25 May 2023
EMA/258995/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

HyQvia

human normal immunoglobulin

Procedure no: EMEA/H/C/002491/P46/011

Note

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

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1. Introduction

On 28 February 2023, the MAH submitted a completed paediatric study for HyQvia, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 161503 "Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases", is part of a clinical development programme. The programme to date includes 11 completed interventional studies (160601,160602, 160603, 160902, 161101, 170901, 161001, 161504, TAK-771-1001, 161403 and 161503), 1 completed non-interventional pregnancy registry study (161301), 2 completed non-interventional post-authorization safety studies on long-term safety in PIDD (161302, 161406) and 3 ongoing studies (161505, TAK-771-3002 and TAK-771-3004).

2.2. Information on the pharmaceutical formulation used in the study

IGI, 10% with rHuPH20 is a dual vial unit consisting of one vial of a liquid solution containing 100 mg/mL protein of which at least 98% is IgG and one vial of a liquid solution containing 160 U/mL rHuPH20. The rHuPH20 was administered at a dose ratio of approximately 80 U/g IgG before the infusion of IGI, 10%. Infusion rates in Study 161503 were based on body weight (BW): up to 600 mL per infusion site for subjects with a BW ≥40 kg, and up to 300 mL per site for subjects with a BW <40 kg.
HYQVIA is an immune globulin infusion (IGI) 10% (human) with recombinant human hyaluronidase. The recombinant human hyaluronidase PH20 (rHuPH20) component of HYQVIA increases dispersion and absorption of the IGI 10%. There is no pediatric formulation for HyQvia. The dose is calculated based on patient weight and the clinical response. There is no dose adjustment for the pediatric population.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final study report for:

- 161503: "Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases"

The purpose of the current study was to acquire additional data on the efficacy, safety, tolerability, immunogenicity, pharmacokinetic (PK), and other parameters of HYQVIA in pediatric subjects (age ≥2 to < 16 years) with primary immunodeficiency diseases (PIDD).

2.3.2. Clinical study

161503: "Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases"

Description

Study 161503 was a Phase 3, open-label, prospective, non-controlled, multicenter study conducted in 17 study centers in the US. The study consisted of 2 treatment periods (Epoch 1 and Epoch 2) and a 1-year safety follow up (Epoch 3), if needed. Epoch 3 was planned for subjects who developed an anti-rHuPH20 antibody titer of ≥160 during Epoch 1 or Epoch 2 and experienced either a study drug-related serious adverse event (SAE) or a related severe AE and were to be followed up for approximately 1 year. No subject met these criteria and Epoch 3 was not initiated.

In Epoch 1, subjects 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. In Epoch 2, HYQVIA treatment was administered at the following intervals:
• For IV-pretreated subjects - every 3 or 4 weeks, depending on the subject's previous IV dosing schedule.
• For SC-pretreated subjects - every 3 or 4 weeks, at the discretion of investigator and subject.

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 time-points during the study completed the study completion visit at the next possible occasion following the 12-month visit.
- Subjects with anti-rHuPH20 antibody titer ≥ 160 during the study and/or at the last measurement continued in Epoch 2 for an additional 2 years of HYQVIA treatment and observation and completed the study completion visit at the next possible occasion following the 36-month visit.

In Epoch 2, after well tolerating the first 2-3 infusions of HYQVIA at the full dose for the final infusion interval (3- or 4-week dose) administered at the study site, subsequent infusions were administered either at home (or an equivalent site) by the subject/caregiver, or at the study site.

Methods

Study participants

Study subjects were between 2 and < 16 years of age at screening, had a documented diagnosis of PIDD, and had received IV or non HYQVIA SC immunoglobulin therapy prior to study enrollment.

Each subject was required to meet all of the following criteria to be eligible for the study:
1. Documented diagnosis of a form of primary immunodeficiency involving a defect in antibody formation and requiring gammaglobulin replacement as defined according to the International Union of Immunological Societies (IUIS) Scientific Committee 2015 (Picard et al., 2015) prior to enrollment. The diagnosis had to be confirmed by the Sponsor´s Medical Director prior to first treatment with IP in the study.
2. Between 2 and < 16 years of age at the time of screening.
3. Been receiving a consistent dose of immunoglobulin G (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. Serum trough level of IgG >5 g/L at screening.

5. If female of childbearing potential, had 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.

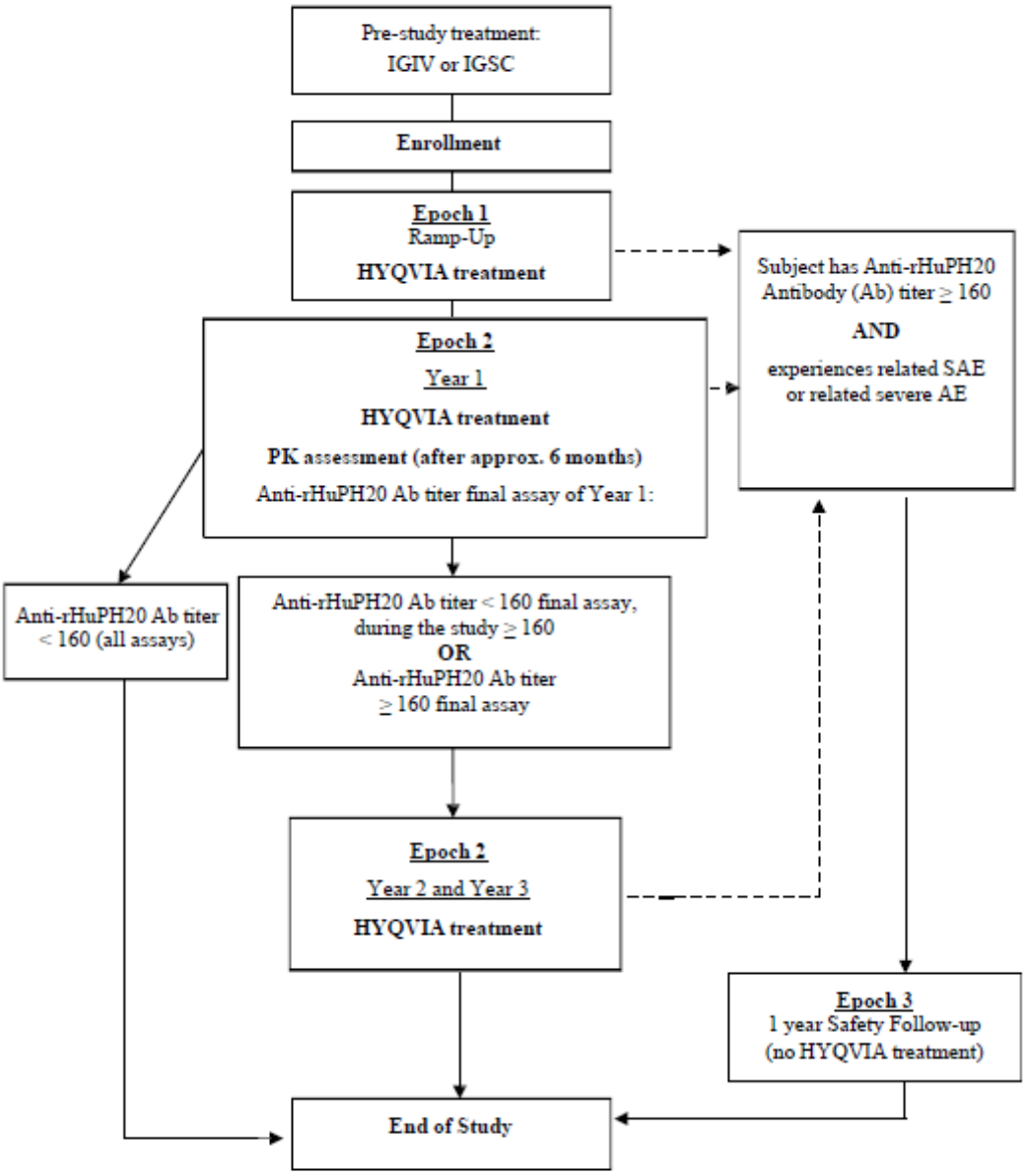
Exclusion Criteria
Subjects who met any of the following criteria were excluded from the study:
1. Subject had a known history of or was positive at screening for one or more of the following: hepatitis B surface antigen, polymerase chain reaction for hepatitis C virus, polymerase chain reaction for human immunodeficiency virus (HIV) Type 1/2.
2. Abnormal laboratory values at screening meeting any one of the following criteria (abnormal tests may have been repeated once to determine if they were persistent):
    a. Persistent alanine aminotransferase and aspartate aminotransferase (AST) > 2.5 times the upper limit of normal for the testing laboratory
    b. Persistent severe neutropenia (defined as an absolute neutrophil count ≤ 500/mm3).

3. Subject had anemia that 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 deficiency (<7.0 mg/dL) with known anti-immunoglobulin A 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 <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 enrollment 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 enrollment.

Study design

A study flowchart is provided in Figure 1.

Figure 1. Study Design Schematic



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

Treatments

HYQVIA (Epoch 1 and Epoch 2):
Immune Globulin Infusion (IGI) 10% (Human) with Recombinant Human Hyaluronidase PH20 (rHuPH20) component. HYQVIA weekly dose is equivalent to 100% (±5%) of pre-study treatment. Administration was by SC infusion.

Infusion Rate:
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)

Infusion volume:
Up to 300 mL per site for subjects with a BW <40 kg, and up to 600 mL per infusion site for subjects with a BW ≥40 kg.

Objectives

Primary Objective
Efficacy of HYQVIA treatment in pediatric subjects with primary immunodeficiency diseases who received prior intravenous (IV) or subcutaneous (SC) immunoglobulin therapy before enrollment into the study.

Secondary Objective
Further efficacy and safety assessments (eg, immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, and pharmacokinetic (PK) parameters.

Outcomes/endpoints

Primary Efficacy Outcome Measure
The rate of acute serious bacterial infections (ASBI), defined as the mean number of ASBIs per subject-year in the intent-to-treat population (ie, Full Analysis Set [FAS]). Acute serious bacterial infections include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, diagnosed according to the Diagnostic Criteria for Acute Serious Bacterial Infections, U.S. Food and Drug Administration (FDA) Guidance for Industry to Support Marketing of Human Immune Globulin Intravenous as Replacement Therapy for Primary Humoral Immunodeficiency (Food and Drug Administration, 2008).

Secondary Outcome Measures
Efficacy:
1. Number of all infections per subject-year.
2. Trough levels of IgG and IgG subclasses for Study Epoch 2.
3. Trough levels of specific antibodies to clinically relevant pathogens (*Clostridium tetani* toxoid, *Haemophilus influenzae*, and Hepatitis B Virus) for Study Epoch 2.

Pharmacokinetics (Epoch 2):
1. For the PK assessment in Epoch 2, the following PK parameters were determined for observed total IgG levels: area under the curve (AUC), apparent clearance (CL/F), maximum concentration (Cmax), minimum concentration (Cmin), time to maximum concentration (Tmax), and terminal half-life. Additionally, baselinecorrected total IgG AUC, Cmax and Tmax were calculated.

Safety:
1. Number and rate per infusion (excluding infections) of SAEs, related and not related.
2. Number and rate per infusion (excluding infections) of all AEs, related and not related.
3. Number and rate per infusion (excluding infections) of local AEs, related and not related.
4. Number and rate per infusion (excluding infections) of systemic AEs, related and not related.
5. Number and rate per infusion (excluding infections) of all temporally associated AEs (starting during or within 72 hours of completion of infusion).
6. Number and rate per infusion (excluding infections) of all causally related and/or temporally associated AEs.
7. Rates of all AEs (excluding infections) defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of infusions.
8. Number/proportion of subjects who develop positive titer (≥160) of binding or neutralizing antibodies to rHuPH20.

Sample size

The planned sample size for enrollment was approximately 40 subjects. A total of 44 subjects were enrolled in this study. A sample size of 35 provides 83% power to reject the null hypothesis (H0) of an ASBI rate greater or equal 1.0 (H0 ≥ 1.0), by means of a 1-sided test and a significance level of 0.01, versus the alternative hypothesis (H1) of less than 1.0 (H1< 1.0), assuming a true rate of 0.5/year. Based on previous clinical experience, a dropout rate of 12% was assumed. Allowing for 12% dropouts, approximately 40 subjects were planned to be enrolled in the study.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Subjects were classified into the following analysis sets: Screened Set, Enrolled Set, FAS, Per-protocol Analysis Set (PPS), Safety Analysis Set, and Pharmacokinetic Analysis Set. The planned sample size for enrollment was approximately 40 subjects. A total of 44 subjects were enrolled in this study. A sample size of 35 provides 83% power to reject the null hypothesis (H0) of an ASBI rate greater than or equal to 1.0 (H0 ≥ 1.0), by means of a 1-sided test and a significance level of 0.01, versus the alternative hypothesis (H1) of less than 1.0 (H1< 1.0), assuming a true rate of 0.5/year. Based on previous clinical experience, a dropout rate of 12% was assumed. Allowing for 12% dropouts, approximately 40 subjects were planned to be enrolled in the study.
Subject disposition, and demographic and other baseline characteristics are summarized, as described in the Statistical Analysis Plan. Disposition summaries and listings were based on all subjects, using the Screened set. Demographics and other baseline characteristics summaries were based on the FAS. A summary of the number and proportion of subjects in different population sets were provided.
The primary endpoint/outcome measure was the rate of ASBIs which were reported as the mean number of ASBIs per subject-year.
The number of infections were counted from the start of the initial dose of HYQVIA (start of Epoch 1) through the end of Epoch 2. HYQVIA was administered in Epoch 1 and Epoch 2, and GAMMAGARD LIQUID was to be received only in Epoch 3.
The secondary endpoints/outcome for the final analysis was to measure the annual rate of infection under HYQVIA treatment and was computed using a Poisson model and presented as point estimate and 95% confidence interval (CI). Total IgG trough levels, IgG subclass trough levels, and trough levels of specific antibodies were summarized using descriptive statistics. Non-compartmental analysis was used to calculate observed total IgG PK parameters and select baseline-corrected parameters at the Epoch 2 Month 6 visit and beyond.
The FDA Guidance for Industry on the evaluation of immunoglobulin IV replacement therapy for primary humoral immunodeficiency recommends the evaluation of efficacy by comparing the rate of serious infections over an observation period of at least 12 months to a fixed value of 1.0 (by showing that the upper one-sided 99% confidence limit is less than 1.0). An interim analysis was performed when all subjects had completed 12 months of study participation in Epoch 2; all but one subject had completed the study at this stage. The final analysis includes all subjects up to study completion and prior to database lock. This final CSR includes all efficacy, safety and other study outcome measures, and therefore represents all data of Study Protocol 161503, designed in alignment with the FDA Guidance for Industry.

Results

Participant flow

A total of 47 subjects were screened in the study; of these, 3 subjects (6.4%) were screen failures, and 44 subjects met eligibility criteria and were enrolled and dosed in the study. At the data-freeze date (16 Nov 2020), 34 subjects (77.3%) who were dosed had completed 12 months of the Epoch 2

study. One subject from the 44 enrolled was followed for a further 24 months after meeting the criteria in Epoch 2. At database lock (01 Nov 2022) all subjects had completed the Epoch 2. No subjects met the criteria for Epoch 3.
The proportion of subjects who discontinued the study before completing Epoch 2 was 10 subjects (22.7%). Of the 10 subjects that discontinued before EOS, 2 subjects completed all Epoch 2 mandatory visits/assessments preceding EOS (see details below). The most frequent reason for premature subject discontinuation was withdrawal by subject, reported in 6 subjects (60%).

Subject disposition Epoch 1.
43 subjects (97.7%) completed Epoch 1. One subject (2.3%) discontinued the study during Epoch 1 due to a TEAE of gastrointestinal disorder (coeliac disease) (Table 1).

Subject disposition Epoch 2.
34 subjects (77.3%) completed Epoch 2. Among the subjects who discontinued during Epoch 2 (9 subjects [20.5%]), the most frequent reason for subjects' discontinuation was withdrawal by the subject, 6 subjects (66.7%) (Table 2). One subject discontinued during Epoch 2 due to physician's decision and 1 subject withdrew due to a TEAE of general disorders and administration site condition (infusion site pain). One subject was prematurely discontinued from the study due to COVID-19 constraint at the site in conducting the final visit. The subject was unable to complete the final visit, prompting the physician to terminate the subject and put the subject on commercial product. This incident of premature discontinuation was reported as "other" reason in the study disposition table. One subject at the end of the first year of Epoch 2 had an anti-rHuPH20 antibody titer of ≥160; the subject began an extended follow-up of 2 years in Epoch 2. A total of 44 subjects were analyzed for efficacy and safety; and 40 subjects were analyzed for PK.

Table 1 Subject Disposition – All subjects

Disposition	All subjects n (%)
Subjects screened [a]	47
Screen failed [b]	3 (6.4)
Enrolled (enrolled set/full analysis set) [b]	44 (93.6)
Subjects dosed (Safety Analysis Set) [c]	44 (100.0)
Completed study [c]	34 (77.3)
Discontinued study prematurely [c]	10 (22.7)
Primary reason for premature discontinuation [d]	
Subject had adverse event(s)	2 (20.0)
Physician Decision	1 (10.0)
Withdrawal by subject	6 (60.0)
Study terminated by Sponsor	0
Death	0
Lost to follow up	0
Other	1 (10.0)
Completed Epoch 1 [c]	43 (97.7)
Discontinued during Epoch 1 [c]	1 (2.3)
Primary reason for premature discontinuation during Epoch 1[e]	
Subject had adverse event(s)	1 (100.0)
Physician Decision	0
Withdrawal by subject	0
Study terminated by Sponsor	0
Death	0
Lost to follow up	0
Other	0
Completed Epoch 2 [c]	34 (77.3)
Discontinued during Epoch 2 [c]	9 (20.5)
Primary reason for premature discontinuation during Epoch 2[f]	
Subject had adverse event(s)	1 (11.1)
Physician Decision	1 (11.1)
Withdrawal by subject	6 (66.7)
Study terminated by Sponsor	0
Death	0
Lost to follow up	0
Other	1 (11.1)

Recruitment

Enrollment Period:
The study was conducted from 25 September 2017 (first subject enrolled) to 2 May 2019 (last subject enrolled) in 44 subjects with PIDD at 17 sites in the US. The database lock date for final analysis was 1 November 2022.

Baseline data

Demographics
A summary of key demographic characteristics is displayed in Table 2. The median age of subjects at the signing of the informed consent was 9.5 years (range: 3 to 15 years). The majority of subjects (23 subjects [52.3%]) were in the age category of 6 to < 12 years, 12 subjects (27.3%) were in the 12 to < 16 years category, and 9 subjects (20.5%) were included in the 2 to < 6 years category. A total of 26 subjects (59.1%) were male and 18 subjects (40.9%) were female; of the female subjects enrolled, 5 subjects (27.8%) were of child-bearing potential. Of the 44 enrolled subjects, 40 subjects (90.9%) were White. The majority of the subjects were not Hispanic or Latino (39 subjects [88.6%]). The median height was 137.80 cm (range: 86.1 to 170.2 cm) and median weight was 34.52 kg (range: 11.9 to 92.7 kg).

Table 2 Demographic and Other Baseline Characteristics – Full Analysis Set

Subject Characteristics	Statistic	All Subjects (N=44)
Age (Years) [a]	n	44
	Mean (SD)	9.0 (3.63)
	Median	9.5
	Min, Max	3, 15
Age Category (Years)	2 to < 6 years	9 (20.5)
	6 to < 12 years	23 (52.3)
	12 to < 16 years	12 (27.3)
Sex [n (%)]	Male	26 (59.1)
	Female	18 (40.9)
	Childbearing Potential [b]	
	Yes	5 (27.8)
	No	13 (72.2)
Race [n (%)]	American Indian or Alaska Native	0
	Asian	0
	Black or African American	2 (4.5)
	Native Hawaiian or Other Pacific Islanders	0
	White	40 (90.9)
	Other	1 (2.3)
	Multiple	1 (2.3)
Ethnicity [n (%)]	Hispanic or Latino	5 (11.4)
	Not Hispanic or Latino	39 (88.6)
Height (cm)	n	44
	Mean (SD)	133.60 (24.024)
	Median	137.80
	Min, Max	86.1, 170.2
Weight (kg)	n	44
	Mean (SD)	37.78 (19.858)
	Median	34.52
	Min, Max	11.9, 92.7

Abbreviations: SD = standard Deviations; Max = Maximum; Min = Minimum.
[a] Age at screening.
[b] Percentage is based on the total number of female subjects in the full analysis set.
Conversion rates: 1in = 2.54cm; 1lb = 0.454kg.
Source: Listing 16.2.4.1, Table 14.1.3.

Baseline Disease Characteristics

A summary of baseline disease characteristics for PIDD is displayed in Table 3. Common variable immunodeficiency disorder was the most commonly diagnosed PIDD in 18/44 subjects (CVID 16 subjects [36.4%]; CVID and "other" 2 subjects [4.5%]), followed by specific antibody deficiency in 16/44 subjects (SAD 6 subjects [13.6%], SAD with hypogammaglobulinemia/low IgG 4 subjects [9.1%], SAD with IgG subclass deficiency and "other" 1 subject [2.3%] and specific antibody deficiency and "other" 5 subjects [11.4%]).

Table 3 Primary Immu8nodeficiency Disease Type – Full Analysis Set

PIDD Type	Statistic	All Subjects (N = 44)
Agammaglobulinemia- X-linked (Bruton's agammaglobulinemia, XLA)	n (%)	1 (2.3)
Agammaglobulinemia/hypogammaglobulinemia- autosomal recessive	n (%)	1 (2.3)
Agammaglobulinemia/hypogammaglobulinemia- autosomal recessive; other	n (%)	1 (2.3)
Common variable immunodeficiency disorder (CVID)	n (%)	16 (36.4)
Common variable immunodeficiency disorder (CVID); other	n (%)	2 (4.5)
Severe combined immunodeficiency	n (%)	3 (6.8)
Specific antibody deficiency	n (%)	6 (13.6)
Specific antibody deficiency with hypogammaglobulinemia/low IgG	n (%)	4 (9.1)
Specific antibody deficiency with IgG subclass deficiency; other	n (%)	1 (2.3)
Specific antibody deficiency; other	n (%)	5 (11.4)
Other	n (%)	4 (9.1)

Abbreviations: IgG = immunoglobulin G; PIDD=Primary Immunodeficiency Diseases.
The category of "Other" contains two subjects with 'IgG subclass deficiency, low IgA', one subject with 'hypogammaglobulinemia' and one subject with 'hypogammaglobulinemia and IgG subclass deficiency'.
Source: Table 14.1.4

Medical History

The most frequently reported medical history by SOC was infections and infestations (38 subjects [86.4%]); followed by immune system disorders (35 subjects [79.5%]); respiratory, thoracic, and mediastinal disorders and surgical and medical procedures (34 subjects [77.3%]) each; gastrointestinal disorders (25 subjects [56.8%]); skin and subcutaneous tissue disorders (19 subjects [43.2%]); nervous system disorders and psychiatric disorders (16 subjects [36.4%]) each; musculoskeletal and connective tissue disorders (13 subjects [29.5%]); metabolism and nutrition disorders, general disorders and administration site conditions, and congenital familial and genetic disorders (10 subjects [22.7%]) each. All other medical histories by SOC were reported in less than 10 subjects.

The most frequently reported history entries by PT were asthma (30 subjects [68.2%]); followed by adenoidectomy and ear tube insertion (16 subjects [36.4%] each); pneumonia, and gastroesophageal reflux disease (14 subjects [31.8%] each); tonsillectomy (13 subjects [29.5%]); immunodeficiency common variable and rhinitis (11 subjects [25.0%] each); headache, otitis media, hypogammaglobulinemia, and attention deficit hyperactivity disorder (10 subjects [22.7%]) each. All other history entries were reported in less than 10 subjects.

Prior Medication

All subjects had taken at least one prior medication. The most frequently (taken by ≥ 10% subjects) reported prior medications by therapeutic class were: drugs for obstructive airway diseases (28 subjects [63.6%]); antihistamines for systemic use (23 subjects [52.3%]); nasal preparations (20 subjects [45.5%]); vitamins (16 subjects [36.4%]); analgesics (11 subjects [25%]); psychoanaleptics (10 subjects [22.7%]); drugs for acid related disorders (9 subjects [20.5%]); psycholeptics (8 subjects [18.2%]); antipruritics, including antihistamines, anesthetics etc. (8 subjects [18.2%]; corticosteroids for systemic use (5 subjects [11.4%]); and anti-inflammatory and antirheumatic

products (5 subjects [11.4%]). All other prior medications by therapeutic class were reported in less than 10 subjects for the most frequently reported prior medications by PT, refer to Table 14.1.6.

Concomitant Medication
Overall, a total of 43 subjects (97.7%) received at least one concomitant medication during the course of the study. The most frequently reported concomitant medications by therapeutic class were drugs for obstructive airway diseases (32 subjects [72.7%]); antibacterials for systemic use and antihistamines for systemic use (31 subjects [70.5%]) each; antiinflammatory and antirheumatic products (30 subjects [68.2%]); analgesics (27 subjects [61.4%]); nasal preparations (26 subjects [59.1%]); vitamins (18 subjects [40.9%]); all other therapeutic products (17 subjects [38.6%]); drugs for acid related disorders (16 subjects [36.4%]); antiemetics and antinauseants, and psycholeptics (15 subjects [34.1%]) each; and antidiarrheals, intestinal antiinflammatory/anti-infective agents (14 subjects [31.8%]). All other concomitant medication, non-drug therapies, and procedures were reported in ≤30% of subjects.

Measurements of Treatment Compliance
Treatment performed at the study site or infusion center was under the direct supervision of the investigator/a licensed healthcare professional (eg, infusion nurse). Non-compliance was reported as a protocol deviation refer to Section 10.2.

Number analysed

The analysis population is summarized in Table 4 below. A total of 44 subjects were enrolled in the study and were included in the FAS, Safety Analysis Set, and PPS. A total of 40 subjects (90.9%) were included in the PK analysis set. Demographic and baseline characteristics were analyzed using the FAS. Efficacy results were analyzed using the FAS except for a sensitivity analysis of the primary endpoint which used the PPS. All safety analyzes were performed using the Safety Analysis Set.

Table 4 Analysis Population – All subjects

	Statistic	All Subjects (N=47)
Number of Screened Subjects	n	47
Number of Enrolled Subjects	n	44
Number of Subjects in the FAS	n (%)	44 (100.0)
Number of Subjects in the PPS	n (%)	44 (100.0)
Number of Subjects in the Safety Analysis Set	n (%)	44 (100.0)
Number of Subjects in the PKAS	n (%)	40 (90.9)

FAS=Full Analysis Set; PPS=Per-Protocol Analysis Set; PKAS=Pharmacokinetic Analysis Set.
Percentages are based on the total number of subjects in the Full Analysis Set.
All subjects who have signed informed consent (screen failures or screen successes) are included in the Screened Set.
All patients who provide informed consent and meet enrollment eligibility are included in the Enrolled Set.
In this study, the FAS and the Enrolled Set are identical.
All patients in the FAS who have no major protocol deviations affecting the efficacy data are included in the PPS.
All subjects who receive at least one dose of HYQVIA are included in the Safety Analysis Set.
All subjects in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results are included in the PKAS.
Source: Listing 16.2.1.2, Listing 16.2.8.1.

All subjects except 1 continued in Epoch 2 after completing Epoch 1. One subject discontinued the study during Epoch 1 due to an AE. Thirty-four subjects completed Epoch 2 of the study whereas only 1 subject had additional per-protocol follow-up in Epoch 2 for 2 years. No subject entered Epoch 3. Among the subjects who discontinued during Epoch 2 (9 subjects), the most frequent reason for subject discontinuation was withdrawal by the subject.

Outcomes

The primary efficacy outcome assessed in Study 161503 was the annual rate of acute serious bacterial infections (ASBIs) per subject defined as the mean number of ASBIs per subject per year. Secondary efficacy endpoints included the annual rate of infection under HYQVIA treatment, and trough levels of IgG, IgG subclasses, and of specific antibodies. Additional efficacy assessments included health-related quality of life assessments using questionnaires filled out by parents or guardians for subjects aged < 13 years such as the Pediatric Quality of Life Inventory (Peds-QL) and the EuroQol five dimensions (EQ-5D-Y). Treatment preference and satisfaction was assessed using the Treatment Satisfaction and Medication Questionnaire (TSQM-9) and the Life Quality Index (LQI). Healthcare resource utilization pertaining to antibiotic use was also assessed.
PK assessments of total IgG levels were performed in Epoch 2: area under the curve (AUC), clearance (CL), maximum concentration (Cmax), minimum concentration (Cmin), time to maximum concentration (Tmax), and terminal half-life (t½). Baseline corrected total IgG AUC, Cmax and Tmax were also calculated.

Annual Rate of Acute Serious Bacterial Infections

The mean rate of ASBIs per subject-year was 0.04, with an upper limit of the 99% CI of 0.20. The mean rate of ASBIs per year was statistically significantly lower than threshold rate of 1.0 ASBI per subject-year (at the 1% level adjusted for the final analysis; p<0.001). The mean (standard error [SE]) rate of all infections per subject-year 3.12 (0.450) with an upper limit of the 95% confidence interval (CI) of 3.95. The mean rate of all infections per subject-year was highest for the youngest age group and decreased with increasing age (4.01, 3.23, and 1.97 in the 2 to < 6, 6 to < 12, and 12 to < 16 years age group, respectively).

Trough Levels of IgG and IgG Subclasses

There were no clinically meaningful differences in serum trough IgG levels between age groups during Epoch 2, with the highest median change from the Month 0 baseline measurement of <1.3 g/L. A similar trend was observed for IgG subclass results with stable levels across Epoch 2 and no notable age group differences for the first 12 months across Epoch 2.

Trough Levels of Specific Antibodies

Trough levels of specific antibodies against *Clostridium tetani* toxoid, *Haemophilus influenzae,* and hepatitis B virus (HBV) showed no substantial difference from the baseline values and were at levels more than 10 times above that considered to be the minimal protective titer.

Pharmacokinetics

There were no notable differences across age groups with respect to the PK parameters based on data at the Epoch 2 Month 6 visit for total or baseline-corrected total IgG.

Quality of Life Assessments

The mean (SD) change in Peds-QL total, EQ-5D-Y, and VAS scores from baseline to end of Epoch 2 were small, indicating no changes in HRQoL and health status from baseline to end of Epoch 2. Similar findings were observed in the treatment satisfaction scales (TSQM-9 and LQI). A trend towards higher treatment satisfaction was observed with HYQVIA in all the TSQM-9 domains (effectiveness, convenience and global satisfaction with treatment) and LQI domains (with the exception of the therapy setting domain).
In the treatment preference questionnaire, most subjects receiving HYQVIA responded "like very much' or 'like" the frequency of administration (88.1%; 50.0%/38.1%); ability to fit treatment into schedule (83.3%; 47.6%/35.7%); and overall convenience (81.0%; 38.1/42.9%). Most subjects responded that

they preferred to receive treatment at home (85.7%) and that they would choose to continue receiving HYQVIA (73.8%). The mean (SE) rate of days wherein subjects were not able to go to school or work or perform normal daily activities due to infection or other illness was 4.28 (0.997) days per subject-year.

Healthcare Resource Utilization

Mean (SE) rate of days on antibiotics was 26.77 (5.445) days per subject-year. The mean rate of hospitalizations was less than 1 per year, and the mean rate of days hospitalized was less than 1 day per year. The mean rate of acute physician visits due to infection or other illness per subject-year was less than 5 visits per year.

Safety results

Safety analyses of the SC treatment with IG, 10% facilitated with rHuPH20 included all 44 subjects with PIDD who had completed Study 161503. All AEs were evaluated by system organ class, preferred term (PT), severity, relationship to treatment, and temporal relationship to treatment.
Safety and tolerability endpoints included:
• The annual rate of related and not related SAEs.
• AEs, including and excluding infections.
• Localized treatment-emergent AEs (TEAEs)
• Systemic TEAEs.
• Rates of TEAEs by number of infusions.

Extent of exposure

Exposure to HYQVIA is summarized in Table 5. Overall, the median duration of exposure for HYQVIA was 14.87 months (range: 0.7 to 38.7 months). The median exposure time to HYQVIA was 1.38 months (range: 0.7 to 1.5 months) and 13.49 months (range: 1.0 to 37.3 months) in Epoch 1 and Epoch 2, respectively. The majority of subjects (36 subjects [81.8%]) had exposure to treatment for 12 to < 24 months. Mean study duration was 14.11 months (range: 0.7 to 38.7 months).

Table 5 Exposure to HYQVIA (Safety Analysis Set)

Variable	Statistic	All Subjects (N = 44)
Exposure (months) [a]		
Epoch 1	n	44
	Mean (SD)	1.26 (0.264)
	Median	1.38
	Min, Max	0.7, 1.5
Epoch 2	n	43
	Mean (SD)	13.00 (5.067)
	Median	13.49
	Min, Max	1.0, 37.3
Overall	n	44
	Mean (SD)	13.97 (5.447)
	Median	14.87
	Min, Max	0.7, 38.7
Exposure group [n (%)] [b]	≤6 weeks	1 (2.3)
	>6 weeks - < 12 months	6 (13.6)
	12 - <24 months	36 (81.8)
	24 - <36 months	0
	≥36 months	1 (2.3)
Study duration (months) [a]	n	44
	Mean (SD)	14.11 (5.493)
	Median	14.93
	Min, Max	0.7, 38.7

IP=Investigational Product; PIDD=Primary Immunodeficiency Diseases.
Epoch 1: Pediatric patients with PIDD who are on intravenous (IV) or non-HYQVIA subcutaneous (SC) treatment with immunoglobulin (IV-pre- treated, SC-pre-treated) are enrolled and treated with HYQVIA subcutaneously with a dose or interval ramp-up period of up to six weeks.
Epoch 2: The ramp-up (Epoch 1) is followed by Epoch 2 with HYQVIA treatment at the following intervals:
(1) For IV-pre-treated subjects: every three or four weeks, depending on the subject's previous IV dosing schedule.
(2) For SC-pre-treated subjects: every three or four weeks, at the discretion of investigator and subject.
Exposure is summarized in terms of each subject's total duration of treatment with IP by Epoch and overall.
Epoch 1 treatment duration is calculated as follows:
- For subjects who went in Epoch 2, it is calculated as (day before the first dose in Epoch 2 - date of first dose in Epoch 1 + 1).
- For subjects who discontinued before entering in Epoch 2, it is calculated as (date of discontinuation - date of first dose in Epoch 1 + 1).

Epoch 2 treatment duration is calculated as the minimum between (date of last dose in Epoch 2 + subject's dosing interval - date of first dose in Epoch 2 + 1) and (date of study completion/discontinuation - date of first dose in Epoch 2 + 1).
Overall treatment duration is calculated as the minimum between (date of last dose + subject's dosing interval - date of first dose + 1) and (date of study completion/discontinuation - date of first dose + 1).
Study duration (days) is calculated as date of completion/discontinuation – date of initial dose of IP + 1.
[a] Exposure/Study duration are converted into months, i.e. divided by 30.4.
[b] For summary purposes, 6 weeks = 42 days, 12 months = 365 days, 24 months = 730 days and 36 months = 1095 days.
Source: Listing 16.2.5.1, Table 14.1.9

Infusions (Epoch 2)

Number of Infusions per Month

There was a total of 633 infusions in Epoch 2. Overall, the median number of infusions per month was 1.10 (range: 1.0 to 1.5) and were comparable across the age groups. The median number of infusions per subject-year overall was 13.18 (range: 11.5 to 17.7) and although comparable among all age groups, the age group of 2 to < 6 years had the lowest median number 13.04 of infusions per subject-year (13.21 and 13.16 for the 6 to < 12 and 12 to < 16 age groups, respectively).
Overall, the median number of infusions per subject for the duration of Epoch 2 was 15.0 (range 1 to 38), with the highest median number of infusions per subject in the 2 to < 6 years age group.

Number of Infusion Sites (Needle-Sticks) per Month

Overall, the median number of infusion sites per month was 2.17 (range: 1.1 to 2.9), with similar median number of infusion sites per month for all the age categories. The mean number of infusion sites per infusion was 1.83 (SD 0.366) with a median number of 2.0 infusions (range: to 2.0) and was comparable throughout all age groups.

Duration of Infusion

Across the age groups, the median (range) duration of infusion ranged from 76.5 (60 to 215) minutes in the 2 to < 6 years group to 88.0 (53 to 150) minutes in the 6 to < 12 years group. Overall, the median duration of infusion was 85.0 (45 to 215) minutes.

Maximum Infusion Rate/Site

Overall, the median maximum infusion rate per site was 160 mL/h (range: 30 to 300 mL/h) with a maximum median infusion rate per site of 300 mL/h reported in the 12 to < 16 years age group which was higher compared with the other age groups.

Infusion Volume/Site

The median infusion volume per site was 85.0 mL (range: 35 to 300 mL) with the highest median infusion volume per site of 142.5 mL (range: 75 to 300 mL) reported in subjects aged 12 to < 16 years compared to the lowest median infusion range of 60.0 mL (range: 35 to 143 mL) in subjects aged 2 to < 6 years.

Number/Proportion of Infusions that were Discontinued, Slowed, or Interrupted Due to an Adverse Event

Overall, a mean of 99.8% (range: 94 to 100%) infusions were completed by subjects across Epochs 1 and 2. No notable difference was observed between the Epoch 1 and Epoch 2 groups for percentage of infusions completed. A mean of 5.9% (SD 8.04, range: 0 to 33%) of infusions were reported to be interrupted. The majority of infusions were completed without interruption across both Epoch 1 and Epoch 2. A mean of 1.1% (SD 5.27, range: 0 to 25%) infusions were discontinued in Epoch 1, while no infusions were discontinued, and no subjects changed regimen due to an AE in Epoch 2.

Overall, 13 subjects (30.2%) had a total of 17 infusions (2.69% of all infusions) that were interrupted due to an AE. Four infusions were interrupted in 3 subjects (33.3%) in the 2 to <6 years age group, 6 infusions were interrupted in 6 subjects (27.3%) in the 6 to <12 years age group, and 7 infusions were interrupted in 4 subjects (33.3%) in the 12 to <16 years age group.

Adverse Events

Overviews of TEAEs excluding and including infections are presented in Table 6 and Table 7, respectively.

Table 6 Treatment-Emergent Adverse Events, Overall Summary (excluding infections): Safety Analysis Set

	Epoch 1 (N = 44)		Epoch 2 (N = 43)		Epoch 1 and 2 Combined (N = 44)	
Category	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any TEAE	29 (65.9)	119	40 (93.0)	417	43 (97.7)	536
Related TEAE [a]	25 (56.8)	85	31 (72.1)	251	34 (77.3)	336
Unrelated TEAE	16 (36.4)	34	36 (83.7)	166	38 (86.4)	200
Any severe TEAE	1 (2.3)	1	2 (4.7)	2	3 (6.8)	3
Related TEAE [a]	1 (2.3)	1	1 (2.3)	1	2 (4.5)	2
Unrelated TEAE	0	0	1 (2.3)	1	1 (2.3)	1
Any serious TEAE	0	0	1 (2.3)	1	1 (2.3)	1
Related TEAE [a]	0	0	0	0	0	0
Unrelated TEAE	0	0	1 (2.3)	1	1 (2.3)	1
Any local TEAE	22 (50.0)	60	29 (67.4)	142	33 (75.0)	202
Related TEAE [a]	22 (50.0)	58	28 (65.1)	134	32 (72.7)	192
Unrelated TEAE	2 (4.5)	2	6 (14.0)	8	7 (15.9)	10
Any systemic TEAE	23 (52.3)	59	37 (86.0)	275	39 (88.6)	334
Related TEAE [a]	12 (27.3)	27	20 (46.5)	117	25 (56.8)	144
Unrelated TEAE	16 (36.4)	32	33 (76.7)	158	35 (79.5)	190
Any temporally associated TEAE [b]	27 (61.4)	91	35 (81.4)	291	38 (86.4)	382
Any related and/or temporally associated TEAE	27 (61.4)	96	35 (81.4)	305	38 (86.4)	401
Any TEAE leading to discontinuation	1 (2.3)	1	1 (2.3)	1	2 (4.5)	2
Any TEAE leading to death	0	0	0	0	0	0

IP=Investigational Product (HYQVIA in Epoch 1 and 2); TEAE = Treatment-emergent adverse event.
If the start date/time of the AE is after date/time of first dose of IP in Epoch 1 and before the date/time of first dose of IP in Epoch 2 then the event is allocated to Epoch 1.
If the start date/time of the AE is after date/time of first dose of IP in Epoch 2 then the event is allocated to Epoch 2.
For the columns of 'Number (%) of subjects': Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
For the columns of 'Number of events': Multiple occurrences of the same event for the same subject are 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.
[b] TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion.
Source: CSR Table 10

Table 7 Treatment-Emergent Adverse Events, Overall Summary (including infections)

	Epoch 1 (N = 44)		Epoch 2 (N = 43)		Epoch 1 and 2 Combined (N = 44)	
Category	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any TEAE	31 (70.5)	142	40 (93.0)	555	43 (97.7)	697
Related TEAE [a]	25 (56.8)	85	31 (72.1)	251	34 (77.3)	336
Unrelated TEAE	25 (56.8)	57	37 (86.0)	304	40 (90.9)	361
Any severe TEAE	1 (2.3)	1	3 (7.0)	3	4 (9.1)	4
Related TEAE [a]	1 (2.3)	1	1 (2.3)	1	2 (4.5)	2
Unrelated TEAE	0	0	2 (4.7)	2	2 (4.5)	2
Any serious TEAE	1 (2.3)	1	3 (7.0)	3	4 (9.1)	4
Related TEAE [a]	0	0	0	0	0	0
Unrelated TEAE	1 (2.3)	1	3 (7.0)	3	4 (9.1)	4
Any local TEAE	22 (50.0)	60	29 (67.4)	142	33 (75.0)	202
Related TEAE [a]	22 (50.0)	58	28 (65.1)	134	32 (72.7)	192
Unrelated TEAE	2 (4.5)	2	6 (14.0)	8	7 (15.9)	10
Any systemic TEAE	29 (65.9)	82	38 (88.4)	413	41 (93.2)	495
Related TEAE [a]	12 (27.3)	27	20 (46.5)	117	25 (56.8)	144
Unrelated TEAE	25 (56.8)	55	36 (83.7)	296	39 (88.6)	351
Any temporally associated TEAE [b]	27 (61.4)	97	36 (83.7)	310	39 (88.6)	407
Any related and/or temporally associated TEAE	27 (61.4)	102	36 (83.7)	324	39 (88.6)	426
Any TEAE leading to discontinuation	1 (2.3)	1	1 (2.3)	1	2 (4.5)	2
Any TEAE leading to death	0	0	0	0	0	0

AE = Adverse event; TEAE = Treatment-emergent adverse event; IP=Investigational Product (HYQVIA in Epoch 1 and 2).
If the start date/time of the AE is after date/time of first dose of IP in Epoch 1 and before the date/time of first dose of IP in Epoch 2 then the event is allocated to Epoch 1.
If the start date/time of the AE is after date/time of first dose of IP in Epoch 2 then the event is allocated to Epoch 2.
For the columns of 'Number (%) of subjects': Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
For the columns of 'Number of events': Multiple occurrences of the same event for the same subject are 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.
[b] TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion.
Source: CSR Table 11

A total of 536 TEAEs (excluding infections) were reported in 97.7% of subjects; of which, 336 TEAEs were reported as related to study treatment in 77.3% of subjects.
A total of 4 serious TEAEs (including infections) were reported in 4 subjects (9.1%) and 1 serious TEAE (excluding infections) was reported in 1 subject (2.3%). No SAEs were reported that were considered by the investigator to be related to HYQVIA. No deaths were reported during the study.

The majority of these TEAEs were mild in severity, the 3 severe TEAEs (all systemic) were reported in 3 subjects (6.8%); of which, 2 severe TEAEs in 2 subjects (4.5%) were related to study treatment, i.e. headache and coeliac disease.
Overall, 334 systemic TEAEs (excluding infections) were reported in 39 subjects (88.6%). The majority of the events were assessed as mild and unrelated to study treatment.
Local TEAEs were reported in 33 subjects (75.0%) and were representative of local reactions at the infusion site. The majority of the events were assessed as mild, none were severe, indicating that HYQVIA was well tolerated at the injection site.
Excluding infections, overall rates of related systemic TEAEs per infusion and per subject were 0.190 and 3.273, respectively. The most commonly reported systemic TEAEs per subject by PT included headache, fatigue, pyrexia, vomiting, nausea, infusion related reaction, pain in extremity, and throat irritation.

Excluding infections, the overall rates of related local TEAEs per infusion and per subject were 0.253 and 4.364, respectively. The most commonly reported local TEAEs by PT included infusion site pain, infusion site pruritus, infusion site erythema, infusion site extravasation, infusion site swelling, and injection site pain. This corresponds to lower overall rate of related systemic TEAEs per subject-year (2.787) compared with related local TEAEs per subject-year (3.716). The overall rate of unrelated local TEAEs per subject-year was 0.194.
Two subjects (4.5%) discontinued the study due to TEAEs. One subject in Epoch 1 prematurely discontinued due to a TEAE of coeliac disease and 1 subject in Epoch 2 prematurely discontinued due to a TEAE of infusion site pain.
Excluding infections, a total of 86.4% of subjects had 382 temporally associated TEAEs and the same percentage of subjects had 401 related and/or temporally associated TEAEs. A total of 88.6% of subjects had 407 temporally associated TEAEs (including infections) and the same number of subjects had 426 related and/or temporally associated TEAEs.

Including infections, a total of 697 TEAEs were reported in 97.7% of subjects; of which, 336 TEAEs were reported as related to study treatment in 77.3% subjects. Including infections, a total of 4 severe TEAEs were reported in 9.1% of subjects; of which, 2 TEAEs in 4.5% subjects were related to study treatment (headache and coeliac disease). All 4 TEAEs were systemic.
Systemic TEAEs (including infections) were reported in 93.2% of subjects; however, the majority of the events were assessed as unrelated to HYQVIA. Local TEAEs were reported in 75% of subjects and represented local reactions at the infusion site. No local severe TEAEs were reported indicating that HYQVIA was well tolerated at the injection site. The proportion of subjects experiencing related systemic TEAEs was lower (56.8% of subjects) compared to the proportion of subjects experiencing related local TEAEs 72.7% of subjects. Assessment of hemolysis and other clinical laboratory parameters did not raise any safety concerns with respect to HYQVIA administration.
One subject developed a titer of binding antibodies against rHuPH20 above the threshold defined as positive (≥160) at Epoch 2 Month 6. Neutralizing antibodies against rHuPH20 were negative for this subject at all time points tested. The subject completed 2 additional years of study treatment and assessments in Epoch 2, as per protocol, including ongoing assessments of antibodies against rHuPH20 - no safety concerns were identified. Additional testing for characterization of antibodies cross-reacting with Hyal 1, 2, and 4 and complement activity were performed per protocol. Antibodies cross-reacting with Hyal 1, 2 and 4 were negative. Complement activity of C3, C4, C1q Binding and Raji cell complex were normal; CH50 was abnormal, but no evidence of complement consumption or immune complex formation was noted.
Overall, 65 TEAEs were reported for this subject, among them 53 AEs were mild, and 12 AEs moderate in nature. No severe, serious or ASBI events were reported for this subject. A total of 47 TEAEs were reported as related to HYQVIA occurred before or after anti-rHuPH20 antibodies titer increase >160 at Epoch 2 Month 6 Visit. Related AEs were mild and moderate in nature, self-resolved in the majority of cases. Anti-rHuPH20 antibodies findings were not associated with modifications in the study drug's peak PK, and no reduction of HYQVIA therapeutic efficacy was noted in the subject.
There were no clinically meaningful differences in serum trough IgG levels between age groups during Epoch 2, with the highest median change from the Month 0 baseline measurement of <1.3 g/L. A

similar trend was observed for IgG subclass results with stable levels across Epoch 2 and no notable age group differences for the first 12 months across Epoch 2.
Overall, the median number of infusions, infusion per month, and number of infusion sites were similar for all age categories, as observed from the mode of administration results. Subjects in the age group of 2 to < 6 years had a lower median number of infusion sites per infusion/month compared with other age groups.
Overall, the median number of infusions per subject for the duration of Epoch 2 was 15.0, with the highest median number of infusions per subject in the age group of 2 to < 6 years. The median (minimum, maximum) duration of infusion (minutes) was similar cross the age groups, with high variability within groups. The age group of 12 to < 16 years had higher median maximum infusion rates per site compared with the other age groups. The median infusion volume per site was 85.0 mL. Subjects aged 12 to < 16 years had a higher median infusion volume per site compared with other age groups. In spite of infusion interruptions, the majority of subjects completed their infusions.
Overall, the median time to reach final dose interval (defined as 3 or 4 weeks) in Epoch 1 was 6.14 weeks and was similar in all the age categories. A total of 32 subjects (74.4%) maintained a treatment interval of 3 or 4 weeks in Epoch 2 for 12 months.

2.3.3. Discussion on clinical aspects

Methodology
The MAH submitted clinical data resulting from the completed interventional Phase 3 study 161503 entitled "Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases". This study was an open-label, prospective, non-controlled, multi-center study conducted in 17 study centers in the United States and part of the clinical development programme. It was conducted with the purpose to acquire additional data on the efficacy, safety, tolerability, immunogenicity, PK, and other parameters of HYQVIA in pediatric subjects aged ≥2 to < 16 years with primary immunodeficiency diseases (PIDD).

The study objectives were the demonstration of efficacy of HYQVIA treatment in pediatric subjects with PIDD who received prior IVIG or SCIG therapy before enrollment into the study as well as further efficacy and safety assessments, tolerability, PK parameters, characteristics of product administration, treatment preference and satisfaction, and health-related quality of life.
Determined key efficacy-endpoints were the annual rate of acute serious bacterial infections (ASBI), the annual rate of infection, and trough levels of total IgG, IgG subclasses, and of specific antibodies. Safety-related endpoints were the number and rate per infusion of treatment-emergent adverse events, as well as their temporal relationship, and number/proportion of subjects who developed positive titers (≥160) of binding or neutralizing antibodies to rHuPH20. PK-related assessments of observed total IgG levels included standard PK parameters (AUC, CL/F, C/Tmax, Cmin, and terminal half-life). The endpoint selection is considered adequate, as endpoints are well-established in clinical studies evaluating SCIG replacement therapy in patients with PIDD in routine clinical practice, and in line with the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg).

The study included 3 Epochs; Epoch 1 and 2 were treatment periods, and Epoch 3 was an optional one-year safety follow-up for those patients who had developed an anti-rHuPH20 antibody titer of ≥160 during the first two Epochs in combination with either a study drug-related SAE or severe treatment-related AE. However, the third Epoch was not initiated, as no study subject had fulfilled these criteria.
In Epoch 1, subjects received on-site HyQvia SC with a dose or interval ramp-up period of up to 6 weeks, followed by a one-year Epoch 2, where HyQvia treatment was administered in 3- or 4-weekly intervals depending on the subject's pretreatment, i.e. IVIG or another SCIG. Home administration was allowed if infusions had been well tolerated on-site.
Based on anti-rHuPH20 binding antibody assay results, Epoch 2 and HyQvia treatment, respectively, was extended up to 3 years or study participation was terminated.

Subjects had a diagnosis of PIDD requiring gammaglobulin replacement, and receiving a stable dose between 0.3-1.0 g/kg/bw Q4W for a period of at least 3 months prior to screening. Serum trough levels had to be >5 g/L at screening. Patients were excluded if they had laboratory values indicating anemia, neutropenia, liver dysfunction, or specific infections, an ongoing history of hypersensitivity or persistent reactions following IVIG/SCIG administration, known intolerance of hyluronidase, and IgA deficiency. The eligibility criteria are considered adequate.

Efficacy and safety results
Study subjects' weekly HyQvia dose was equivalent to the IG treatment received before. The infusion rates and volumes were administered weight-based according to the SmPC.

Overall, 44 paediatric subjects met the eligibility criteria and thus, were enrolled and received study medication. 34/44 (77.3%) thereof completed the study. Reasons for premature study discontinuation were withdrawal by subject (6), adverse events (2), COVID-19 constraint (1) and physician's decision (1). Until the database lock date for final analysis of November 2022, the 34 subjects had completed the Epoch 2, and no subject met the criteria for entering Epoch 3.

As primary immunodeficiencies appear to affect males and females about equally, the study population was imbalanced as to gender. The age distribution is considered suboptimal, however, may be accepted as at least 20% of all patients were included in the youngest cohort. Most patients had a diagnosis of CVID or a specific antibody deficiency. In the context of the primary disease, the most frequently reported medical history by SOC was infections and immune system disorders as well as metabolism and nutrition disorders, and concomitant medications were drugs for obstructive airway diseases, antibiotics, anti-inflammatory products and analgesics.

According to the primary objective of the study, the rate of ASBI, defined as the mean number of ASBIs per subject-year in the intent-to-treat population (FAS) was assessed. Only one subject experienced two ASBIS, resulting in a mean rate of ASBIs per subject-year of 0.04, which is statistically lower than the threshold rate of 1.0 ASBI per subject-year, and thus acceptable (cf. Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg). Thus, the primary endpoint of the study was met.
The mean rate of all infections per subject-year is well within the range of a healthy reference population. Total serum IgG, IgG subclass and specific antibody trough levels were stable from baseline throughout the study and no meaningful differences between age groups were observed.
No changes in HRQoL and health status were observed from baseline to the end of the study suggesting satisfaction with the HyQvia treatment in the studied population. Other assessed outcomes such as the mean rate of days of absence from school or work due to illness or those associated with healthcare resource utilization, i.e. days on antibiotics, hospitalization rate or acute physician visits substantiate the efficacy of HyQvia in the investigated study subjects.

Overall, the median duration of exposure for HYQVIA was 14.87 months and the majority of subjects had a treatment exposure for 12-24 months. The mean number of infusion sites per infusion was low, the time required for the total infusion and infusion rate per site were within the usual range for HyQvia across the different paediatric age groups as well as the infusions per month. The number of infusions per subject-year was balanced across the age groups. A small percentage of infusions was interrupted due to treatment-related adverse events (TEAEs); however, no infusion was discontinued and no subject changed in regimen due to a TEAE.
Most events were reported in Epoch 2 due to the longer treatment and observation period. The frequencies of TEAE categories were comparable between both safety analysis sets, either in- or excluding infections. Overall, almost all subjects experienced TEAEs. The majority experienced mild and local TEAE. A few severe TEAEs were observed, two thereof were assessed as related to study treatment (headache and coeliac disease). Serious adverse events (SAEs) were rare, and observed SAEs were assessed to be unrelated to HyQvia treatment. Most commonly reported TEAE in both treatment Epochs that were deemed related to HyQvia treatment were local infusion site reactions such as infusion/injection site pain, pruritus, erythema, swelling, and systemic TEAEs such as

headache, fatigue and infusion-related nausea/vomiting. The frequencies gradually decreased over time. Overall, the rates of related local and systemic per infusion and per subject seem to be comparable compared with the literature considering slightly different subject numbers and observation periods (cf. Wassermann et al., 2016). Those TEAEs that continued to occur at a later stage of the study were headache and injection-site reactions. In each of the both Epochs, one subject experienced a TEAE that led to treatment discontinuation (coeliac disease, see above and injection site pain), thus, discontinuation rates are low. Parameters indicative of hemolysis did not significantly change throughout the study, and none of the viral serology laboratory values were clinically significant. Antibodies against rHuPH20 without neutralizing function were detected in a single patient, however, were not associated with reduced efficacy; no additional antibodies were observed. Thus, the immunogenic effect of HyQvia was slightly lower in this very study compared with the paediatric study population included in the pivotal study.

3. CHMP overall conclusion and recommendation

The efficacy of HyQvia was confirmed in the selected paediatric study population, as the replacement therapy was effective in maintaining Ig trough levels and preventing serious bacterial and all kinds of infections in PIDD patients throughout the study period. The safety analysis of study 161503 did not reveal any unusual findings, thus, the treatment seemed to have been tolerated adequately. Most patients favoured treatment continuation with HyQvia. It is therefore concurred that the benefit-risk ratio remains unchanged and that no amendments of the Product Information are necessary.

☒ Fulfilled:

No regulatory action required.