinations were conducted. Vital signs, clinical laboratory parameters (hematology, urine, pregnancy, viral pathogens) including anti-rHuPH20 antibodies were determined regularly (approximately every 3 months).

For this study, no samples were stored long-term in a biobank for future analyses.

The healthcare resource utilization (HRU) included hospitalizations, length of stay per hospitalization, acute physician visits, ER visits, days on antibiotics and days missed from work/school or unable to perform normal daily activities.

Data sources and management

Source Data

During the study, the MAH contained source data in source documents (original records or certified copies), which were in paper and/or electronic format. Source data for this study comprised the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. No data was entered directly into the electronic case report form (eCRF).

Subject diary

An electronic subject diary was provided to each subject/caregiver at enrolment to record the following information:

- Occurrence of AEs (including infections). The investigator provided guidance for the subject/caregiver regarding identification and documentation of AEs.
- Concomitant medication used.
- Details of the product administration as specified in Study protocol Section 8.7.
- Days missed from school/work or unable to perform normal daily activities due to infection or other illness.
- Non-study-required outpatient visits (including urgent care visits to see healthcare providers) and hospitalizations.

Subjects and/or their parent/legally authorized representatives were trained on use of the diary. The investigator had to review the diary for completeness and request the missing information periodically and in a timely manner. Untoward events recorded in the diary were reported as AEs according to the investigator’s discretion and clinical judgment.

Subject entries in the diary served as source records for this study. During study participation, the investigator had access to the database holding the subject diary data. After the study closure, the investigator has received the diary records for their subjects, including audit trail records, in PDF format. The data were transmitted to the CRF by a validated transfer.

Electronic patient-reported (EPR) modules were used to enable deployment of required subject diaries to subjects based on protocol requirements. Additionally, EPR compliance reports were in place to enable the monitoring of subject compliance, and proactive follow-up, if required. EPRs were deployed in local languages, as needed.

Concerning study documentation, case report forms and document and data retention, the MAH refers to the study protocol:

Study Documentation and Case Report Forms

According to the MAH, the investigator maintained complete and accurate paper format study documentation in a separate file. Study documentation included information defined as "source data" (see Section 8.8 of the study protocol), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor. The investigator complied with the procedures for data recording and reporting. Any corrections to paper study documentation were performed as follows: 1) the first entry was crossed out entirely, remaining legible; and 2) each correction was dated and initiated by the person correcting the entry; the use of correction fluid and erasing were prohibited. The investigator was responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs was provided in electronic form.

If eCRFs were provided by the sponsor, only authorized study site personnel recorded or changed data on the CRFs. If data was not entered on the CRFs during the study visit, the data was recorded on paper, and this documentation was considered source documentation. Changes to a CRF was required documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject remained in the investigator file at the study site in accordance with the data retention policy (see Section 17.3 of the study protocol).

The handling of data by the sponsor, including data quality assurance, complied with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study was described in the data management plan.

Document and Data Retention

The investigator retains study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

CHMP comment:

Based on the provided information concerning the data sources and variables, the MAH conducted the study as planned and with no significant changes as described in the final approved study protocol.

Study size

Approximately 40 pediatric subjects with PIDD were planned to be enrolled. A total of 49 subjects were screened; 42 subjects received investigational product (IP); and 39 subjects completed Epoch 2. All the 42 subjects were analyzed for safety and efficacy of HyQvia. For information on sample size calculation refer to section "statistical methods".

CHMP comment:

By enrolment of 42 subjects, the study size was acceptable and the initially planned number of 40 enrolled subjects was reached.

Data transformation

The MAH states that throughout the study data handling and recordkeeping procedures were performed by the study sponsor to ensure that the captured data were accurate, consistent, complete, and reliable (described in the study protocol (Section 17 of the study protocol)).

The investigator was responsible for the procurement of data and for the quality of data recorded on the CRFs. The eCRFs were provided by the sponsor, and only authorized study site personnel recorded or changed data on the eCRFs. The data available on the paper source documents, were transferred to eCRFs. Changes to a CRF required documentation of the reason for each change recorded in audit trail. An identical (electronic/paper) version of the complete set of CRFs for each subject remained in the investigator file at the study site in accordance with the data retention policy (refer to study protocol Section 17.3). The handling of data by the sponsor, including data quality assurance, complied with regulatory guidelines (e.g. ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study were described in the data management plan.

Statistical methods

In the final study report, it is described that subjects were classified into the following analysis sets: Screened Set, Enrolled Set, Full Analysis Set, and Safety Analysis Set.

Sample Size Calculation:

The study was not designed for statistical hypothesis testing. The sample size selected for the study was primarily determined by the objective to collect safety data on HyQvia in a sufficient number (about 40) of pediatric (age 2 to <18 years) subjects with PIDD who had received prior immunoglobulin therapy before enrolment into this study. In addition, the guideline of the CHMP (Committee for Medicinal Products for Human Use, 2015) on the clinical investigation of human normal immunoglobulin for SC and/or intramuscular administration indicated that at least 40 subjects should be included to evaluate replacement therapy in primary immunodeficiency syndromes. Thus, a total of 42 subjects were enrolled in this study.

Planned Statistical Analysis:

Subject disposition and demographic and other baseline characteristics were summarized as described in the Statistical Analysis Plan. Disposition summaries and listings were based on the Screened Set and demographics, whereas other baseline characteristics summaries were based on the Safety Set. A summary of number and proportion of subjects in different population sets were provided.

Assessment of safety was the primary objective of this study. The primary endpoints/outcome measures (number and rate per infusion [excluding infections] of all severe related AEs, and number and rate per infusion [excluding infections] of related SAEs), were analyzed using descriptive statistics. In addition, incidence of all severe related AEs and related SAEs were calculated as rate per infusion and rate per subject-year.

A point estimate and corresponding 95% confidence interval (CI; by the Wilson score method) for the proportion of subjects with one or more related SAEs and the proportion of subjects with one or more severe related AEs were presented for the primary outcome measures. These outcome measures were also summarized by clinically meaningful subgroups: sex and age groups.

For all the secondary safety outcome variables, descriptive methods, mainly frequency tables, were used for all secondary safety endpoints. In addition, AEs were summarized in terms of AEs per subject (rate per subject), AEs per infusion, AEs per subject-year.

Descriptive statistics were also performed for all the secondary efficacy outcome variables as well as for other outcome variables (mode of product administration, HRQoL, infections, Healthcare Resource Utilization [HRU]).

A single, formal, prospectively planned interim analysis of data (cut-off date: 14 May 2020) was performed to update the scientific community, on the interim safety, tolerability, and immunogenicity of HyQvia in pediatric subjects with PIDD.

Missing unused, and spurious data

According to the MAH, data that appeared to be spurious (e.g., outliers, incompatible with life) were queried by Clinical Data Management and then were either corrected or explained in the Clinical Study Report (CSR) if not correctable. Outliers were not excluded from analysis unless otherwise specified. Any exclusion of data from analysis was appropriately footnoted in the relevant TFLs.

Quality control

Throughout the study, the investigator complied with the protocol and applicable regulatory requirements, fulfilled his responsibility to conduct all aspects of the study at the study site and verified by signature the integrity of all data transmitted to the MAH. The study monitor ensured appropriate training of the personnel and verifying that each study site conducted the study according to the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements. Data handling and recordkeeping procedures were performed by the study sponsor to ensure that the captured data were accurate, consistent, complete, and reliable, as described in the study protocol. Audits were performed by the MAH as described in the clinical quality management plan.

CHMP comment:

Based on the provided information concerning the quality control, statistical methods and data transformation, the MAH conducted the study as planned and with no significant changes as described in the final approved study protocol.

CHMP comment:

Research Methods:

Notably, in the final study report the MAH does not comment on potential measures that were taken to minimize bias in the study. Please discuss how bias in the study has been minimized by addressing potential sources of bias (e.g. concerning the enrolment of eligible subjects) and describing the resulting measures that were taken throughout the study to minimize bias (OC 1) (see also Assessor comment after "Descriptive data").

7.5.1. Results

Participants

A total of 42 subjects met eligibility criteria and were enrolled and dosed in the study. All these subjects were included as Enrolled Set, which was identical to the Full Analysis Set and Safety Analysis Set. Of all the subjects enrolled in this study, most of the subjects (39 [92.9%] subjects) completed Epoch 2. One subject from HyQvia new starter group discontinued Epoch 2 and entered Epoch 3 due to a severe related treatment-emergent AE (TEAE) of emotional distress. Three (7.1%) subjects prematurely discontinued the study: 1 (2.4%) subject before completing Epoch 1 (HyQvia new starter) and 2 (4.8%) subjects before completing Epoch 2 (both HyQvia pre-treated subjects). Reason for study discontinuation in all 3 subjects was withdrawal by the subject and none of these 3 subjects discontinued due to any TEAE.

CHMP comment:

The MAH clearly presents the number of participants involved in analyses and the proportion of subjects excluded throughout the study including reasons.

Descriptive data

There was over four-fold higher proportion of male subjects (81.0%; n=34/42) than the female subjects (19.0%; n=8/42) enrolled, and the distribution was similar across both the groups. Most (97.6%, n=41/42) of the subjects enrolled were white and had median body mass index of 18.55 (range: 12.3 to 32.7) kg/m2; and this was similar across both the groups. Within the subjects enrolled in this study, the most commonly diagnosed primary immunodeficiency was of the common variable type (42.9% n=18/42), followed by X-linked agammaglobulinemia (38.1%, n=16/42) (Table 2).

Table 2: from Table 4 of the clinical study report: PIDD Diagnosis-Safety Analysis Set

PIDD Term	HyQvia new starters (N=23)	HyQvia pre-treated (N=19)	All Subjects (N = 42)
Agammaglobulinemia – AR [n (%)]	1 (4.3)	1 (5.3)	2 (4.8)
Congenital Agamma – XLA [n (%)]	8 (34.8)	8 (42.1)	16 (38.1)
Common Variable Immunodeficiency [n (%)]	11 (47.8)	7 (36.8)	18 (42.9)
Severe Combined Immune Deficiency [n (%)]	0	1 (5.3)	1 (2.4)
Other: Activated Phosphokinase 3 Delta Receptor Syndrome (APDS) [n (%)]	0	1 (5.3)	1 (2.4)
Other: Hypogammaglobulinemia [n (%)]	1 (4.3)	0	1 (2.4)
Other: Nemo Immune-deficiency [n (%)]	2 (8.7)	0	2 (4.8)
Other: PI3K-Delta Syndrome [n (%)]	0	1 (5.3)	1 (2.4)

Abbreviations: AR = Autosomal Recessive; IgG = immunoglobulin G; PIDD=Primary Immunodeficiency Diseases; PI3K = Phosphoinositide 3-kinase; XLA = X=linked Agammaglobulinemia.

HyQvia new starters: Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 and treated with HyQvia.

HyQvia pre-treated: Subjects already treated with HyQvia by time of enrollment (HyQvia pre-treated) were enrolled directly in Epoch 2 and treated with HyQvia.

The median age of the subjects was 11.5 (range: 3 to 17) years (HyQvia new starter subjects: 11.0 (range 3 to 17) years and HyQvia pre-treated subjects: 12.0 [range 3 to 17] years) (Table 3):

Table 3: from Table 3 of the clinical study report: Demographic and Baseline Characteristics-Safety Analysis Set

Subject Characteristics	Statistic	HyQvia new starters (N=23)	HyQvia pre-treated (N=19)	All subjects (N=42)
Age (Years) [a]	n	23	19	42
	Mean (SD)	10.3 (3.82)	11.7 (4.33)	11.0 (4.07)
	Median	11.0	12.0	11.5
	Min, Max	3, 17	3, 17	3, 17
Age Group (Years)	2 to <6 years	3 (13.0)	3 (15.8)	6 (14.3)
	6 to <12 years	11 (47.8)	4 (21.1)	15 (35.7)
	12 to <18 years	9 (39.1)	12 (63.2)	21 (50.0)

Medical History

All enrolled subjects (included under Safety Analysis Set) had at least one medical history. The most frequently (≥10 subjects) reported medical history by SoC was immune system disorders (57.1%, n=24/42); followed by congenital, familial and genetic disorders (52.4%, n=22/42); respiratory, thoracic, and mediastinal disorders (40.5%, n=17/42); and infections and infestations (38.1%, n=16/42). All other medical histories by SoC were reported in less than 10 subjects.

The most frequently (≥10 subjects) reported history by PT were Bruton's agammaglobulinemia (35.7%, n=15/42) and immunodeficiency common variable (38.1%, n=16/42). All other medical history was reported in less than 10 subjects.

Prior Medications

Over 90% of the subjects had taken at least one prior medication (92.9%, n=39/42). All the 39 subjects who had taken at least one prior medication had taken the immune sera and immunoglobulins (immunoglobulins, normal human) whereas, analgesics (Anilides) and anti-bacterials for systemic use (Penicillins with extended spectrum) were reported for 1 (2.4%) subject each.

Concomitant Medications

Overall, a total of 38 (90.5%) subjects received at least one concomitant medication during the study. The most frequently reported concomitant medications in ≥10 subjects by therapeutic class included: anti-bacterials for systemic use (23 [54.8%] subjects); analgesics (16 [38.1%] subjects); cough and cold preparations (13 [31.0%] subjects); medications for obstructive airway diseases (11 [26.2%] subjects); and antihistamines for systemic use (10 [23.8%] subjects). During this study, 14 (33.3%) subjects were treated with any other non-therapeutic products. The rest of the concomitant medication, non-drug therapies, and procedures were reported in less than 10 subjects.

CHMP comment:

Notably, all participants of the study were Hispanic or Latino and all but one patient were white (for one patient race was "not applicable" as not collected by local regulations). Thus, the significance of this study may be restricted to the Caucasian population and potential differences between ethnicities cannot be determined.

Furthermore, in this study, PIDD most frequently diagnosed was the primary immunodeficiencies of the common variable type (42.9% n=18/42) and the X-linked agammaglobulinemia (38.1%, n=16/42). For the other types of PIDD, only a limited number of subjects was included. Overrepresentation of males in the study set is due to the high proportion of X-linked agammaglobulinemia in the study. The MAH should include the topic of the enrolment of eligible subjects, in particular regarding a potential selection bias of the target population (high proportion of X-linked agammaglobulinemia in the study, overall representation of the frequencies of the different PIDD types in the study population) in the discussion of the bias in this study (cf. OC1).

Of note, most patients in the study were 6 to <18 years old. Only 3 patients who were 2 to <6 years old were enrolled.

Patient's medical histories, prior and concomitant medications are in line with the known susceptibility of the patients to infections associated with PIDD.

Main results and adverse events/adverse reactions

Efficacy Evaluations

Trough levels of IgG (Epoch 1 and Epoch 2)

The baseline defined for HyQvia new starter subjects was the study baseline visit and for HyQvia pre-treated subjects Epoch 2 Month 0 visit was defined as the baseline visit.

Overall, no substantial differences in total IgG trough levels across timepoints were observed in the change from baseline values to Epoch 2 Month 12. The mean and median change in IgG trough levels from baseline to Epoch 2 Month 0 were 0.143 g/L and -0.220 g/L, at Epoch 2 Month 6 were 0.100 g/L and -0.235 g/L and Epoch 2 Month 12 were -0.306 g/L and 0.220 g/L, respectively. Similar trend in change from baseline in trough levels were observed for HyQvia new starters and HyQvia pre-treated subjects. Serum levels of mean and median trough IgG at the Epoch 2 Month 0 visit were 8.801 g/L and 8.535 g/L, respectively, at the Epoch 2 Month 6 visit were 8.862 g/L and 8.735 g/L, respectively and at the Epoch 2 Month 12 visit were 8.469 g/L and 8.720 g/L, respectively. The decrease in the mean total serum IgG trough levels at Month 12 could be attributed to a 11-year old male who had a critically low trough serum IgG level of 1.43 g/L (change from baseline: -8.00 g/L) at Epoch 2 Month 12 visit. This was attributed to an event of inflammatory bowel disease that was ongoing at study completion. In this case this clinically significant abnormal IgG value constituted an unrelated AE, which was attributed to the alternate etiology of inflammatory bowel disease.

Overall, there were no clinically meaningful differences in trough IgG levels across age groups during Epoch 2, with the highest mean change from the baseline measurement of -1.276 g/L and the highest median change from the baseline measurement of -1.145 g/L during the study. Mean IgG levels in subjects across age groups at baseline and Month 0 remained similar however, for age group of 12 to <18 years, the mean IgG levels at Month 6 and Month 12 was comparatively higher than the other two age groups of 2 to <6 years and 6 to <12 years.

A total of 13 subjects reported abnormal IgG levels between baseline and Epoch 2 Month 12 visit, with a clinically significant abnormal value in 6 subjects. Among 5 of these 6 subjects, the abnormal values were attributed to pre-existing disease.

A slight change from baseline in the mean trough levels within all the IgG subclasses were observed at different timepoints. Between the IgG subclasses, the change from baseline values at Epoch 2 Month 12 showed quite high variability. The mean and median changes from baseline of IgG subclass trough levels were similar across HyQvia new starters and HyQvia pre-treated subject.

In terms of trough levels of specific antibodies to clinically relevant pathogens, at the Epoch 2 Year 1 termination visit, all the subjects had mean trough levels of specific antibodies against Clostridium tetani toxoid, Haemophilus influenzae B, and Hepatitis B Virus (HBV) nearly 10 times the levels considered to be the minimal protective titer.

Health-related quality of life

Quality of life was assessed using the Peds-QL and EQ-5D questionnaires. A parent or a legally authorized representative completed the questionnaires on behalf of subjects aged less than 13 years and subjects aged 13 to <18 years completed the questionnaires themselves.

The responses on Treatment Preference Questionnaire were obtained for 15 of 42 subjects (HyQvia new starters: 6 subjects; HyQvia Pre-treated: 9 subjects). At baseline, majority of the subjects that responded to the questionnaire preferred administration of the immunoglobulin therapy at home (14/15 subjects, 93.3%). The responses were similar across HyQvia new starters and HyQvia pre-treated subjects.

The data on Treatment Preference Questionnaire could be obtained from 20 subjects at the end of Epoch 2. From the available data, at the end of Epoch 2, all the analyzed subjects (n=20, 100%) reported that they would choose to continue using HyQvia treatment. These subjects also provided positive responses (liked very much/liked) towards preference for HyQvia in terms of the ability to fit treatment into schedule (total subjects with 'liked very much' or 'liked' responses: 100.0%; subjects with 'liked very much' (responses: 50.0% / subjects with 'liked' responses: 50%). About ≥90% of the subjects that responded to the questionnaire provided positive responses towards preference for HyQvia with respect to the overall convenience (95.0%; 30.0%/65.0%) and the number of needle-sticks per month (90.0%; 45.0%/45.0%). Furthermore, majority of subjects provided positive responses to frequency of administration (85.0%; 45.0%/40.0%), total time spent for the treatment per month (75%; 35.0%/40.0%), ease of administration (85.0%; 35.0%/50.0%), potential to self-administer (85.0%; 50.0%/35.0%), amount of time the administration takes (80.0%; 35.0%/45.0%), complexity of the administration process (70.0%; 25.0%/45.0%), and self-administer without medical supervision (85.0%; 45.0%/40.0%).

Responses to the TSQM-9 were obtained for 13 of 42 subjects at baseline. The mean (SD) TSQM9 scores for medication at baseline were 82.05 (18.308), 67.95 (23.587), and 84.07 (10.970) for effectiveness, convenience, and global satisfaction, respectively. At the end of Epoch 2, the mean (SD) TSQM-9 scores for the effectiveness (n=23), convenience (n=24), and global satisfaction (n=24) were 76.09 (22.686), 73.84 (14.137), and 80.06 (16.582), respectively.

Regarding the treatment satisfaction with HyQvia assessed using TSQM 9 scale at the end of Epoch 2, due to the amount of missing ePROs data and thus the small sample size available (n=23 for the effectiveness evaluation, n=24 each for convenience and global satisfaction evaluation) the results should be interpreted with caution for this outcome parameter.

Similar to TSQM 9, the data should be interpreted with caution for the QoL assessments by Peds-QL and EQ-5D questionnaires at the end of Epoch 2, due to the amount of missing ePROs data as well as the small size for the Peds-QL total score (2 to 4 years old [n=1]; 5 to 7 years [n=1]; 8 to 12 years [n=3]; 13 to <18 years [n=8]) and the EQ-5D questionnaire (n=12).

The subjects were not able to go to school or work or to perform normal daily activities due to infection or other illness at a rate of 7.51 days per subject-year. The rate of hospitalizations was less than 1 per subject-year, and the rate of days hospitalized was also less than 1 day per subject-year. The rate of acute physician visits due to infection or other illness was less than 1 visit per subject-year. All these

rates were similar across HyQvia new starter subjects and HyQvia pre-treated subjects, with a relatively lower rate observed among the HyQvia new starters.

The rate of days on antibiotics was 64.02 days per subject-year. The rates of days on antibiotics were similar across HyQvia new starter subjects and HyQvia pre-treated subjects, with a relatively lower rate observed among the HyQvia new starters.

During the study, 1 ASBI of pneumonia (bacterial pneumonia) was reported in 1 (2.4%) subject who belonged to HyQvia new starter group; this event was reported as an SAE, which was assessed as not related to HyQvia treatment.

The rate of all infections per subject-year was 1.486; the rates were similar across both the HyQvia new starter and HyQvia pre-treated groups.

Safety Evaluations

The MAH states that the mean dose received per body mass per week was 0.13 (range: 0.1 to 0.3; SD=0.046) g/kg/week across all the subjects during Epoch 2. Overall, the mean HyQvia treatment exposure during Epoch 2, number of infusions, infusion per month, and number of infusions sites were similar across HyQvia new starters and HyQvia pre-treated groups, as observed from the mode of administration results. A mean of 18.9 infusions were administered per subject, with 1.28 mean infusions administered per month. The mean duration of infusion (overall: 89.0 mins) was similar across the HyQvia new starters and HyQvia pre-treated subjects, with a comparatively lower duration observed among the HyQvia new starters, which may be attributable to lower volume infusions received by HyQvia new starters during Epoch 1 or Epoch 2.

The mean number of infusion sites per infusion was 1.47 (SD=0.466) and was similar across HyQvia new starters and HyQvia pre-treated subjects. The maximum infusion rates per site (overall mean: 177.64 mL/h/site) were comparable across both the groups. The mean infusion volume per site was 139.72 mL. HyQvia pre-treated subjects had a comparatively higher mean infusion volume per site compared with HyQvia new starters. Despite infusion interruptions, almost all the subjects completed their infusions.

Two (2) severe related TEAEs (1 local and 1 systemic) were reported during the study, both reported in 1 (2.4%) 11-year old subject from the HyQvia new starters group, who had several ongoing medical conditions. This subject discontinued the HyQvia treatment due a severe related TEAE of emotional distress, entered Epoch 3, and completed the study. No severe related TEAEs were reported in the HyQvia pre-treated subjects.

Tables 4 and 5 summarize the severe TEAEs by SOC and PT and the overall TEAEs/ARs (excluding infections), respectively.

Table 4: from Table 10 of the clinical study report: Severe Related Treatment-Emergent Adverse Events, by SOC and PT (excluding infections)-Safety Analysis Set

	HyQvia new starters (N=23)		HyQvia pre-treated (N=19)		Total (N=42)	
System Organ Class/ Preferred Term	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Subjects with any Severe Related TEAE [a]	1 (4.3)	2	0	0	1 (2.4)	2
General disorders and administration site conditions	1 (4.3)	1	0	0	1 (2.4)	1
Infusion site pain	1 (4.3)	1	0	0	1 (2.4)	1
Psychiatric disorders	1 (4.3)	1	0	0	1 (2.4)	1
Emotional distress	1 (4.3)	1	0	0	1 (2.4)	1

Abbreviations: TEAE = Treatment-emergent adverse event.

HyQvia new starters: Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 and treated with HyQvia

HyQvia pre-treated: Subjects already treated with HyQvia by time of enrollment (HyQvia pre-treated) were enrolled directly in Epoch 2 and treated with HyQvia.

For the columns of 'Number (%) of subjects': Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.

For the columns of 'Number of events', multiple occurrences of the same event in the same subject were counted multiple times.

[a] TEAEs recorded in the study database as "possibly related" or "probably related" to HyQvia were considered HyQvia-related adverse events, or equivalently, Adverse Reactions (AR).

Table 5: from Table 9 of the clinical study report: Treatment-Emergent Adverse Events and Adverse Reactions, Overall Summary (excluding infections)-Safety Analysis Set

	HyQvia new starters (N=23)		HyQvia pre-treated (N=19)		Total (N=42)	
Category	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any TEAE	18 (78.3)	102	11 (57.9)	50	29 (69.0)	152
Any AR [a]	12 (52.2)	42	3 (15.8)	7	15 (35.7)	49
Any severe related TEAE [a]	1(4.3)	2	0	0	1(2.4)	2
Any serious TEAE	0	0	3 (15.8)	4	3(7.1)	4
Any serious related TEAE [a]	0	0	0	0	0	0
Any local TEAE	11 (47.8)	38	3 (15.8)	3	14 (33.3)	41
Any local AR [a]	11 (47.8)	37	3 (15.8)	3	14 (33.3)	40
Any systemic TEAE	15 (65.2)	64	10 (52.6)	47	25 (59.5)	111
Any systemic AR [a]	3 (13.0)	5	1(5.3)	4	4(9.5)	9
Any temporally associated TEAE [b]	13 (56.5)	49	6 (31.6)	9	19 (45.2)	58
Any related and/or temporally associated TEAE [a,b]	13 (56.5)	52	6 (31.6)	11	19 (45.2)	63
Any local related and/or temporally associated TEAE [a,b]	11 (47.8)	38	3 (15.8)	3	14 (33.3)	41
Any systemic related and/or temporally associated TEAE [a,b]	6 (26.1)	14	4 (21.1)	8	10 (23.8)	22

Abbreviations: AR = Adverse reaction; Related = HyQvia -related; TEAE = Treatment-emergent adverse event.

HyQvia new starters: Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 and treated with HyQvia

HyQvia pre-treated: Subjects already treated with HyQvia by time of enrollment (HyQvia pre-treated) were enrolled directly in Epoch 2 and treated with HyQvia.

For the columns of 'Number (%) of subjects': Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.

For the columns of 'Number of events', multiple occurrences of the same event in the same subject were counted multiple times.

[a] Adverse events recorded in the study database as "possibly related" or "probably related" to HyQvia are considered HyQvia-related adverse events, or equivalently, Adverse Reactions (AR).

[b] Temporally associated TEAEs are defined as TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion.

Generally, a higher proportion of the TEAEs/ARs were reported among the HyQvia new starter subjects than the HyQvia pre-treated subjects and the proportion of subjects experiencing local ARs (excluding infections) (33.3% subjects) was higher compared to the proportion of subjects experiencing systemic ARs (excluding infections).

Amongst the total amount of 41 local related and/or temporally associated TEAEs, the most commonly reported (≥10%) local TEAEs by PT were infusion site pain and infusion site pruritus. Most of the local TEAEs/ARs were assessed as mild, only 1 was severe.

The majority of the total 111 systemic TEAEs were assessed as mild and unrelated. Amongst the total amount of 22 systemic local related and/or temporally associated TEAEs (excluding infections), the most commonly reported systemic TEAEs by PT were pyrexia and gastrointestinal disorders.

Excluding infections, overall rates of systemic ARs (related systemic TEAEs) per infusion and per subject were <0.1 and 0.214, respectively. Excluding infections, the overall rates of local ARs (related local TEAEs) per infusion and per subject were <0.1 and 0.952, respectively. This corresponds to lower overall rate of systemic ARs per subject-year (0.171) compared with local ARs per subject-year (0.762).

A total of 8 serious TEAEs (including infections) were reported in 7 (16.7%) subjects (dental caries, inflammatory bowel disease, idiopathic orbital inflammation, pyrexia, acute sinusitis, pharyngitis, pilonidal cyst and pneumonia) and 4 serious TEAEs (excluding infections) were reported in 3 (7.1%) subjects. Six out of 8 serious TEAEs were reported in the HyQvia pre-treated subjects, while the remaining 2 serious TEAEs were reported in the HyQvia new starters. However, none of these serious TEAEs were considered to be related to HyQvia by the investigator.

No death among analyzed subjects was reported during the conduct of this study.

None of the subjects developed binding anti-rHuPH20 antibodies with a titer ≥160, and therefore none was assessed for neutralizing anti-rHuPH20 antibodies (as per protocol). Most of the subjects had a negative test result for binding anti-rHuPH20 antibodies or a titer of 5; the highest titer was 80.

Assessment of hemolysis and other clinical laboratory parameters did not raise any safety concerns with respect to HyQvia administration. No substantial changes from baseline were observed in the vital signs and physical examinations among the study subjects during the study.

CHMP comment:

The MAH presents adverse events adequately in a tabular format. The most frequently described adverse events were general disorders and administration site conditions, which were already identified through the development program for HyQvia.

It has to be noted that questionnaires Peds-QL and TSQM-9 were completed by only a limited sample size (roughly a third to half of the subjects) from the 42 enrolled subjects. Generally, treatment preference and satisfaction with HyQvia and physical and mental health stayed largely at the same level during the study. Also, the rate of hospitalizations and the amount of days on which the subjects were not able to go to school or work or to perform normal daily activities due to infection or other illness was at a low level.

7.6. Discussion

The MAH states that overall, the safety data in this study are consistent with results obtained in Clinical Studies 160603 and 160902, as well as in the literature among patients with PIDD.

None of the reported SAEs were considered by the investigator to be related to HyQvia. The total number of SAEs (8 serious TEAEs [including infections] were reported in 7 subjects and 4 serious TEAEs [excluding infections] were reported in 3 subjects).

One 11-year old subject discontinued treatment with HyQvia during Epoch 2 due to a severe related TEAE of emotional distress who entered Epoch 3, and then completed the study.

The subject had several ongoing medical conditions. Overall, the AEs and ARs (regardless of the location [local/systemic], severity [mild/moderate/severe], and causality [related/related and/or temporally associated]) were observed at a relatively higher proportion among the HyQvia new starters than the HyQvia pre-treated subjects.

Most of the related TEAEs were mild in severity, with only 2 severe related TEAEs (1 local and systemic) both reported in 1 (2.4%) subject from the HyQvia new starter group, the 11-year old boy, mentioned above. Local TEAEs were reported in 14 (33.3%) subjects and were representative of local ARs at the infusion site (except for 1 local TEAE of infusion site rash in HyQvia new starter subject). The majority of the local TEAEs were reported among HyQvia new starter subjects. Except for 1 severe event, all the local TEAEs were assessed as mild. Excluding infections, the overall rates of local ARs (related local TEAEs) per infusion, per subject, and per subject-year were <0.1 (rate: 0.050), 0.952, and 0.762, respectively; this corresponded to lower overall rate of systemic ARs per subject-year (0.171) compared with local ARs per subject-year (0.762).

Overall, the rates of systemic TEAEs per infusion, per subject, and per subject-year were 0.140, 2.643, and 2.115, respectively; most of these events were assessed as mild and unrelated to HyQvia. During the total study period, the rates of systemic ARs per infusion, per subject, and per subject-year were <0.1 (rate: 0.011), 0.214, and 0.171, respectively.

None of the subjects developed binding anti-rHuPH20 antibodies with a titer ≥160, and therefore none were assessed for neutralizing anti-rHuPH20 antibodies (as per protocol). Assessment of hemolysis and other clinical laboratory parameters did not raise any safety concerns with respect to HyQvia administration.

In terms of efficacy evaluations, the total IgG levels in general were similar across Epoch 2. Given the overall mean trough IgG level at baseline was 8.776 g/L and at Epoch 2 Month 12 was 8.469 g/L, the mean IgG levels during Epoch 2 were well above what could be considered a putative therapeutic protective threshold of 7 g/L.

The serum trough IgG levels between age groups during Epoch 2 also showed no clinically meaningful differences; with the highest mean change from the baseline measurement of -1.276 g/L and the highest median change from the baseline measurement of -1.145 g/L during the study. A similar trend was observed for IgG subclass levels with no substantial changes from baseline across Epoch 2 and no notable age group differences.

At the time of the completion visit, the mean trough levels of specific antibodies against Clostridium tetani toxoid, Haemophilus influenzae B, and HBV in all subjects were at 10 times the levels considered to be the minimal protective titers.

A total of 795 infusions were administered during the study. Overall, the mean number of infusions per month was 1.28 (SD=0.184), with similar proportions observed across HyQvia new starter subjects and HyQvia pre-treated subjects. The mean number of infusion sites per month was 1.67 (SD=0.777), with similar mean number of infusion sites per month observed across HyQvia new starter subjects and HyQvia pre-treated subjects. The mean duration of infusions among all the study subjects was 89.0 mins, and was comparatively lower among the HyQvia new starter subjects (mean: 79.2 [SD=30.29] mins) than HyQvia pre-treated subjects (mean: 104.7 [SD=35.07] mins). This could be attributed to the relatively higher mean infusion volume per site (overall: 139.72 [SD=89.755] mL) noted among the HyQvia pre-treated subjects (178.23 [SD=98.523] mL) than the HyQvia new starters (112.39 [SD=71.427] mL).

The rate of ASBI occurrences among the study population was as low as 0.019 per subject-year. The efficacy of HyQvia was further demonstrated by the annualized rate of all infections per subject,

consistent with results obtained in Clinical Studies 160603 and 160902. The rate of all infections per subject-year was 1.486; the rate was similar across both the HyQvia new starter and HyQvia pre-treated groups. The most frequently reported infections (occurring in ≥10% subjects) by PT included: rhinitis, gastroenteritis, and nasopharyngitis.

At the end of Epoch 2, the treatment preference questionnaire indicated a high preference for the HyQvia treatment. Most of the analyzed subjects provided positive responses for the majority of questions in the Treatment Preference Questionnaire, in particular for ability to fit treatment into schedule, the overall convenience, and number of needle-sticks per month. All the subjects expressed a preference for continuing treatment with HyQvia. Besides treatment preference, the current study further evaluated treatment satisfaction with HyQvia using the TSQM-9 assessment, as well as quality of life using the Peds-QL and EQ-5D questionnaires. However, given the small sample size due to the amount of missing ePROs data, result of these outcome parameters should be interpreted with caution.

In terms of HRU outcome measures, the rate of hospitalizations was less than 1 per subject-year and the rate of days hospitalized was also less than 1 day per subject-year. The rate of days wherein a subject was not able to go to school or work or to perform normal daily activities due to infection or other illness was low (7.51 days per subject-year). The rate of acute physician visits due to infection or other illness was less than 1 visit per subject-year. The rate of days on antibiotics of 64.02 days per subject-year and the total days on antibiotics (mean 146.1 days) are for specific infections not treated by immunoglobulins such as pneumocystis pneumonia.

CHMP comment:

Apart from commenting on the small sample size concerning the TSQM-9 assessment and quality of life Peds-QL and EQ-5D questionnaires, the MAH does not discuss possible further limitations of the study. Moreover, no statement with regards to the generalisability of the study was posed.

The MAH is asked to further discuss the limitations (e.g. concerning study population, impact of home administration on AE reporting, missing data…) and comment on generalisability of the results to other (pediatric) populations (OC 2).

The results of the current study are in line with the findings of the PASS 161302 that confirmed rare occurrence of rHuPH20-reactive binding antibodies with no evidence for neutralizing activity in the subjects.

The Health-Related Quality of Life and Health Resource Use questionnaires did not reveal significant fluctuations in physical or mental health or satisfaction of the patient with the treatment during study progression. Overall, the subject's satisfaction with HyQvia treatment was high.

7.7. Conclusion

The MAH states that HyQvia was found to be safe and tolerable among pediatric subjects (2 to <18 years old) with PIDD. During the course of this study, the rate of TEAEs, both local and systemic, was low; a total of 2 treatment-related severe TEAEs at a rate of <0.1 (rate: 0.003) TEAE per infusion were reported and none of them were deemed serious. The rate per infusion of serious TEAEs (excluding infections) was <0.1 (rate: 0.005) with only 4 serious TEAEs (excluding infections) reported in 3 HyQvia pre-treated subjects. None of these were related to the treatment. Most of the ARs reported during the study were mild in severity. The rates of local ARs and systemic ARs were lower among the HyQvia pre-treated group compared to the HyQvia new starter group.

No substantial difference in the total IgG trough levels and IgG subclass levels across timepoints from baseline was observed, and the protective IgG levels were maintained throughout Epoch 2 among all the study subjects with similar levels observed across age groups.

Since none of the subjects developed binding anti-rHuPH20 antibodies with a titer ≥160 at any timepoint, the levels of neutralizing anti-rHuPH20 antibodies were not assessed for any subject.

The rate of ASBI occurrences among the pediatric subjects with PIDD was as low as 0.019 per subject-year. The efficacy of HyQvia was further demonstrated by the annualized rate of all infections per subject, consistent with results obtained in Clinical Studies 160603 and 160902. The rate of all infections per subject-year was 1.486; the rate was similar across both the HyQvia new starter and HyQvia pre-treated group.

The majority of the subjects achieved a treatment interval of 4 weeks and maintained a treatment interval of 3 or 4 weeks for 12 months during Epoch 2. Overall, HyQvia was able to be administered subcutaneously at the same dosing interval as IV immunoglobulin therapies for PIDD, with a mean of 1.28 infusions per month and duration of 89.0 mins, with a good tolerability profile for both local and systemic ARs. For all the analyzed subjects, HyQvia was the preferred mode of immunoglobulin therapy for continuation.

CHMP comment:

The current PASS provides further data on the use of HyQvia in the pediatric population.

Overall, the rate of reported AEs is low and reflects the known safety profile for HyQvia. Two (2) severe TEAEs related to HyQvia treatment were reported (infusion site pain and emotional distress), both in the same subject, who discontinued the Epoch 2 of the study due to emotional distress.

The study confirms that high levels of rHuPH20-reactive binding antibodies are rare. Most of the subjects had a negative test result for binding anti-rHuPH20 antibodies or a titer of 5. Neutralizing antibodies were not assessed as no subject developed anti-rHuPH20 antibodies with a titer ≥160 could be detected, which supports a previous PASS with HyQvia (161302) that the formation of neutralizing antibodies upon administration of HyQvia does not pose a risk to the efficacy of the product.

Stable and sufficiently protective IgG levels determined throughout the study and a low rate of acute serious bacterial infections (ASBI) occurrences among the pediatric subjects with PIDD (0.019 per subject-year) underline the efficacy of HyQvia treatment.

The Health-Related Quality of Life and Health Resource Use questionnaires did not reveal significant fluctuations in physical or mental health or satisfaction of the patient with the treatment during study progression. Overall, the subject's satisfaction with HyQvia treatment was high.

No new safety concerns were identified following HyQvia treatment in pediatric subjects with PIDD who had received immunoglobulin therapy prior to study enrolment.

The benefit-risk balance remains unchanged.

An update to the RMP resulting from the data presented in this PASS final study report was submitted.

8. PRAC advice

N/A

9. Risk management plan

The MAH was requested to submit an updated RMP version 13.1 with this variation. Compared to the last by the EMA approved version, there were no changes concerning the safety concerns of HyQvia.

The (main) proposed RMP changes were the following:

9.1. Safety Specification

Epidemiology of the indications and target population

In the new version 13.1 of the RMP, the MAH updated and added citations and information about PIDD and SIDD. Novel text passages added by the MAH are indicated below in yellow.

Primary immunodeficiency syndromes	
Incidence	Primary immunodeficiency diseases (PIDD) are recognised as inherited, heterogeneous disorders of the immune system that result in increased rates of severe infections, immune dysregulation associated with autoimmune diseases, and the development of malignancies [1,2]. The International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies currently recognises more than 430 PID syndromes that can be caused by defects in 408 distinct genes including 64 gene defects identified or confirmed since 2018 [3,4]. However, some forms of PIDD are extremely rare, so fewer than 20 types comprise more than 90% of all PIDDs [1]. The estimated incidence of PIDD (in aggregate) has historiccaly been reported as between as 1 per 10,000 persons and 1 per 50,000 persons [1,5] but with improved definition of clinical phenotypes the collective incidence has been re-estimated to be at least 1 per 1000 to 1 per 5000 persons[3].

Secondary Immunodeficiencies	
	Congenital acquired immune deficiency syndrome (AIDS) (with recurrent bacterial infections) Globally, it is estimated that more than 1,000 infants are born with HIV each day [39]. In 2011 there were an estimated 7.6 per 100 000 population diagnosed with HIV in the EU, representing an increase of 16% of cases compared to 2004 [40]. *Multiple Myeloma* Worldwide, incidence ranges from 0.4 to 6 cases per 100,000 person years, representing 0.8% of all cancer diagnoses [41-45]. In 2016 an age-standardized incidence rate was estimated at 2.1 / 100,000 persons [46]. Incidence rates are highest and appear to be on the rise in North America, Australia, New Zealand, and Europe unlike rates in Asian countries which have remained considerably stable [41,43,45,47]. *Chronic lymphocytic leukaemia (CLL) with hypogammaglobulinemia* Hypogammaglobulinemia, a common immunodeficient abnormality, develops in up to 85% of CLL patients and is highly associated with increased susceptibility to infection in all patients [48,49]. Global incidence of CLL varies, in part due to the reported differences associated with ethnicity among the population [50,51]. The estimated incidence of CLL in Europe is approximately 6.96 cases per 100 000 population annually, whereas a lower incidence of 4.5 cases per 100 000 population has been reported in the US [52,53]. *Allogeneic HSCT/with hypogammaglobulinemia* HSCT is used for a broad spectrum of indications worldwide, with a frequency that varies considerably among the world regions. In Europe allogeneic HSCTs account for 38% of all HSCT procedures [54]. In other regions such as Asia and the Eastern Mediterranean/Africa allogeneic HSCT are more common representing 58% and 65% of procedures.
Prevalence:	The most prevalent secondary immunodeficiency is the one caused by HIV and causes the acquired immunodeficiency syndrome, which prevalence varies worldwide. There were approximately 37 million individuals living with HIV at the end of 2020 of which 73% (~27 million) were receiving antiretroviral therapy (ART) by mid-2017 [55]. Some examples of SID include the following: *Congenital AIDS (with recurrent bacterial infections)*

Secondary Immunodeficiencies	
	Allogeneic HSCT/with hypogammaglobulinemia Globally transplant rates for allogeneic HSCT range from a low of 0.2 procedures per 10 million population in Vietnam, to as high as 434.9 procedures per 10 million population in Israel [54]. In 2017, 18,281 allogenic HSCT procedures were performed in Europe [71]. During allogeneic HSCT bone marrow ablation is performed in order to remove diseased marrow which is then replaced by healthy stem cells of a donor. As recipients of allogeneic HSCT undergo recovery, replaced cells require time to progressively mature into functional immune cells leaving patients relatively immunodeficient. During recovery patients who have undergone transplantation are highly susceptible to viral, bacterial and fungal infections, and may suffer a higher incidence of infections possibly related to secondary hypogammaglobulinemia [72-74]. Secondary hypogammaglobulinemia can occur in an estimated 20% to 25% of allogeneic HSCT patients within the first 100 days after transplantation [75,76].

Clinical trial exposure

The cut-off dates for the cumulative duration of exposure and the cumulative numbers for the age groups and genders were updated to 13-January-2021 by the MAH.

Populations not studied in clinical trials

The MAH updated the sections of the special populations "breast-feeding women" and "children". Significant changes were the removal of the statement "There were no adverse events reported in infants assessed as related to HyQvia in median follow-up time of 100 weeks" in the section "breast-feeding women" (marked in ~~red~~) and the inclusion of information from the study 161504 in the section "children" (marked below in yellow).

From table SIV.2 of the current RMP: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Breast-feeding women	pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Development and reproductive toxicology studies have been conducted with recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy and foetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to recombinant human hyaluronidase were transferred to offspring in utero. The effects of antibodies to the recombinant human hyaluronidase component of HyQvia on the human embryo or on human foetal development are currently unknown. The Company has conducted study 161301 (Pregnancy Registry in US and EU) to obtain long-term safety data on both mother and child in the event of pregnancy exposure to HyQvia. The last patient out from the pregnancy registry (US and EU study 161301) was in December-2019. HyQvia was evaluated in 9 mothers (4 mothers before delivery and 5 mothers after delivery), 7 in the HyQvia arm and two in the alternative product arm. In addition, 7 infants were enrolled (5 in the HyQvia arm and 2 in the alternative product arm). ~~There were no adverse events reported in infants assessed as related to HyQvia in median follow-up time of 100 weeks.~~ Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies and no antibodies were detected. Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Type of special population	Exposure
Children	HyQvia was evaluated in 24 paediatric patients, including 13 patients between 4 and < 12 years and 11 between 12 and < 18 years, who were treated for up to 3.3 years with an overall safety experience equivalent to 48.66 patient-years (as described in section Clinical efficacy and safety). No appreciable differences in the pharmacodynamic effects or efficacy and safety of HyQvia were observed between paediatric patients and adults. A prospective, Phase 4, multicentre study (161504) in Europe conducted by the Company evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy. No new safety concerns were identified. No subject was positive (titer ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD.

Post-authorisation experience

The MAH updated the exposure / cumulative sales numbers for HyQvia:

SV.1.2. Exposure

Based on the above methodology, cumulative global patient exposure since the international birth date is estimated to be approximately ~~13,598,856~~20,405,401 grams corresponding to approximately ~~4,023~~5,026 patients exposed per month. Since post-marketing exposure is based on shipment data, it is not currently possible to break down the patient exposure by region, indication, gender, age, or other factors.

Table SV.1: Cumulative Sales of HyQvia (16-MAY-2013 to 31-~~May-2020~~October-2021)*

	Cumulative
Units distributed (grams)	~~13,598,856~~20,405,401
Estimated number of patients exposed per month	~~4,023~~5,026

*Cumulative average of the estimated number of unique patients exposed during the given period of time.

Missing information

In the new RMP version 13.1, the MAH updated the table "presentation of the missing information" concerning limited information on safety in pregnant and lactating women and limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years (removed text in ~~red~~ and added text indicated in yellow).

SVII.3.2. Presentation of the missing information

Missing information: Limited information on safety in pregnant and lactating women	
Evidence source:	While the limited data from 161301 does not suggest a different safety profile for pregnant and lactating women, the low number of participants in the study makes it difficult to draw conclusions for safety in pregnant and lactating women. **Population in need of further characterisation:** Use in pregnant or breast-feeding women. The Company has conducted study 161301 (Pregnancy Registry in US and EU) to obtain long-term safety data on both mother and child in the event of pregnancy exposure to HyQvia. The last patient out from the pregnancy registry (US and EU study 161301) was in December-2019. Though small in sample size (9 mothers [4 mothers before delivery and 5 mothers after delivery], 7 in the HyQvia arm and two in the alternative product arm. Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies and no antibodies were detected~~.), the study confirmed no evidence of a different safety profile in pregnant and/or breast-feeding women.~~.).

Missing information: Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	
Evidence source:	The safety of drug in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years has been identified as missing information because limited data about the use of HyQvia in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years is available from the clinical trial development program. Given cumulative data from studies 160603/160902 and as presented in the SmPC and CCDS, HyQvia was evaluated in 24 paediatric patients, including 13 patients between 4 and < 12 years and 11 between 12 and < 18 years, who were treated for up to 3.3 years with an overall safety experience equivalent to 48.66 patient-years. No appreciable differences in the pharmacodynamic effects or efficacy and safety of HyQvia were observed between paediatric patients and adults. A prospective, Phase 4, multicentre study (161504) in Europe conducted by the Company evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy. No new safety concerns were identified. No subject was positive (titer ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD **Population in need of further characterisation:** Use in neonates or infants <2 years old. Further characterisation on the effect of prolonged use in patients under the age of 18 years.

Assessor comment: *The changes in part II "safety specification" of the RMP are well-founded and thus acceptable.*

9.2. Summary of the safety concerns

Compared to the last by the EMA approved version, there were no changes concerning the safety concerns of HyQvia.

Table SVIII.1: Summary of the Safety Concerns

Summary of 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

Summary of safety concerns	
	measles, mumps, rubella, and varicella • Interference with serological testing after infusion of immunoglobulin.
	Infusion site reactions (infusion site leaking).
	Thromboembolic events (TEEs).
	Haemolysis/Haemolytic anaemia.
	Aseptic meningitis syndrome (AMS).
Important potential risks	Transmissible infectious agents.
	Spread of localised infection.
	Renal dysfunction/failure.
	Drug administration error: incorrect sequence of administration of products.
Missing information	Limited 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 clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

9.3. Pharmacovigilance plan

The MAH removed the studies 161302 and 161504 from the list of additional pharmacovigilance studies since these studies have been finalized. The updated Pharmacovigilance plan is as follows:

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
161406 – Non-Interventional Post-Marketing Safety Study on the Long-Term Safety of HyQvia (Global) Ongoing	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 related to potential antibody development against rHuPH20.	Protocol Submission	17-September-2015 (Amendment 2)
			First interim analysis	After 50 subjects have been enrolled
			Last interim analysis	Not later than 6 months before LOS
			Final report	Q2 2022
161503 – Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HyQvia in Paediatric Subjects with Primary Immunodeficiency Diseases. (US study).	*Primary Objective:* Safety of HyQvia treatment in paediatric subjects with PIDD who have received prior IV or SC immunoglobulin therapy before enrollment into the study. *Secondary Objective:*	Limited information on long-term treatment in patients under the age of 18 years. Limited clinical data on the potential for long-term local and systemic	Final report	2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	Further safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, efficacy (immunoglobulin G [99] trough levels), and PK parameters.	reactions related to potential antibody development against recombinant human hyaluronidase in the paediatric population.		

Assessor comment:

The MAH removed the studies 161302 and 161504 from the list of additional pharmacovigilance studies since these studies are completed. The editorial changes in part III "pharmacovigilance plan" of the RMP are sufficiently justified and thus acceptable.

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

9.4. Risk minimisation measures

Routine risk minimisation measures

In Part V.3 "Summary of risk minimisation measures" and Part VI "Summary of the risk management plan" of the current RMP, the studies 161504 (category 3) and 161302 (category 1) were removed (indicated in ~~red~~) as additional pharmacovigilance activities and from "Other studies in post-authorisation development plan".

From Table Part V.3 of the current RMP: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
18 years	SmPC Section 4.6 SmPC Section 4.8 SmPC Section 5.1 SmPC Section 5.2 PL Section 2 **Additional risk minimisation measures:** None.	**activities:** Study 161503 (Category 3) ~~Study 161504 (Category 3).~~
Missing information: Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** ~~Study 161302 (Category 1)~~ Study 161406 (Category 3) Study 161503 (Category 3) ~~Study 161504 (Category 3)~~

From Table II.B of the current RMP: Summary of important risks

Missing information: Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.6 SmPC Section 4.8 SmPC Section 5.1 SmPC Section 5.2 PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	Study 161503 (Category 3) ~~Study 161504 (Category 3)~~

Missing information: Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	~~Study 161302 (Category 1)~~ Study 161406 (Category 3) Study 161503 (Category 3) ~~Study 161504 (Category 3)~~

From Table II.C.2 of the current RMP: Other studies in post-authorisation development plan

Study ~~161302~~

~~Purpose of the study: To obtain long-term data (including assessment of antirHuPH20 antibodies) on safety of HyQvia.~~

~~Study~~ 161406

Purpose of the study: To evaluate safety data in patients with PID This study is a post market commitment to the FDA. (US only).

Study 161503

Purpose of the study:

To evaluate safety of HyQvia treatment in paediatric subjects with PIDD who have received prior IV or SC immunoglobulin therapy before enrollment into the study.

Further safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, efficacy (immunoglobulin G trough levels), and PK parameters.

~~Study 161504~~

~~Purpose of the study:~~

~~To evaluate safety of HyQvia treatment in paediatric subjects with PID who have received prior immunoglobulin therapy before enrollment.~~

~~Further safety assessments, tolerability, characteristic of product administration and efficacy (IgG trough levels).~~

Additional risk minimisation measures

Educational material has already been listed as an additional risk minimisation measure. In the current RMP version, the MAH adds further information regarding the specific types of educational material that should be provided (indicated in yellow) following procedure EMEA/H/C/002491/II/0070/G.

Objectives	To educate prescribers and users on the correct administration procedure of HyQvia and ensure they are well informed and able to use HyQvia according to the guidance provided in the SmPC and thereby mitigating the risk of Drug administration error.
Rationale for the additional risk minimisation activity	The PRAC requested the marketing authorisation holder (MAH) to propose educational materials. The focus of the educational materials would be to ensure that the sequence of administration of HyQvia and its excipient human recombinant hyaluronidase is appropriate and as per the SmPC.
Target audience and planned distribution path	The educational materials are aimed at ensuring the appropriate sequence of administration of HyQvia and its excipients, to mitigate the risk of drug administration error in patients who participate in home administration. The MAH shall ensure that in each Member State where HyQvia is marketed, all health care professionals and patients who are expected to use HyQvia have access to/are provided with the following educational material: • **Physician educational material** • **Patient information pack** **Physician educational material**: • The Summary of Product Characteristics • Guide for healthcare professionals (HCP) **Guide for Healthcare Professionals (HCPs)**: o Information on HyQvia, including the approved indication according to the SmPC o Detailed description of the administration procedures for infusing HyQvia with a syringe driver pump and with a peristaltic infusion pump with counseling points to emphasize with the patient at each process step - Proper preparation and administration of HyQvia (i.e., infusion of the recombinant human hyaluronidase vial (HY) before the human normal immunoglobulin 10% vial (IG)) - Following aseptic technique - Identification of early signs and symptoms of potential adverse events (e.g., local infusion site

	reactions, allergic-type hypersensitivity reactions) and measures to be taken in case reactions occur, including when to contact the HCP o Patients and/or their caregivers will be asked to demonstrate to the HCP trainer that they can successfully administer HyQvia. Proper technique should be reviewed at regular intervals. o The importance of reporting adverse reactions such as infusion-related reactions and allergic-type hypersensitivity reactions **The patient information pack**: • Patient information leaflet • A patient/carer guide • A patient diary • **Patient/carer guide**: o A detailed, step-by-step description of the correct preparation and administration technique for infusing HyQvia o Detailed description for the self-administration, infusion of HyQvia with a syringe driver pump and with a peristaltic infusion pump o A description of the potential risks(s) associated with the use of HyQvia namely: local infusion site reactions and allergic-type hypersensitivity reactions (signs and symptoms) o Recommendations for managing possible adverse events associated with HyQvia treatment as well as when to contact the HCP o Importance of reporting adverse events along with instructions on how to report o Website feature allows for clickable animations to guide patients through administration sequence. • **Patient diary**:
	o An infusion log will be provided to document the time, date, dose, infusion-site location, and any reactions the patient experiences o The infusion log will also include a description of precaution(s) needed to minimise the potential adverse events associated with the use of HyQvia o The infusion log will help facilitate regular monitoring of the patient´s health status and facilitate discussions with the HCP
Plans to evaluate the effectiveness of the interventions and criteria for success	Given the nature of the error, effectiveness will be measured via a detailed review of post marketing data included in the next PBRER (Q2 2025).

Assessor comment:

In part V "risk minimisation measures" of the RMP, the MAH removed the finalized studies 161302 and 161504. Further, detailed information on educational material for healthcare professionals and patients including a dairy for patients were added following the procedure EMEA/H/C/002491/II/0070/G.

The amendments are sufficiently justified and thus acceptable.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Addition of specific information on educational material for healthcare professionals and patients and inclusion of a dairy for patients are endorsed.

9.5. Annexes

The studies 161302 and 161504 have been moved from Table 1 Annex 2 "Planned and ongoing studies" to Table 2 Annex 2 "Completed studies", and they have been removed from Annex 3 Part C "Previously agreed protocols for ongoing studies and final protocols not reviewed by the regulatory authority".

Furthermore, in Annex 6, the MAH added details of proposed additional risk minimisation activities, namely the provision of educational material (refer to section "additional risk minimisation measures" of this AR).

Also, Annex 7 ("Other supporting data"-Literature) and Annex 8 ("Summary of changes to the RMP") have been updated.

Assessor comment:

The changes in the annexes are in line with the described amendments in the RMP parts II, III, V and VI. The annexes have been updated appropriately.

9.6. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

10. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are being updated to include a paragraph on the pediatric population reflecting the PASS study:

HyQvia was evaluated in 42 pediatric subjects (age 2 to <18 years), in a Phase 4, non-controlled, multicenter study in pediatric subjects who had received prior immunoglobulin therapy. No new safety concerns were identified following HyQvia treatment in pediatric subjects with PIDD.

The Package Leaflet (PL) has not been altered, as the information in the SPC concerns PASS study data that had no negative impact on safety.

Changes are made to the Opinion Annex II conditions (Section D) regarding the RMP and additional risk minimisation measures (see above evaluation).

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

CHMP comment:

The changes to the SmPC and Annex II are, in general, acceptable.

However, in the pivotal study 160603 there were 8 of the 24 paediatric patients who had total anti-rHuPH20 antibodies positive at certain time points, 2 of these had levels at or above 1:160. None had neutralising antibodies. This information should be added to 4.8. prior to the PASS Study information.

Furthermore the PASS study 161504 is not mentioned in the listing of studies that have been performed – please add.

See OC 4 a +b

10.1.1. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, HyQvia is removed from the additional monitoring list as the PASS is fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

11. Request for supplementary information

11.1. Major objections

Clinical aspects

None

RMP aspects

None

11.2. Other concerns

Clinical aspects

OC 1: Please discuss how bias in the study has been minimized by addressing potential sources of bias. For example, please discuss the enrolment of eligible subjects, in particular a potential selection bias of the target population (high proportion of X-linked agammaglobulinemia in the study, representation of the frequencies of the different PID types in the study population). Further, please describe the resulting measures that were taken throughout the study to minimize bias. Even though an imbalance of the study population might not change the overall validity of the data or have an

impact on section 5.1 in the SmPC, a potential bias in the study has not been discussed in the final study report at all and a statement by the MAH concerning the points mentioned above should be included (OC 1).

OC 2: The MAH is asked to further discuss the limitations (e.g. concerning study population, impact of home administration on AE reporting, missing data…) and comment on generalisability of the results to other (pediatric) populations.

OC 3 The MAH is requested to expand on whether the intended submission of an Addendum to the CSR will affect the current outcome data of PASS study 161504.

SmPC

OC 4:

Section 4.8
Paediatric population

a) Please update text as highlighted in yellow

> In the pivotal study 160603 there were 8 of the 24 paediatric patients with total anti-rHuPH20 antibodies positive, 2 of 8 had levels at or above 1:160. None had neutralising antibodies.
>
> A prospective, Phase 4, multicentre study in Europe evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy (Study 161504). No new safety concerns were identified. No subject was positive (titer ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PID~~D~~.
>
> Results of clinical studies indicate similar safety profiles in adults and paediatric population, including the nature, frequency, seriousness and reversibility of adverse reactions.

b) In the tabulated list of adverse reactions in section 4.8 ("The safety of HyQvia was evaluated in 4 clinical studies (160602, 160603, 160902, and 161101) in 124 unique patients with PID receiving 3,202 infusions") the PASS study 161504 is not mentioned; this should be updated.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

Clinical aspects

None.

RMP aspects

None.

12.2. Other concerns

Clinical aspects

Question 1

Please discuss how bias in the study has been minimized by addressing potential sources of bias. For example, please discuss the enrolment of eligible subjects, in particular a potential selection bias of the target population (high proportion of X-linked agammaglobulinemia in the study, representation of the frequencies of the different PID types in the study population). Further, please describe the resulting measures that were taken throughout the study to minimize bias. Even though an imbalance of the study population might not change the overall validity of the data or have an impact on section 5.1 in the SmPC, a potential bias in the study has not been discussed in the final study report at all and a statement by the MAH concerning the points mentioned above should be included.

Summary of the MAH's response

The first subject was enrolled in study 161504 within 12 months of the approval of the paediatric indication of HyQvia in Europe. Selection bias was mitigated by asking investigators to include all successive PID subjects who were already treated with, or who were considered for, HyQvia treatment, reducing the risk that investigator concerns about compliance or predicted response (channelling bias) to HyQvia might have influenced enrolment. In addition, to strengthen external validity, inclusion and exclusion criteria were intentionally minimal and broad enough to capture subjects with any PID type who were treated with, or who were considered for, treatment with HyQvia.

More than 38% of enrolled subjects had congenital X-linked agammaglobulinemia (XLA) in our study. Whereas this may be higher than expected in an adult population, XLA is one of the most common PID subtypes occurring in the paediatric population because age at onset for many PID subtypes occurs in adulthood. For example, age at onset and age at diagnosis for patients with CVID, one of the most common PID subtypes, typically occur in the third and fourth decades of life, respectively (mean [median] age at onset: 26.3 [24] years; mean [median] age at diagnosis: 35.3 [33] years). Since this study was specifically intended to enrol a paediatric population, it is not unexpected that 38% of this sample has the XLA subtype.

Assessment of the MAH's response

The MAH adequately describes the potential selection bias as well as measures how bias was avoided in the study and discusses representation of the target population in the study. **Issue resolved.**

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 2

The MAH is asked to further discuss the limitations (e.g. concerning study population, impact of home administration on AE reporting, missing data…) and comment on generalisability of the results to other (pediatric) populations.

Summary of the MAH's response

Study 161504 was conducted at 16 centres across seven countries. Included centres were large, academic hospital systems, typical of where PID patients receive treatment worldwide. Despite this global generalizability, there are several limitations associated with this study. Unfortunately, the impact of home administration on AE reporting is unknown. We acknowledge that this setting of administration may lead to underreporting or overreporting of AEs; however, more research is needed to understand the potential magnitude and direction of bias. Though missing data related to home infusion date and infusion rate was more prevalent than expected, we do not have evidence that AEs were impacted in a similar manner. We especially do not believe that reporting of serious AEs was significantly impacted by home administration given the serious nature of these events.

Assessment of the MAH's response

Limitations of the study have been described including home administration which bears the risk of underreporting of AEs. However, the significance of potential under- or over reporting could not be evaluated and remains unclear. **Issue resolved.**

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 3

The MAH is requested to expand on whether the intended submission of an Addendum to the CSR will affect the current outcome data of PASS study 161504.

Summary of the MAH's response

The MAH supports the opinion that the submission of the Addendum to the CSR does not affect the current outcome data of PASS study 161504. The purpose of this Addendum to the Clinical Study Report (CSR) is i) to provide updated Protocol Deviation Listings in Appendix 16.2.2 as well as revised language in CSR section 10.2 'Protocol Violations/Deviations' to cover deviations involving the lack of seroconversion evaluations of study subjects for HIV-2 infection as well as ii) to refer in Section 10.2 to the outcome of a quality investigation on a previously mentioned potential issue with CME/BD BodyGuard™ infusion pump systems.

Ad i) Lack of seroconversion evaluations of study subjects for HIV-2 infection:

Per study protocol, the subjects should be evaluated for HIV-1 and HIV-2 infections at screening and excluded if they had a positive test result. Subjects should also have been evaluated for HIV-1 and HIV-2 infections at study completion. Evaluations for HIV-1 were performed on all subjects, however not for HIV-2. The potential impact of the central laboratory not performing the HIV Type-2 test on the study results is described below: • No subject entered the study with a known history of HIV Type-1 or Type-2. • HIV Type-2 has low prevalence in the study countries in comparison with the HIV Type1. • In this post-authorization study, HIV Type-1 and Type-2 infections are not listed as contraindications to the use of the study drug (Baxalta Innovations GmbH, 2018). Therefore, given this information and the fact that the primary objective of the study was safety of the treatment in the post-authorization setting, the assessment was made that subject safety and data integrity were not impacted.

Ad ii) Outcome of a quality investigation on a previously mentioned potential issue with CME/BD BodyGuard™ infusion pump systems:

While section 10.2, item 1 of the CSR had already mentioned a quality issue related to the potential of under-infusion (infusion administration flow rate) when using the CME/BD BodyGuardTM infusion pump system at high flow rate settings, a respective quality investigation had still been ongoing at the time of the CSR. The investigation confirmed that there was **no serious breach of GCP or the study protocol and thus no impact on patient safety or data integrity**. The potential of under-infusion leading to a reduced clinical effect was communicated to IQVIA by MESM Ltd. (Third Party Vendor) on 13 Sep 2021. The study protocol recommended low infusion rates for the first two doses, with a maximum of 300mL/h/site for subjects with BW of ≥40 kg. The protocol also specified that if infusions had been tolerated after the subject received two IP infusions at the dose for the final infusion interval, then investigators may choose an infusion rate schedule at their own discretion. Below are some more details on this issue: • MESM shared that their supplier CME/BD had informed them of a possible issue with CME/BD BodyGuard™ infusion pump systems. BD identified potential flow rate issues when using the CME/BD BodyGuard Microsets/Bodysets infusion sets. The investigation conducted by BD showed an increased risk of under-infusion (affecting flow rate) when using the pump system at high flow rate settings. Deviations of nominal accuracy (5-7%) were detected above 500 mL/h and were most prevalent and significant (>20%) when running infusions at flow rates ≥800 mL/h. The per protocol recommended maximum infusion rate, as described above, was 300 mL/h/site (subjects ≥ 40 kg). BD's investigation into the root cause of this issue is ongoing. • There was a total of 795 infusions performed during the study. The infusion rate was recorded for 667 infusions. On average, the reported infusion rates per infusion site fell between 20 mL/h/site and 300 mL/h/site. The data on infusion rate per infusion site was missing for a total 128 infusions and this information could not be retrieved from the sites as the subjects did not record the infusion rates for these home-infusions. • The SmPC-recommended maximum infusion rate of 300 mL/h/site was shared with the study sites for home and clinic visits. It is therefore unlikely that the infusion rates which have not been recorded exceeded this limit. • During the study, all the subjects were routinely tested for IgG levels. The IgG values were within the expected range in all but
1 subject (where the IgG reduction was attributed to an SAE of inflammatory bowel disease). This provides further evidence that the IP infusions were performed properly and in accordance with the study protocol and the pump manufacturer's instructions. Therefore, the MAH concluded that there was no impact on patient safety or data integrity. **The malfunctioning was relevant for the high flow rates only, which was not the case for the study.**

Assessment of the MAH's response

The MAH submitted an addendum to the CSR with the purpose to provide additional information on protocol deviation (PD) listings concerning missing seroconversion evaluations of subjects who might have been infected with HIV-2 at study entry. Moreover, information on the results of a quality investigation of the used infusion pump systems 'CME/BD BodyGuard™' is provided.

At screening of study 161504, patients should have been screened for HIV-1 and -2, however, the testing was not performed for species HIV-2. The CSR section 10.2 was updated accordingly. Overall, 173 subject-level PDs were documented in 42 subjects during the study, 45 (instead of 47) were considered major PDs. However, it seems that category 'laboratory assessments not performed' was not updated, thus, the missing testing is regarded and classified as minor protocol deviation. It is concurred that the prevalence of HIV-2 in the study countries is very low (2-4%) and, more important, that there is no contraindication to the administration of HyQvia in these patients. Thus, the unknown serostatus of study subjects with potential HIV-2 infection is deemed tolerable and the classification as minor PD can be accepted as it does not carry significant consequences, i.e. increase the risk or decrease the benefit to the patient or significantly affects subject's right, safety or welfare and/or integrity of the research data. **Issue resolved.**

The potential impact of under-infusion when using systematically higher flow rates with the CME/BD BodyGuard infusion pump was further investigated. The MAH concludes 'that there was no serious breach of GCP or the study protocol and thus no impact on patient safety or data integrity'. The vast majority of infusion rates was documented during the study, and the applied rates (20-300mL/h) were well below the threshold (>500 mL/h) of malfunctioning of the infusion pump system. Subject's measured IgG trough levels were within the envisaged therapeutic range suggesting no relevant dysfunction of the infusion system. The amended text in CSR section 10.2 is therefore agreed as no further regulatory action is considered necessary. **Issue resolved.**

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

SmPC

Question 4
OC 4:

Section 4.8
Paediatric population

a) Please update text as highlighted in yellow

In the pivotal study 160603 there were 8 of the 24 paediatric patients with total anti-rHuPH20 antibodies positive, 2 of 8 had levels at or above 1:160. None had neutralising antibodies.

A prospective, Phase 4, multicentre study in Europe evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy (Study 161504). No new safety concerns were identified. No subject was positive (titer ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD.

Results of clinical studies indicate similar safety profiles in adults and paediatric population, including the nature, frequency, seriousness and reversibility of adverse reactions.

b) In the tabulated list of adverse reactions in section 4.8 (*"The safety of HyQvia was evaluated in 4 clinical studies (160602, 160603, 160902, and 161101) in 124 unique patients with PID receiving 3,202 infusions")* the PASS study 161504 is not mentioned; this should be updated.

Summary of the MAH's response

Regarding point a): Takeda respectfully disagrees with EMA´s request to add the "8 of 24 paediatric patients with total anti-rHuPH20 antibodies as positive" language to section 4.8 of the SmPC, since titers less than 160 are not related to de novo anti-drug antibody formation, but rather related to the passive transfer of anti-rHuPH20 antibodies that are present in the IgG component of the HyQvia product itself. Approximately 5% of the US adult population test positive for rHuPH20-reactive antibodies in the absence of exposure to rHuPH20 (Rosengren 2018) 3 Study was designed to estimate a 'threshold' factor to distinguish samples that were positive for the generation of host antibodies versus positive values that could reflect passive transfer of anti-rHuPH20 antibodies in specific lots of KIOVIG from different donor populations, which was the basis of the 160-titer cut-off value (please refer to the Halozyme Report included under "Additional Information" in the submission package). In addition, subjects in the pivotal Study 160603 submitted with HyQvia´s original MAA in September 2011 ("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"), who were identified to have X-Linked Agammaglobulinemia (XLA), Severe combined immunodeficiency (SCID), or Hyper IgM and were not capable of producing mature antibody responses, also had anti-rHuPh20 antibody titer less than 160 in their plasma (please refer to the data in Table 1 extracted from the CSR of study 160603)

Table 1
PID Types and Anti-rHuPH20 Antibody Titers for Subjects Without Ability to Produce Antibodies (Study 160603)

Gender	Type of PID	Maximal Titer
Male	XLA	Negative
Male	XLA	Negative
Male	XLA	1:10
Male	XLA	Negative
Male	SCID + Hypogammaglobulinemia	Negative
Male	SCID	1:10
Male	Hyper IgM syndrome	1:80
Male	Hyper IgM syndrome	1:20
Male	XLA	1:40
Male	XLA	1:80

Based on the arguments above, Takeda believes that including information of titers <160 in the HyQvia SmPC is not particularly helpful to prescribers, and rather could be misleading, when in fact it would only be an attribute of all polyclonal Ig products because they are generated from normal donors who have naturally occurring anti-rHuPH20 antibodies. Therefore, Takeda suggests the

following text in section 4.8 of the SmPC (please refer to the updated PI in the submission package): "In the pivotal study 160603 there were 2 of the 24 paediatric patients with total anti-rHuPH20 antibody levels at or above 1:160. None had neutralising antibodies".

Regarding point b):

Takeda respectfully disagrees to the PASS study 161504 being added to the tabulated list of adverse reactions in section 4.8. According to the SmPC guideline from September 2009 4, section 4.8 should always include a pediatric population sub-section. From the PASS study 161504, the frequency, type, and severity of adverse reactions in children have been determined to be the same as in adults. No additional safety issues have been found. Consequently, Takeda suggests that the pediatric PASS trial data be included under the pediatric part rather than being combined with the clinical study tabulation.

Assessment of the MAH's response

Ad a) The proposed approach to include information on patients with anti-rHuPH20 antibody levels at or above 1:160 can be accepted based on the applicant's justification. **Issue resolved.**

Ad b) As the safety results of study 161504 are mentioned in the paediatric subsection of section 4.8, the rationale is acceptable. **Issue resolved.**

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 5

Additional monitoring: Pursuant to Article 23(3) of Regulation No (EU) 726/2004, HyQvia is removed from the additional monitoring list as the PASS is fulfilled. Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

MAH response: Takeda agrees with the assessor´s proposal to remove the additional monitoring from the proposed SmPC. Please refer to the updated SmPC.

Assessment of the MAH's response

The request was adequately addressed. **Issue solved.**

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

13. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 27 October 2022.