Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

BLA Clinical Review Memorandum

Application Type	Efficacy Supplement- BLA
STN	125402/818
CBER Received Date	March 8, 2022
PDUFA Goal Date	April 7, 2023
Division / Office	Division of Clinical Evaluation General Medicine/Office of Clinical Evaluation
Priority Review (Yes/No)	No
Reviewer Name	Sairah Thommi, MD
Review Completion Date	April 7, 2023
Supervisory Concurrence Team Lead GMB1 Branch Chief GMB1 Division Director, DCEGM	 Melanie Blank, MD Elizabeth Hart, MD Tejashri Purohit-Sheth, MD
Applicant	Takeda
Established Name	Immune Globulin 10% (Human) with Recombinant Human Hyaluronidase
(Proposed) Trade Name	HYQVIA®
Pharmacologic Class	Immune Globulin, Subcutaneous (Human)
Formulation(s), including Adjuvants, etc.	Dual vial unit with two solutions. One solution of IgG (100 mg/mL) and another solution of Recombinant Human Hyaluronidase (160 U/mL)
Dosage Form(s) and Route(s) of Administration	2.5 grams protein / 200 U Hyaluronidase; 5.0 grams protein / 400 U Hyaluronidase; 10.0 grams protein / 800 U Hyaluronidase; 20.0 grams protein / 1600 U Hyaluronidase; 30.0 grams protein / 2400 U Hyaluronidase. For subcutaneous use.
Dosing Regimen	Dose given every 3-4 weeks.

	When switching from IGIV to HYQVIA, start 1 week after last infusion. Give the one week dose, then increase the dose to an every 2 week dose followed by an every 3 week dose and 4 week dose (if needed) at the appropriate times.
Indication(s) and Intended Population(s)	Primary Immunodeficiency (PI) in adults and pediatric patients age 2 and older
Orphan Designated	No

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GLOSSARY

AE	adverse event
AR	adverse reaction
ASBI	acute serious bacterial infections
AUC	area under the curve
BLA	biologics license application
BW	body weight
CFR	Code of Federal Regulations
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CL	clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CMC	chemistry, manufacturing, and controls
CR	complete response
CVID	Common Variable Immunodeficiency
DPMH	Division of Pediatrics and Maternal Health
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
IAR	Infusion Associated Reaction
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGI	immune globulin infusion
IGIV	intravenous immunoglobulin
IGSC	immunoglobulin subcutaneous
ISE	integrated summary of efficacy
ITP	Idiopathic Thrombocytopenic Purpura
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OPT	Office of Pediatric Therapeutics
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	Primary Immunodeficiency
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SC	subcutaneous
SCID	Severe Combined Immunodeficiency
SE	standard error
T_{max}	time to maximum concentration
TRALI	transfusion-related acute lung injury
XLA	X-linked agammaglobulinemia Common Variable Immunodeficiency

1. Executive Summary

On March 8, 2022, Takeda submitted a 505(b)(2) efficacy supplement for Hyqvia, a 10% immune globulin (IG) infusion with recombinant human hyaluronidase (rHuPH20). The efficacy supplement contains the interim results of Study 161503 in children, intended to fulfill the Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR) and a proposal for revised pediatric labeling. The proposed labeling updates also include changes based on the results of Study 161301, a pregnancy registry that was one of the Post-Marketing Commitments (PMC #3). During the review period, Takeda also submitted the study report for Study 161504, a European pediatric study, and the results of Study 161406, a study that evaluated the long-term changes in adverse events in subjects taking Hyqvia, intended to fulfill PMC #2.

505(b)(1) Approval and Post-marketing Requirement/ Commitments

Hyqvia was first approved by FDA for the treatment of adults with Primary Immunodeficiency (PI) on September 12, 2014. The pre-administration of rHuPH20 was intended to allow larger volumes of IG 10% to be infused subcutaneously (SC) thereby allowing less frequent administration (every 3-4 weeks as opposed to weekly SC administration without rHuPH20).

In accordance with the provisions of section 505B of the Food Drug and Cosmetic Act [21 U.S.C. 355c, also referred to as the Pediatric Research Equity Act (PREA)], the approval of Hyqvia included a post-marketing requirement (PMR#1) to complete a pediatric study in subjects aged 2 to 16 years of age by February 28, 2027.

During the review of the original biologics license application (BLA), FDA noted the development of anti-rHuPH20 antibodies in 15 (17%) out of 87 subjects in Studies 160603 (the pivotal study) and 160902 (the extension study). Because it was unknown if long-term exposure to anti-rHuPH20 antibody-complexes in target organs (testicular tissue, mesenteric tissue, and brain tissue) could affect the benefit-risk of Hyqvia, PMC #2[1] was issued to assess the long-term safety of Hyqvia. The assay for anti-rHuPH20 antibodies was validated at a titer of 160, therefore this was the cut-off used to identify positive levels.

PMC #3 was for a pregnancy registry with a primary objective of characterizing the course and pregnancy outcomes of pregnant women who were taking Hyqvia. The development of the enrolled infants at birth and for the first 2 years of life were assessed.

Primary Immunodeficiencies

PI represents a heterogenous group of disorders resulting from largely inherited defects of the immune system. It is estimated that 1-2% of the population worldwide are affected.[2] The major antibody deficiency syndromes of clinical significance include X-linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), and IgG subclass deficiency.

1 There is no PMC#1; The PREA requirement was named PMR#1
2 Modell, Vicki, et al. "Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network." *Immunologic research* 64 (2016): 736-753.

Hypogammaglobulinemia increases susceptibility to infections. Subjects with PI are at increased risk for recurrent, severe bacterial infections, especially respiratory tract infections. The mainstay of treatment is intravenous immunoglobulin (IGIV) and subcutaneous immunoglobulin (IGSC). These treatments provide antibodies to prevent serious bacterial diseases and are the mainstay of treatment for most humoral PI.

Pediatric Data and Analyses

Pediatric data from Studies 161503 (PMR #1), 161504 (European pediatric study), and from the pivotal study (Study 160603) were evaluated by the clinical review team to ensure a comprehensive evaluation of the efficacy and safety of Hyqvia in children.

Study 161503, submitted to fulfill the PREA PMR under IND 13840, was a Phase 3, open-label study wherein 44 pediatric subjects 2 to 16 years of age with primary immunodeficiency were administered Hyqvia every 3-4 weeks after an initial ramp-up period, and monitored for adverse events, laboratories, physical exams, vital signs, quality of life questionnaires, concomitant medications and non-drug therapies. Subjects were followed for one year unless they developed anti-rHuPH20 antibodies, in which case they were to be followed for an additional 2 years. If subjects who were positive for anti-rHuPH20 had a serious adverse event (SAE) or severe adverse event that was drug-related, they were to be followed for one additional year. The primary efficacy measure was based on demonstrating prevention of serious bacterial infections defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess over the course of 1 year to allow for seasonal variations in infection rates. In accordance with FDA guidance, “FDA guidance for industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency,” published in June 2008.[3] The endpoint would be met if the upper bound of the one-sided 99% confidence interval for the rate of serious bacterial infections is < 1.0 per subject-year.

In September 2015, the Agency agreed with the licensure strategy to submit an efficacy supplement based on an interim analysis of at least 40 pediatric subjects who had completed 1 year of Hyqvia administration. The efficacy supplement included data on each of the enrolled subjects (n=44). All subjects had completed 1 year of follow-up. There was only one subject (2%) who tested positive for anti-rHuPH20 antibodies and had to be followed for the additional 2 years. The subject did not have any serious, severe, or immune-related treatment emergent adverse events (TEAEs). There was a mean rate of 0.04 (upper 99% CI 0.21) serious bacterial infections per subject-year. The study met its primary efficacy endpoint.

To evaluate safety, pediatric data from Studies 161503, 161504, and 160603 were pooled. Adverse Events (AEs) were independently reviewed. Narratives were reviewed for all concerning AEs and interactive review with the sponsor was conducted as needed. The frequency of AEs in pediatric subjects was compared to the frequency of AEs seen in adults who took Hyqvia in the pivotal study (Study 160603).

3 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human

The European study, Study 161504, also considered in this review, was a multi-center, prospective, single-arm study of Hyqvia in pediatric subjects with PI. Forty-two subjects enrolled in the study. Thirty-nine subjects completed one-year of follow-up. Similar to Study 161503, the study was designed to continue for an additional 2 years if subjects developed antibodies to rHuPH20 ≥ 160, and an additional one year if there was a SAE or severe AE thought to be drug related. No subjects in Study 161504 tested positive for anti-rHuPH20 antibodies ≥ 160.

Study 160603, the pivotal study that supported the original approval, enrolled 24 pediatric subjects who were younger than 16 years of age. These subjects were included in the safety analysis.

The most frequent systemic adverse events (AE) within 72 hours of treatment and in >5% of subjects were: headache, fever, vomiting, fatigue, abdominal pain, diarrhea, nausea, upper respiratory tract infection, cough, rash, and sinusitis. Local AEs within 72 hours of treatment and in > 5% of subjects included: infusion site pain, pruritis, erythema, extravasation, and swelling. There were no pediatric deaths. There were 8 serious Treatment Emergent Adverse Events (TEAEs) in Study 161504 (severe dental caries, moderate inflammatory bowel disease, severe idiopathic orbital inflammation, mild pyrexia, mild acute sinusitis, moderate pharyngitis, moderate pilonidal cyst, and moderate pneumonia) and 4 serious TEAEs in Study 161503 (mild adenovirus infection, severe *Clostridium Difficile* colitis, moderate severity bacterial pneumonia, and moderate tonsillar hypertrophy); all events were considered unrelated to Hyqvia. In Study 160603, all SAEs in pediatric subjects were assessed as unrelated to the product in the original review. The safety profile of Hyqvia in pediatric subjects with PI was similar to the safety profile seen in adults and was deemed acceptable.

Long-term safety and tolerability including assessment of anti-rHuPH20

Study 161406 was a prospective, single arm, open-label, multicenter surveillance study to assess safety and tolerability of Hyqvia in adults who were being treated with or had been prescribed Hyqvia. Study 161406 was reviewed here because of concerns regarding the short and long-term effects of anti-rHuPH20 antibodies, and the implications the findings of this study might have on our assessment of safety in children. Out of 196 subjects tested at least once for anti-rHuPH20 antibodies, fourteen (7%) were positive for anti-rHuPH20 antibodies at a titer ≥ 160. Eight of the subjects who tested positive for anti-rHuPH20 antibodies were positive at baseline.

The adverse events in the subjects who developed anti-rHuPH20 antibodies at a titer ≥ 160 were within the expectations of this class of product. No clinical concerns regarding the development of anti-rHuPH20 antibodies were identified. The findings provided reassurance regarding the safety of the product, and reduced concerns regarding the long-term ramifications of anti-rHuPH20 antibody development.

The Pregnancy Registry (PMC #3)

Study 161301 was an observational two-arm, multicenter, post-authorization pregnancy registry that included 9 mothers and 7 infants born to mothers who were exposed to Hyqvia or an alternative immunoglobulin treatment during pregnancy. Participation in the pregnancy registry was voluntary. There were only 5 maternal – fetal pairs in the registry where Hyqvia exposure during pregnancy resulted in an infant with known outcomes.

Two of the 5 infants (40%) exposed to Hyqvia during pregnancy had congenital malformations (one cleft lip and another talipes calcaneovalgus). One of the infants (with talipes calcaneovalgus) with congenital abnormalities was enrolled in the study after birth. The other infant (with cleft lip) was enrolled late in the pregnancy. Because Hyqvia contains recombinant human hyaluronidase, which alters connective tissue permeability with the hydrolysis of hyaluronic acid, this reviewer believes it is possible that these adverse events could be related to Hyqvia. Neither of the two infants born to mothers who had taken alternative immunoglobulin treatments during pregnancy had congenital malformations. It is possible that selection bias played a role in the increased enrollment of infants with congenital malformations in the Hyqvia arm of the registry. The clinical implications of this finding are not clear, but they represent a concerning safety signal.

One infant was breastfed during the study. No mothers tested positive for anti-rHuPH20 at or above titers of 160 during the study. However, only two mothers in the Hyqvia arm and two mothers in the alternative treatment arm were assessed for anti-rHuPH20 antibodies. Insufficient data were accrued to make any conclusions regarding the effect of anti-rHuPH20 antibodies or lactation on fetal/infant development.

Conclusions

Based on the review of the data submitted, the Division determined that the PREA post-marketing requirement was fulfilled. The primary efficacy endpoint in the primary pediatric study (161503) was met. The benefit/risk is favorable in the pediatric population that was studied (age 2 years to < 16 years of age). As such, the indication for PI will be expanded to children 2 years of age and older. The Pediatric Review Committee (PeRC) agreed with the Division's determination to expand labeling to the pediatric population.

A safety signal was identified in subjects enrolled in the pregnancy registry. Given the potential concerns that the use of this product during pregnancy could lead to an increased risk of congenital anomalies, labeling was updated to include the results of the pregnancy registry and spontaneous reporting of congenital malformations to date. In addition, FDA agreed to another PMC to further explore pregnancy concerns (a claims-based study of pregnancy outcomes in mothers taking Hyqvia). There were insufficient data to support the proposed labeling changes related to lactation.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Study 161503:
Study 161503, the pivotal pediatric study, treated 44 pediatric subjects (age 2 to less than 16 years) with Primary Immunodeficiency (PI) diseases in a Phase 3, open-label, prospective, non-controlled, multicenter study.

Table 1: Demographic Data, Study 161503

Parameter	All Subjects (N= 44)
Age (years)	--
Mean (SD)	9 (3.6)
Median	9

Min, Max	3, 15
Age Category n(%)	--
2 to < 6 years	9 (20%)
6 to <12 years	23 (52%)
12 to <16 years	12 (27%)
Gender n (%)	--
Male	26 (59%)
Female	18 (41%)
Race n (%)	--
Black / African American	2 (4%)
White	40 (91%)
Other	1 (2%)
Multiple	1 (2%)
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islanders	0
Ethnicity n (%)	--
Hispanic or Latino	5 (11%)
Not Hispanic or Latino	39 (89%)

Abbreviations: SD= Standard Deviation
Adapted from sBLA 125402/818; Interim Clinical Study Report p. 64-65

Study 161504:
Study 161504 was a Phase 4, multi-center, post-authorization, prospective, non-controlled study on the safety, tolerability, and immunogenicity of Hyqvia in 42 pediatric subjects with PI in Europe.

Table 2: Demographic Data, Study 161504

Subject Characteristic	**Statistic**	**All Subjects (N= 42)**
Age (years)	Mean (SD)	11 (4.1)
--	Min, Max	3, 17
Age Group n(%)	2 to <6 years	6 (14%)
--	6 to <12 years	15 (36%)
--	12 to <18 years	21 (50%)
Sex n(%)	Male	34 (81%)
--	Female	8 (19%)
Ethnicity n(%)	Hispanic or Latino	0
--	Not Hispanic or Latino	42 (100%)
Race (n%)	American Indian or Alaska Native	0
--	Asian	0
--	Native Hawaiian or Other Pacific Islanders	0
--	White	41 (98%)
--	Not Applicable – Not Collected per Local Regulations	1 (2%)

Abbreviations: BMI= body mass index; max= maximum; min= minimum; SD= standard deviation
Source: Original sBLA 125402/818; Clinical Study Report 161504 dated October 14, 2021, p.71-72.

Of note, Study 160603 (the original pivotal study) and Study 160902 (extension study) contributed pediatric safety data to this review. The pediatric demographic information is detailed in the Clinical Review Memo for Hyqvia dated September 10, 2014.

In addition, Study 161301 provided data from a pregnancy registry and Study 161406 provided a long-term safety study of Hyqvia. Both of these studies have demographic information that can be reviewed in their study sections (6.4.10.1.1 and 6.6.10.1.1).

Clinical Reviewer Comment: *In both pediatric studies, study populations were mostly white (94% overall). This does not reflect the expected demographics of PI in the United States.[4] However, based on previous knowledge of IGSC, this reviewer does not believe it is likely that the demographics of the study population limit the interpretability of safety or efficacy data. However, because of lack of diversity in the study population, it is not possible to evaluate differences in outcomes across race/ethnic subgroups.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	--
☐	Observer-reported outcome	--
☒	Clinician-reported outcome	--
☐	Performance outcome	--
☐	Patient-focused drug development meeting summary	--
☐	FDA Patient Listening Session	--
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	--
☐	Observational survey studies	--
☐	Natural history studies	--
☐	Patient preference studies	--
☐	Other: (please specify)	--
☐	**If no patient experience data were submitted by Applicant, indicate here.**	--

4 Kobrynski, Lisa, Rachel Waltenburg Powell, and Scott Bowen. "Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007." *Journal of clinical immunology* 34 (2014): 954-961.

Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	--
☐	Patient-focused drug development meeting	--
☐	FDA Patient Listening Session	--
☐	Other stakeholder meeting summary report	--
☐	Observational survey studies	--
☐	Other: (please specify)	--

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiency (PI) is a heterogeneous group of disorders in which there is an intrinsic defect in the tissues, cells, and/or proteins of the immune system, in most cases due to a genetic defect, resulting in immune deficiency. It is estimated that 1-2% of the population worldwide is affected. Diseases include, but are not limited to, X-linked agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiency (SCID), and congenital agammaglobulinemia.

Many of these disorders are characterized by hypogammaglobulinemia and/or defective antibody production and, therefore, are clinically manifested as increased susceptibility to recurrent, severe respiratory tract and other infections (both viral and encapsulated bacterial in origin) which have the potential to be life-threatening.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Replacement therapy with polyclonal human normal immunoglobulin is the cornerstone of management for significant primary antibody deficiency disorders. No viable alternatives exist to this essential, basic component of treatment, particularly in the context of severe, persistent, or recurrent bacterial infections. For most patients, replacement therapy is a lifelong requirement. Replacement therapy increases life expectancy and reduces the frequency and severity of infections. Subcutaneous and intravenous preparations are therapeutically equivalent.

Additional infection prevention measures include avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often involves broad spectrum antimicrobials and prolonged treatment courses.

2.3 Safety and Efficacy of Pharmacologically Related Products

The FDA Guidance for Industry: “Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency” (hereinafter referred to as the FDA Guidance for IGIV products) states that a statistical demonstration of a serious infection rate per

person-year of less than 1.0 is adequate to provide substantial evidence of efficacy. Numerous marketed immune globulin products (both intravenously and subcutaneously administered) have demonstrated serious bacterial infection (SBI) rates of less than 1.0 per person-year. There are currently eight licensed Immune Globulin Subcutaneous (Human) (IGSC) products in the U.S.: Cuvitru® (Baxalta US, Inc.), Hizentra® (CSL Behring), Xembify® (Grifols USA), Hyqvia® (Baxter Healthcare Corporation, Baxter Bioscience), Cutaquig® (Octapharma), Gammagard Liquid® (Baxter Healthcare Corporation), Gamunex-C®, (Grifols Therapeutics Inc), and Gammaked® (Kedrion Biopharma).

All products are indicated for replacement therapy in patients with PI. Hyqvia is currently only indicated in adults. All other IGSC products listed above have been approved for use in children 2 years of age and older. Gamunex-C is also approved to treat Idiopathic Thrombocytopenic Purpura (ITP) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP); Hizentra is also approved for maintenance therapy of CIDP; Gammaked is also indicated for CIDP and ITP.

The safety profile for immune globulins as a class is well-established. The incidence of adverse reactions (AR) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. In general, common ARs for immune globulins typically include local Infusion Associated Reactions (IARs) (i.e., swelling, redness, heat, discomfort at the injection site), headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. IGIV products carry an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. IGSC products carry and obligate boxed warning for thrombosis. Warnings and Precautions for this class of products include hypersensitivity/ anaphylaxis, aseptic meningitis, hemolysis, transfusion-related acute lung injury (TRALI) and transmission of infectious agents.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Hyqvia was approved in the European Union on May 16, 2013. Hyqvia was approved to treat PI in adults on September 12, 2014 in the United States. As of May 2022, Hyqvia has been licensed in 45 countries.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

A PREA post-marketing requirement (PMR) was issued to study children aged 2-16 years of age with PI. The initial study protocol was to be submitted by March 1, 2025 and the final study report was to be submitted by July 31, 2027.

Regulatory Activity

Written Response, 9/22/2015	FDA agrees with licensure strategy to submit an efficacy supplement with clinical data from an interim safety analysis after at least 40 pediatric subjects have completed 1 year of study participation with ongoing follow-up provided for subject(s) who had anti-rHuPH20 antibody titers ≥ 160.
Amendment 1, Protocol 161503, dated 7/20/2017	The primary objective was changed to efficacy from safety. The primary endpoint was updated to the rate

	of acute serious bacterial infections (ASBI), instead of a safety assessment of number and rate per infusion (excluding infections) of related SAEs and all severe related AEs. This choice of primary efficacy outcome is consistent with the FDA guidance document "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency" published in June 2008.
Internal Meeting, 4/14/2022	The decision to complete PREA with data from 1 subject pending study completion (subject completed 1-year of data but developed antibodies and is in Epoch 2) was discussed. Given feedback to the Sponsor (listed above) allowing for efficacy supplement review prior to the completion of the study, the decision was made to proceed with filing.
Major Amendment, 7/14/2022	In response to the amendment received July 5, 2022 containing the study report and data for Study 161504 ("Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases"), the Agency notified the Sponsor that an additional 3 months will be added to the review timeline to ensure adequate time to review.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a comprehensive clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to the FDA Guidance for electronic submissions. Study 161504 ("Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases") and Study 161406 ("Non-interventional post-marketing safety study on the long-term safety of Hyqvia") were submitted during the review of the application. The submission of Study 161504 during the review resulted in a Major Amendment as discussed in Section 2.5.

3.2 Compliance With Good Clinical Practices And Submission Integrity

All studies were completed according to Good Clinical Practices.

Study 161504 was conducted outside of the United States. The sponsor submitted the investigator's qualifications, research facilities, protocol and results, statistical analysis

plan, names and addresses of the IRB and Independent Ethics Committees, and sample consent and assent forms.

3.3 Financial Disclosures

Covered clinical study: Study 161503: Efficacy, Safety, Tolerability, Immunogenicity, and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases
Was a list of clinical investigators provided? X Yes ☐ No
Total number of investigators identified: 22
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 25 Is an attachment provided with the reason? ☐ Yes ☐ No

An investigator reported payment of approximately $37,000 (Speaking Honoraria, Advisory Board) from Shire during the time of the clinical trial and within 1 year after.

Another investigator reported payment of approximately $100,000 (honoraria and consulting fees) during the time the trial was completed and for one year after.

Covered clinical study (name and/or number): 161504 “Post-Authorization Safety, Tolerability, and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases”
Was a list of clinical investigators provided? X Yes ☐ No

Total number of investigators identified: 26
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☒ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 21 Is an attachment provided with the reason? ☐ Yes ☐ No

One investigator reported a grant (b) (4) .

Clinical Reviewer Comment: *Study 161503 enrolled 44 subjects at 17 sites. The maximum number of subjects enrolled in any site was 7. The two investigators that disclosed financial arrangements enrolled 7 and 3 subjects at each site. The sponsor submitted plans to minimize potential bias, which were deemed acceptable by this reviewer.*

One investigator from Study 161504 reported a grant as a disclosable payment. The corresponding clinical site enrolled 2 subjects into the study. The sponsor submitted their procedures to minimize potential bias, which were deemed acceptable by this reviewer.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

No formulation changes have been implemented since the original BLA acceptance. Please refer to the original review for additional information.

4.2 Assay Validation

Please refer to the CMC review for a detailed review and discussion of the assay validation.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology review from the initial BLA for a detailed discussion of product nonclinical pharmacology/ toxicology.

4.4 Clinical Pharmacology

No pediatric specific dose requirements were necessary to achieve the desired serum IgG levels. Please see the clinical pharmacology review for additional details.

4.4.1 Mechanism of Action

- IG 10% provides the therapeutic effect and rHUPH20 is intended to improve dispersion, absorption, and bioavailability of IG 10%.
- IG 10% supplies a broad spectrum of opsonizing and neutralizing IG antibodies against a wide variety of bacterial and viral agents. It also contains a spectrum of antibodies capable of interacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IG have not been fully elucidated.
- rHuPH20 is intended to facilitate the increased bioavailability of IG 10% by temporarily increasing the permeability of the subcutaneous tissue. Hyaluronan, a polysaccharide found in the intercellular ground substance of connective tissue, binds large quantities of water and forms large, random coil structures that create barriers to flow through the subcutaneous interstitial matrix. Hyaluronan is degraded by the naturally occurring enzyme hyaluronidase and has a half-life of approximately 5 days. rHuPH20 accelerates the breakdown of hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates dispersion, increased absorption into the capillaries and lymphatics and improved bioavailability of IG 10%, theoretically resulting in more of the infused IG reaching the vascular space. In the doses administered, rHuPH20 acts only locally and does not result in detectable levels in the circulation.

4.4.2 Human Pharmacodynamics (PD)

Please refer to the original memo for BLA 125402 for a detailed discussion of product PD.

4.4.3 Human Pharmacokinetics (PK)

Refer to the memo of the PK Reviewer and address any clinical implication of ADME issues. Describe, if any, the relevance of PK in product-product, product-demographic and product-disease (e.g., renal failure, liver failure) interactions: summary tables are useful here. Cover PK aspects related to dose selection, but summarize efficacy and safety trials on dose response in Section 7 Integrated Overview of Efficacy, and Section 8 Integrated Overview of Safety, respectively.

Please refer to the original memo for BLA 125402 for a detailed discussion of product PK.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses for this pediatric study were supported by the submitted data. No statistical concerns were identified. Please refer to the memo from the statistical reviewer for additional details.

4.6 Pharmacovigilance

The Division of Pharmacovigilance recommended:

- Routine pharmacovigilance
- A retrospective claims-based pregnancy study to be conducted as a post-marketing commitment (PMC) to further characterize the safety of Hyqvia use during pregnancy.

Clinical Reviewer Comment*: Based on the increased rate of congenital abnormalities seen in infants born to mothers who took Hyqvia during pregnancy (see Section 6.4.11.1 for additional information), this reviewer agreed with The Division of Pharmacovigilance to issue a PMC. Please see Section 11.6 for additional information regarding the PMC.*

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This clinical reviewer assessed pediatric data from Study 161503 (PMR study), Study 160603 (pivotal study), and Study 161504 (European study) to assess safety. The reviewer also reviewed adult safety data from Study 160603 (to serve as a comparison for pediatric safety data) and Study 161406. In addition, the data from Study 161301 (the pregnancy registry) was reviewed.

The reviewer referred to the FDA guidance document (FDA Guidance for IGIV products).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following were reviewed in eCTD:

Sequence	STN- 2nd Level	STN- 3rd Level	Modules
586	818	0	1, 5
628	818	2	1
633	818	4	1
634	818	5	1
645	818	7	1
649	818	8	1, 5
655	818	11	1, 5
657	818	12	1, 5
660	818	13	1, 5
672	818	16	1, 5
676	818	17	1
685	818	19	1
708	818	20	1

705	818	21	1
711	818	22	1
715	818	24	1
721	818	25	1
731	818	26	1
740	818	27	1
744	818	28	1
748	818	30	1, 5
752	818	31	1
753	818	32	1, 2
757	818	33	1
758	818	34	1
686	871	0	1, 5
750	894	0	1, 5
759	818	36	1
765	818	38	1
762	818	37	1
769	818	39	1
770	818	40	1

5.3 Table of Studies/Clinical Trials

The following were submitted to support the application:

- Interim Study Report of 161503: "Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases." This was completed to satisfy the post-marketing requirement to study the product in a pediatric population.

Country:	United States
Subject age range:	3-15 years old
Number of subjects planned to be enrolled:	Approximately 40 subjects
Number of subjects enrolled:	44
Demographics:	Please see section 1.1
Control group	External control
Extent of exposure	Range 0.7-18.5 months at the time of data lock
Duration of follow-up	Range 0.7-20.4 months at the time of data lock
Primary endpoint met?	Yes. There was a mean rate of acute serious bacterial infections (ASBIs) per subject-year 0.04 with a 99% upper CI of 0.21.
Conducted under IND	Yes. This was conducted under IND 13840.

- Clinical Study Report of 161504: "Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases." This study was a Phase 4, multi-center, post-authorization, prospective, non-controlled study on the safety, tolerability, and immunogenicity of Hyqvia in pediatric subjects with PI in Europe. The study was conducted from May 30, 2017 to January 15, 2021.

Countries:	16 centers across Europe
Subject age range:	3- 17 years old
Number of subjects planned to be enrolled:	Approximately 40 subjects
Number of subjects enrolled:	42 subjects
Demographics:	Please see section 1.1
Control group	Non-controlled
Extent of exposure	0.3- 19.1 months
Duration of follow-up	3.6- 20.4 months
Primary endpoint met?	The primary outcome was the number and rate of safety events.
Conducted under IND	No

- Clinical Study Report of 161301: "Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia." The study was a non-interventional, open-label, two-arm, multicenter, post-authorization pregnancy registry of women treated with Hyqvia. There were prospective (2 subjects, all Hyqvia treated) and retrospective (7 subjects; 5 in Hyqvia arm and 2 in the alternative product arm) components.

- Clinical Study Report of 161406: "Non-interventional post-marketing safety study on the long-term safety of Hyqvia." This was a prospective, uncontrolled, open-label, non-interventional, multicenter surveillance study to assess safety and tolerability data on adults treated with Hyqvia including assessment of anti-rHuPH20 antibodies.

- Synopses of Study 160603 and 160902: Study 160603 titled "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 (PIDD)" and Study 160902 (its extension study) titled ""Long-Term Tolerability and Safety of Immune Globulin Subcutaneous Solution (IGSC) Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases" were submitted to provide support to this efficacy supplement.

5.4 Consultations

The Division of Pediatrics and Maternal Health (DPMH) and the Office of Pediatric Therapeutics (OPT) were consulted regarding the concern that two out of 5 (40%) infants born to mothers taking Hyqvia during pregnancy had congenital abnormalities (cleft lip and talipes calcaneovalgus).

A summary of their findings is below.

DPMH

- Causation is difficult to determine given the small number of subjects, late enrollment into the study (as a potential source of bias), and lack of adjudication between the congenital anomalies and Hyqvia exposure during pregnancy.
- Consider a descriptive pregnancy safety study. DPMH recommends issuing a PMR for a small population of pregnant patients.
- Consider not releasing the Sponsor from the current post-marketing commitment, given the enrollment was 3.5 years which is an insufficient duration.
- Consider international databases if completing a MarketScan study.

OPT

- A conclusive causality assessment regarding the congenital anomalies and Hyqvia cannot be made because of insufficient information.
- It is unlikely that Hyqvia resulted in fetal malformations given hyaluronidase is not expected to enter the maternal circulation.

5.5 Literature Reviewed

Baylis, Allison. "Head and Neck Embryology: An Overview of Development, Growth and Defect in the Human Fetus." (2009).

Camenisch, Todd D., et al. "Regulation of cardiac cushion development by hyaluronan." *Experimental & Clinical Cardiology* 6.1 (2001): 4.

Ferguson, Mark WJ. "Palate development." (1988): 41-60.

Kirschbrown, Whitney P., et al. "Development of a subcutaneous fixed-dose combination of pertuzumab and trastuzumab: results from the phase Ib dose-finding study." The Journal of Clinical Pharmacology 59.5 (2019): 702-716.

Knowles, Stephen P., et al. "Safety of recombinant human hyaluronidase PH20 for subcutaneous drug delivery." Expert Opinion on Drug Delivery 18.11 (2021): 1673-1685.
Morcos, Peter N., et al. "Pharmacokinetics and pharmacodynamics of single subcutaneous doses of tocilizumab administered with or without rHuPH20." International journal of clinical pharmacology and therapeutics 51.7 (2013): 537-548.

Shapiro RS, Wasserman RL, Bonagura V, Gupta S. Emerging Paradigm of Primary Immunodeficiency Disease: Individualizing Immunoglobulin Dose and Delivery to Enhance Outcomes. J Clin Immunol. 2017 Feb;37(2):190-196. doi: 10.1007/s10875-014-9990-x. Epub 2014 Jan 30. PMID: 24477950.

Solis, Mairim Alexandra, et al. "Hyaluronan regulates cell behavior: a potential niche matrix for stem cells." *Biochemistry research international* 2012 (2012).

Wynne, Chris, et al. "Comparison of subcutaneous and intravenous administration of trastuzumab: a phase I/Ib trial in healthy male volunteers and patients with HER2-positive breast cancer." The Journal of Clinical Pharmacology 53.2 (2013): 192-201.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1, Study 161503

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

A phase 3, open-label, prospective, non-controlled, multicenter study. The study was started September 26, 2017. The data freeze data was November 16, 2020 for the interim report submitted.

6.1.1 Objectives (Primary, Secondary, etc)

Primary: To evaluate the efficacy of Hyqvia with the rate of acute serious bacterial infections (ASBI), i.e., mean number of ASBI per subject per year.

Secondary: Assess safety (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, and PK parameters.

Clinical Reviewer Comment*: The objectives are in alignment with the endpoints.*
A single phrase, sentence or paragraph describing the purpose/objective and rationale of the study should be included.

6.1.2 Design Overview

The study was a Phase 3, open-label, prospective, externally controlled (compared to an historical benchmark), multicenter study conducted in the United States.

The study consists of 2 study Epochs with a possibility for an Epoch 3, which was not needed.

Epoch 1: Hyqvia SC treatment with a dose or interval ramp-up period of up to 6 weeks

Epoch 2:

1. Treatment: HYQVIA SC every 3-4 weeks

After 1 year in Epoch 2, the anti-rHuPH20 binding antibody results decided the next steps in the study:

- Subjects with anti-rHuPH20 <160 at all timepoints, completed the study at the next occasion following the 12- month visit
- Subjects with anti-rHuPH20 ≥ 160 at any point during the study would continue in Epoch 2 for an additional 2 years of HYQVIA treatment and complete the study at the next possible occasion following the 36- month visit

2. Pharmacokinetic Assessment: After the 6-month assessment

Epoch 3 (if needed):

- Subjects with anti-rHuPH20 antibody titer ≥ 160 during Epoch 1 or Epoch 2 and who experience either a study drug related serious adverse event (SAE) or related severe AE will be followed accordingly
- Subjects will continue anti-rHuPH20 testing for approximately 1 year (about every 3 months)
- If conducted, subjects are planned to be treated with GAMMAGARD LIQUID IV or SC at the discretion of the investigator and subject.

Clinical Reviewer Comment: *The single arm design with a benchmark comparator (based on expected rates of ASBI in PI in the absence of treatment) is in alignment with the FDA guidance document "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency" published in June 2008.*

12- month assessment was adequate to determine efficacy in the context of seasonal variation in infection rates.

Of note, data for analysis was locked on November 16, 2020, before the study was completed. This review is based on an interim analysis report after all subjects completed 1 year of follow-up in Epoch 2. However, one study subject, who had prolonged follow-up given positive anti-rHuPH20 antibodies ≥ 160 during the study, was enrolled in Epoch 2 at the time of study lock but has now completed the study. This reviewer agrees this was an appropriate approach to review these study results.

6.1.3 Population

Inclusion:
Subjects who met all of the following criteria could be enrolled:

1. Diagnosis of primary immunodeficiency involving a defect in antibody formation and requiring immunoglobulin replacement prior to enrollment
2. Age between 2 and less than 16 years of age
3. Receiving a consistent dose of IgG for at least 3 months prior to screening
4. Serum trough level IgG >5 g/L at screening
5. If female of childbearing potential, had negative pregnancy test and agreed to adequate birth control measures during the study
6. Subject or legally authorized representative was willing and able to comply with protocol

Exclusion:
Subjects would be excluded if they fit any of the below criteria:

1. Had a known history or was positive at screening for: hepatitis B surface antigen, polymerase chain reaction (PCR) for hepatitis C virus, PCR for human immunodeficiency (HIV) Type 1/2
2. Persistent abnormal labs:
    a. Persistent alanine aminotransferase and aspartate aminotransferase > 2.5 times the upper limit of normal for the lab
    b. Persistent severe neutropenia (absolute neutrophil count ≤ 500/mm^3)
3. Anemia that precluded phlebotomy for lab studies per practices at that lab site
4. 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. Severe immunoglobulin A deficiency (<7.0 mg/dL) with known anti-immunoglobulin A antibodies and a history of hypersensitivity
6. Allergy to hyaluronidase
7. Active infection and receiving antibiotic therapy for treatment of infection at time of screening
8. Bleeding disorder with 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. Severe dermatitis that would preclude adequate sites for safe product administration in the opinion of the investigator
10. Subject had participated in another clinical study involving an investigational product or device within 30 days prior to enrollment or was scheduled to participate in another clinical study involving an investigational product or device during the study
11. Family member or employee of the investigator
12. If female, subject was pregnant or lactating at time of enrollment

Clinical Reviewer Comment*: Eligibility criteria were appropriate to determine efficacy for this subject population. All subjects were on stable doses of immunoglobulins for at least 3 months. Therefore, no subjects were treatment naïve. This conforms with other development programs for similar products, but likely results in an overestimation of safety and tolerability.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Epoch 1 (ramp up):

- HYQVIA (Immune Globulin Infusion 10% with recombinant human hyaluronidase) SC injection
- One treatment interval of one week, then one treatment interval of two weeks, then one treatment interval of three weeks (for subjects who are planned to be treated every 4 weeks)

Epoch 2 (final dosing)

- HYQVIA dose every 3 or 4 weeks

Epoch 3 (if needed)

- GAMMAGARD LIQUID (either intravenously or subcutaneously)

Clinical Reviewer Comment: *At study completion, Epoch 3 was not initiated. So, no information about GAMMAGARD is included in this review.*

6.1.5 Directions for Use

Storage and Packaging

rHuPH20

rHuPH20 is supplied as a sterile, liquid preparation in single-use glass vials. The product should be inspected visually for particulate matter and discoloration (should be clear, colorless), and should not be used if discoloration or particulate matter are observed. Store under refrigerated conditions (2° to 8°C or 36° to 46°F). The product should not be frozen or used if the expiration date is exceeded.

IGI, 10%
IGI 10% is supplied as a sterile, liquid preparation in single-use glass vials. Solution is clear or slightly opalescent and colorless or pale-yellow. The product is to be visually inspected for particulate matter and discoloration and should not be used if either is observed. Store IGI 10% under refrigerated conditions (2° to 8°C or 36° to 46°F). The product is not to be frozen or used past its expiration date.

Administration
rHuPH20 is administered at a dose ratio of 80 U/g IgG before the infusion of IGI 10%. Use the full vial of rHuPH20 associated with each vial of IGI, 10%. Inject rHuPH20 at approximately 1-2 mL/min, or faster if tolerated, through the same needle that will later be used to infuse IGI 10%. As soon as the rHuPH20 infusion is complete, and within 10 minutes of its completion, connect the same tubing and subcutaneous needle used to infuse the rHuPH20 to IGI 10% for delivery.

Infusion Rate
Epoch 1 (ramp up)
- If body weight (BW) < 40 kg: 5 mL/hour/site (at start) to 80 mL/hour/site (maximum, if tolerated)
- If BW ≥ 40 kg: 10 mL/hour/site (at start) to 240 mL/hour/site (maximum, if tolerated)

Epoch 2 (final dosing)
- If BW < 40 kg: 10 mL/hour/site (at start) to 160 mL/hour/site (maximum, if tolerated)
- If BW ≥ 40 kg: 10 mL/hour/site (at start) to 300 mL/hour/site (maximum, if tolerated)

Infusion Volume
- If BW < 40 kg: up to 300 mL per infusion site
- If BW ≥ 40 kg: up to 600 mL per infusion site

6.1.6 Sites and Centers

The study was conducted at 17 sites across the United States.

6.1.7 Surveillance/Monitoring

The following assessments were performed at study site visits as outlined in the schedule of study procedures and assessments: physical exam, determination of adverse events, assessment of concomitant medications and non-drug therapies, vital signs, quality of life (QOL) questionnaires, and laboratories.

Subjects given a subject diary for recording the following details by either the subject or the subject's legally authorized representative: adverse events, concomitant medication use, details of product administration (infusion date, start/stop time, lot number, volume infused, maximum infusion rate achieved, number and location of infusion sites), days not able to attend school/work or perform daily activities due to an illness/infection, non-study required outpatient visits (including urgent care visits) and hospitalizations.

PK assessments were performed pre-infusion (trough level of previous infusion), Day 4, 10, 21, and 28 (for subjects on four-week treatment intervals), and 6-months in Epoch 2.

The internal safety monitoring committee (ISMC) monitored the safety of subjects during the study. The ISMC reviewed accumulating data on a regular basis.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Outcome Measures

- The rate of acute serious bacterial infections (ASBI), defined as the mean number of ASBIs per subject-year in the intent-to-treat population

Secondary Efficacy Outcome Measures

- Number of all infections per subject-year
- Trough levels of IgG and IgG subclasses for Epoch 2
- Trough levels of specific antibodies to clinically relevant pathogens (*Clostridium tetani* toxoid, *Haemophilus influenzae*, and Hepatitis B virus) for Epoch 2

Secondary Pharmacokinetics Outcomes Measures

- For total IgG levels: area under the curve (AUC), apparent clearance, maximum concentration (C_{max}), minimum concentration, time to maximum concentration (T_{max}), terminal half-life. Baseline corrected total IgG AUC, C_{max} , and T_{max} where calculated.

Secondary Safety Outcome Measures

- Number and rate per infusion (excluding infections) of related and not related SAEs, AEs, local AEs, systemic AEs, causally related and temporally associated AEs (starting within 72 hours of end of infusion).
- Rates of all AEs (excluding infections)
- Number/proportion of subjects who developed positive titer (≥ 160) of binding or neutralizing antibodies to rHuPH20

6.1.9 Statistical Considerations & Statistical Analysis Plan

Efficacy

Occurrence of ASBI were presented as point estimates of the mean rates per person-year and associated confidence intervals (CIs). Based on historical data, demonstrating an ASBI rate of less than 1.0 per person-year is adequate to provide evidence of efficacy. Therefore, the null hypothesis was that the ASBI rate was greater than or equal to 1.0 (at the significance level of 0.01 (1-sided)).

Please refer to the statistical reviewer's memo for more details.

Pharmacokinetics

For Epoch 2, the PK parameters AUC, clearance (CL), C_{max}, minimum concentration (C_{min}), T_{max}, and terminal half-life were determined for IgG.

Safety

All safety outcomes were analyzed using descriptive statistics. Outcomes were summarized in terms of subject- years as appropriate.

6.1.10 Study Population and Disposition

Analysis sets included the following:

The **Screened Set** included all subjects who signed the informed consent. This included screened successes and failures.

The **Enrolled Set** included all subjects who provided informed consent and met eligibility criteria.

The **Full Analysis Set (FAS)**, for this study, is identical to the enrolled set. All efficacy analyses were based on this set.

The **Per-protocol Analysis Set** consists of all subjects in the FAS without major protocol deviations that could affect primary efficacy data. This analysis set was only used for the primary efficacy analysis, including for the sensitivity analysis of efficacy.

All subjects who received at least one dose of Hyqvia were included in the **Safety Analysis Set**. All safety analyses were done using this analysis set.

The **Pharmacokinetic Analysis Set** included all subjects in the Safety Analysis Set without major protocol deviations or events that could affect PK results, and who had at least one post-dose concentration data for PK assessments.

6.1.10.1.1 Demographics

Table 3: Demographic Data, Pediatric Study 161503

Parameter	**All Subjects (N= 44)**
Age (years)	--
Mean (SD)	9 (3.6)
Median	9.5
Min, Max	3, 15
Age Category n (%)	--
2 to < 6 years	9 (20%)
6 to <12 years	23 (52%)
12 to <16 years	12 (27%)
Gender n (%)	--
Male	26 (59%)
Female	18 (41%)
Race n (%)	--
Black / African American	2 (4%)
White	40 (91%)
Other	1 (2%)
Multiple	1 (2%)
Asian	0
American Indian or Alaska Native	0

Native Hawaiian or Other Pacific Islanders	0
Ethnicity n (%)	--
Hispanic or Latino	5 (11%)
Not Hispanic or Latino	39 (89%)
Height (cm)	--
Mean (SD)	134 (24)
Median	138
Min, Max	86, 170
Weight (kg)	--
Mean (SD)	38 (20)
Median	34
Min, Max	12, 93

Abbreviations: SD= Standard Deviation, min= minimum, max= maximum, cm= centimeters, kg= kilograms
Source: Adapted from sBLA 125402/818; Interim Clinical Study Report Study 161503 p. 137-138

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 4: Study 161503, Underlying Conditions Causing Primary Immunodeficiency

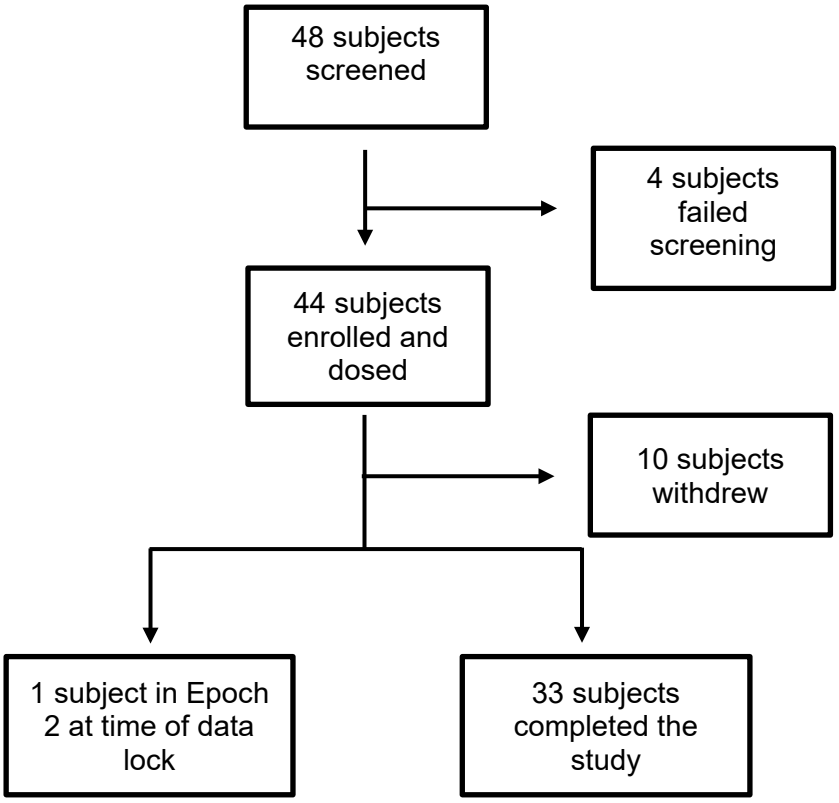
PI Type	**All Subjects** N=44
Common variable immune disorder (CVID)	18 (41%)
Specific antibody deficiency	11 (25%)
with hypogammaglobulinemia/ low IgG	4 (9%)
with IgG subclass deficiency; other	1 (2%)
Other	4 (9%)
Agammaglobulinemia	3 (7%)
Severe combined immunodeficiency	3 (7%)

Abbreviations: PI= Primary Immunodeficiency , IgG= Immunoglobulin G
The “Other” category includes two subjects with IgG subclass deficiency/low Immunoglobulin A, one subject with hypogammaglobulinemia, and one subjects with hypogammaglobulinemia/IgG subclass deficiency.
Source: adapted from sBLA 125402/818; Interim Clinical Study Report Study 161503 p. 139

Baseline Clinical Data:
The most frequent medical histories (apart from immunodeficiency) were asthma (30 subjects [68.2%]), adenoidectomy and ear tube insertion (16 subjects [36.4%]), pneumonia (14 subjects [31.8%]), gastroesophageal reflux (14 subjects [31.8%]), tonsillectomy (13 subjects [29.5%]), rhinitis (11 subjects [25%]), headache (10 subjects, [22.7%]), otitis media (10 subjects, [22.7%]), and attention deficit hyperactivity disorder (10 subjects, [22.7%]).

6.1.10.1.3 Subject Disposition
One subject discontinued the study during Epoch 1 due to an adverse event and did not enroll in Epoch 2. All other subjects continued to Epoch 2. No subjects were enrolled in Epoch 3.

Figure 1: Subject Disposition, Study 161503



Source: adapted from sBLA 125402/818; Interim Clinical Study Report Study 161503 p. 60.

Protocol Deviations

There were 30 major protocol violations at the time of data-freeze. Eleven of these protocol deviations (3 major and 8 minor) were related to the COVID-19 pandemic.

Table 5: Protocol Deviations, Study 161503

Protocol Deviation	Number of Events
Follow-up call post infusion not completed	2
Reconsent not taken	6
Expired kits were used	1
Post-infusion PK samples were not done	2
Shipping issues of investigational product	3
Study procedure conduction issues	1
IRB approval expired	1
Documentation was inconsistent	3
COVID-19 related issues	3
Incorrect lab kit	2
Enrollment issue	1

Source: adapted from sBLA 125402/818; Interim Clinical Study Report Study 161503 p. 63.

Clinical Reviewer Comment*: The full list of protocol deviations was reviewed and not considered impactful to the primary endpoint.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

There was a mean rate of 0.04 (upper 99% CI 0.21) acute serious bacterial infections per subject-year.

No subjects had sepsis, bacterial meningitis, osteomyelitis, or a visceral abscess. One subject (2.3%) had two events of bacterial pneumonia.

Clinical Reviewer Comment: *The study met its primary endpoint to establish efficacy of their product in the pediatric population.*

Prior to completion of this review, the Sponsor submitted the final study report for Study 161503. The mean rate of ASBIs per subject-year was 0.04 with an upper 99% CI of 0.20, consistent with the interim study results.

6.1.11.2 Analyses of Secondary Endpoints

Number of all infections per subject-year
There was a mean rate of 3.2 (upper limit of CI 4.05) infections per subject-year.

Trough levels of IgG and IgG subclasses for Epoch 2
There was not a substantial difference in total trough IgG levels at different timepoints or between age groups.

Table 6: Serum Trough Levels of IgG Over Time, Study 161503

--	2 to < 6 years	6 to < 12 years	12 to < 16 years
Epoch 2, Month 0 (mean, median)	9.427, 9.580	10.063, 10.000	10.789, 10.035
Epoch 2, Month 6 (mean, median)	8.700, 9.340	9.003, 9.210	10.102, 10.145
Epoch 2, Month 12 (mean, median)	9.040, 9.490	9.351, 9.205	9.046, 8.775

Source: adapted from sBLA 125402/818; Interim Clinical Study Report, Study 161503 p. 9.

Trough levels of specific antibodies to clinically relevant pathogens
Trough antibody levels to *Clostridium tetani* toxoid, *Haemophilus influenzae*, and hepatitis B virus showed no substantial difference from baseline to study completion/termination.

Clinical Reviewer Comment: *The final study report showed a mean rate of 3.12 infections per subject-year with a standard error (SE) of 0.45, and an upper limit of the 95% CI of 3.95. These rates were consistent with the findings in the interim report.*

6.1.11.3 Subpopulation Analyses

Efficacy and safety data were compared between pooled data of adult and pediatric subjects. Please see Sections 7 and 8 for more details.

6.1.11.4 Dropouts and/or Discontinuations

Of the 10 subjects who withdrew prematurely, reasons given included:

- 2 subjects (20%) had adverse events
- 1 (10%) was due to physician decision
- 6 (60%) were secondary to subject withdrawal
- 1 (10%) was "other" reason related to site constraints to conduct the final study visit due to COVID-19

The two subjects who discontinued secondary to Treatment Emergent Adverse Events (TEAEs) were because of a severe celiac disease flare thought to be probably related to the study drug and another was infusion site pain (the highest severity for this subject was moderate).

Clinical Reviewer Comment*: Thirty-three out of 44 (75%) subjects completed the study. This is a relatively high drop-out rate, which may have contributed to the improvement in TEAEs over time (i.e., subjects who had events were more likely to withdraw).*

This reviewer did not believe either of the TEAEs that led to discontinuation of the study product changed the overall benefit-risk of Hyqvia in subjects with PI.

6.1.12 Safety Analyses

6.1.12.1 Methods

Each subject and their caregiver were to be given a paper diary to record adverse events, medication use, product administration details, days of missed school/work or inability to perform daily activities because of illness, hospitalizations, and acute physician visits.

In addition, abnormal values for labs, vital signs, or abnormal physical exam findings were to be reported as adverse events if considered clinically significant by the investigator.

6.1.12.2 Overview of Adverse Events

<u>Adverse Events</u>
There were 675 treatment emergent adverse events (TEAEs) including infections in 43 subjects (98%). Of these, 320 TEAEs in 34 subjects (77% of subjects) were thought to be related to the study treatment.

Severe TEAEs
Four severe TEAE in 4 subjects (9%) occurred. Two of these severe TEAEs were thought related to the study treatment in 2 subjects; one event was listed as celiac disease, and another as headache.

Local TEAEs
There were 200 local TEAEs in 33 subjects (75.0%). There were 190 local TEAE reported as related in 32 (73%) subjects. The proportion of subjects with local TEAEs improved over time.

Systemic TEAEs
There were 315 systemic TEAE in 39 subjects (89%). There were 130 systemic related TEAE in 25 subjects (57%).

The most common systemic TEAE (in ≥ 10% of subjects) were:

- Gastrointestinal disorders (56 events in 26 [59%] of subjects)
- Nervous system disorders (79 events in 23 [52%] of subjects)
- General disorders and administration site conditions (39 events in 19 [43%] of subjects)
- Injury poisoning and procedural complication

6.1.12.3 Deaths

No deaths occurred in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Four serious TEAEs, all considered unrelated to Hyqvia, in 4 subjects (9%) were reported. Three of the serious TEAEs were infections (1 event of each of a mild adenovirus infection, a severe *Clostridium Difficile* colitis, and a moderate severity bacterial pneumonia). Excluding infections, the only serious systemic TEAE (moderate severity tonsillar hypertrophy) reported occurred in one patient (2%). There were 0.02 per subject-year or 0.001 per infusion serious TEAEs (excluding infections). All serious TEAEs were resolved by the time of study reporting. None of the serious TEAEs resulted in a changed dose or discontinuation of the study product.

Clinical Reviewer Comment: *In the time between the interim analysis and the conclusion of the study, there were no additional serious TEAEs. This reviewer agreed that the serious TEAEs were not related to the product.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Positive Titer of antibodies to rHuPH20
One subject was positive for antibodies to rHuPH20 (titers ≥ 160) during the study starting in Epoch 2 at 6 months. The subject remained negative for neutralizing antibodies. The subject reported local and systemic TEAEs (mostly headaches). All TEAEs fully resolved, and none were serious, severe, or thought to be immune-related.

Clinical Reviewer Comment: *The adverse events were reviewed for this subject before and after becoming positive (titers ≥ 160) for anti-rHuPH20. There was no significant worsening in adverse event reporting that was thought related to anti-rHuPH20 antibodies noted.*

Because only one subject developed ant-rHuPH20 antibodies, it is not possible to draw definitive conclusions about the effects of the antibodies. However, at this time risks appear theoretical, without any observed clinical sequela related to the presence of anti-rHuPH20.

6.1.12.6 Clinical Test Results

Vital signs remained relatively stable throughout the study. As expected for a pediatric population, height and weight increased from baseline. One subject (2%) reported a TEAE of mild increase in systolic blood pressure during the infusion, which resolved.

A review of clinical lab parameter changes did not raise safety concerns.

6.1.13 Study Summary and Conclusions

Study 161503 was a Phase 3, open-label study following pediatric subjects 2 to less than 16 years of age with primary immunodeficiency. The interim analysis was completed when all 44 subjects completed 1 year of follow-up, but one subject was still being followed for additional safety data.

The study met its primary efficacy endpoint. There was a mean rate of 0.04 (upper 99% CI 0.21) acute serious bacterial infections per subject-year.

One subject developed positive titers (≥ 160) for anti-rHuPH20. The subject did not have any serious, severe, or immune-related treatment emergent adverse events (TEAE). Four severe TEAE in 4 subjects (9%) occurred. Two of these severe TEAEs were thought related to the study treatment in 2 subjects; one was celiac flare and another was headache. Four serious TEAEs, all considered unrelated to Hyqvia, in 4 subjects (9%) were reported. Three of the serious TEAEs were infections. Excluding infections, the only serious systemic TEAE (tonsillar hypertrophy) reported occurred in one patient (2%). None of the serious TEAEs resulted in a changed dose or discontinuation of the study product.

6.2 Trial #2, Study 160603 (Original Pivotal Trial, Phase 3)

Study 160603 was the pivotal study that supported the original BLA. It was open-label, non-controlled, multi-center Phase 3 study in 87 subjects from December 18, 2008 to November 11, 2010. Please refer to the original BLA Clinical Memo (BLA 125402) for additional details regarding Study 160603.

6.2.1 Objectives (Primary, Secondary, etc)

Title: “Efficacy, tolerability and pharmacokinetic comparison of immune globulin intravenous (human), 10% (GAMMAGARD LIQUID/KIOVIG) administered intravenously or subcutaneously following administration of recombinant human hyaluronidase (rHuPH20) in subjects with primary immunodeficiency diseases (PIDD).”

The primary objective was to evaluate the efficacy of IGI 10% administered monthly subcutaneously when facilitated by pre-administration of rHuPH20 in preventing acute serious bacterial infections (ASBI) in Primary Immunodeficiency (PI) subjects.

The secondary objective, in addition to further evaluate efficacy, was to evaluate the tolerability of SC administration of IGI 10% and rHuPR20.

6.3 Trial #3, Study 160902

Title: “Long-Term Tolerability and Safety of Immune Globulin Subcutaneous Solution (IGSC) Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases”

Study 160902 was an extension study to the pivotal study (160603). It was a long-term safety study of 66 subjects. Please refer to the original BLA Clinical Memo (BLA 125402) for details regarding Study 160902.

6.3.1 Objectives (Primary, Secondary, etc)

Primary Objective:

- Evaluate the long-term tolerability and safety in subjects with PID. After discontinuation of rHuPH20, subjects were observed for potential delayed adverse reactions.

Secondary Objectives:

- Monitor the long-term efficacy of IGSC, 10% after administration of rHuPH20 in subjects with PID
- To assess the practicability of treating PID with IGSC, 10% after administering rHuPH20 in a home treatment environment

6.4 Trial #4, Study 161301 (Pregnancy Registry)

Title: "Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia."

This study was a pregnancy registry to collect safety data from pregnant women treated with Hyqvia and the infants born to them. The study was conducted from March 25, 2015 to December 17, 2019.

6.4.1 Objectives (Primary, Secondary, etc)

Primary objective: To obtain clinical safety data on the possible effects of Hyqvia use on the course and outcome of pregnancy including the growth and development of the fetus/infant.

Secondary objective: To obtain laboratory safety data and other safety assessments during pregnancy and from the infant post-partum.

6.4.2 Design Overview

The study was an observational, open-label, two-arm, multicenter, post-authorization registry of pregnant women treated with Hyqvia. There were prospective (2 subjects, all Hyqvia treated) and retrospective (7 subjects; 5 in Hyqvia arm and 2 in the alternative product arm) components.

Arm 1 (alternative product arm): Subjects who stopped Hyqvia and received an alternative product or treatment chosen by the treating physician.

Arm 2 (Hyqvia arm): Subjects who received Hyqvia.

Each mother was followed from enrollment to within 6 months after the delivery/end of pregnancy. Infants were followed from enrollment to 2 years of age (unless discontinued early).

6.4.3 Population

Inclusion Criteria

- Pregnancy occurred during or after treatment with Hyqvia
- Subject or legal representative was willing to provide informed consent

There were no exclusion criteria.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Treatments were not protocol mandated; instead, they were dictated by the clinical practice of the treating physician.

6.4.5 Directions for Use

There were not directions for use included in the protocol. Instead, product information could be found in the package insert or summary of product characteristics for each product. Subjects were treated per standard of care.

6.4.6 Sites and Centers

There were 8 sites: 1 in the United States, 1 in the Czech Republic, 3 in Germany, 1 in Poland, and 2 in Slovakia.

6.4.7 Surveillance/Monitoring

If pregnancy during or after treatment with Hyqvia was confirmed, subjects were enrolled in Arm 1 (alternative product arm) or Arm 2 (Hyqvia arm), depending on treatment per standard medical care.

Approximately every 3 months, subjects had safety assessments including rHuPH20 antibodies. The fetus growth and development were followed. After delivery, the pregnancy outcome was recorded and the mother ended the study at the next visit (which should have been within 6 months of delivery/end of pregnancy). The infant was then followed for 2 years (unless they were withdrawn early), including recording of growth, development and milestones.

6.4.8 Endpoints and Criteria for Study Success

Primary endpoint:

- Incidence of all serious adverse events (SAEs) in expectant mothers and infants

Secondary endpoints:

- Incidence of non-serious adverse events (both related and not related to their immunoglobulin treatment or alternative treatment) in expectant mothers and infants
- Incidence of local/immunologic adverse events in expectant mothers
- Development of binding and neutralizing anti-rHuPH20 antibodies in expectant mothers
- Pregnancy complications
- Growth and development of the fetus
- Neonatal assessments including status at birth

- Growth measures and development milestones for the infant

6.4.9 Statistical Considerations & Statistical Analysis Plan

Subjects were analyzed in each of the study arms (Hyqvia versus alternative treatment) and together. Subjects who changed their treatment assignment during the course of the study remained with the initial treatment assignment throughout the observation period.

There were only two instances of imputation of missing data:

- "Severe" was assigned to any adverse event that was missing severity information
- "Related" was assigned to any adverse event that was missing causality data

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

The **Enrolled Set** included all subjects who met eligibility criteria and signed informed consent.

The **Safety Set** included all subjects in the enrolled set.

6.4.10.1.1 Demographics

Table 7: Mother Demographic Data, Study 161301

Parameter	**Overall** (N=9)	**Hyqvia** (N=7)	**Alternative Treatment** (N=2)
Mean age at enrollment	33.7 years	33.9 years	33.0 years
White/Caucasian	9 (100%)	7 (100%)	2 (100%)
Mean pre-pregnancy weight	--	69.3 kg	60.0 kg

Source: adapted from sBLA 125402/818; Full Study Report Study 161301, page 68-69

Overall, 8 mothers (89%) had an underlying diagnosis of Common Variable Immunodeficiency and 1 mother (11%) had Hyper Immunoglobulin M Syndrome.

Antenatal diagnostic procedures were reported in 3 (33%) out of 9 enrolled mothers. These procedures included ultrasound (n=3, 33%), serology (n=2, 22%), and nuchal translucency screening (n=1, 11%).

Table 8: Infant Demographic Data, Study 161301

Parameter	**Hyqvia** (n=5)	**Alternative Treatment** (n=2)
Male	2 (40%)	1 (50%)
Female	3 (60%)	1 (50%)
Non-Hispanic/Latino	5 (100%)	2 (100%)
White/Caucasian	5 (100%)	2 (100%)

Source: adapted from sBLA 125402/818; Full Study Report Study 161301, page 69.

Clinical Reviewer Comment*: All of the subjects were White/Caucasian and non-Hispanic/Latino (if ethnicity was known), which is not expected for this disease state. This could result in missed findings (along with the small sample size) for risks associated with other races and ethnicities.*

6.4.10.1.3 Subject Disposition

Mothers
Nine subjects were screened and enrolled.

All screened subjects were included in the Enrolled Set. Four mothers enrolled before delivery and 5 mothers enrolled after delivery. Seven subjects completed follow-up. Two discontinued early; 1 due to subject withdrawal and another was lost to follow-up.

Infants
Two infants (born to 2 different mothers out of the 9 that participated in the study) were not enrolled in the study. One mother was lost-to follow up after delivery without consenting their infant to participate. Another mother withdrew consent to participate in the trial prior to delivery.

6.4.11 Efficacy Analyses

Efficacy analyses were not done in this study.

6.4.11.1 Analyses of Primary Endpoint(s)

Serious Adverse Events in Mothers
Two serious adverse events (SAEs) occurred in 1 mother (14%) in the Hyqvia arm. The subject had thrombocytopenia and pre-eclampsia. Both SAEs were deemed unrelated to Hyqvia.

Serious Adverse Events in Infants
Two SAEs occurred in 2 (40%) infants in the Hyqvia arm (N=5). Both SAEs were mild in severity. One subject had talipes calcaneovalgus and another had a cleft lip. Both SAEs were assessed as not related to Hyqvia treatment by the investigators.

No SAEs occurred in the alternative product arm.

Clinical Reviewer Comment: *This reviewer is concerned that the increased rate (40%) of congenital abnormalities (talipes calcaneovalgus and cleft lip) seen in this pregnancy registry may reflect an increased rate of risk associated with this product. Because this product contains hyaluronidase, which can change the composition of connective tissue through the hydrolysis of hyaluronic acid, we believe there is a plausible mechanism of action that Hyqvia could have been related to these two malformations.*

It is worth considering if there was a selection bias in the study (i.e., infants with abnormalities were more likely referred for this registry trial). The sponsor has divided the subjects included into prospective and retrospective cohorts. The prospective cohort

(n=2) was enrolled when the outcome of the pregnancy was unknown and the condition of the fetus had not been assessed through prenatal testing, such as ultrasound, at the time of enrollment. The retrospective cohort (n=5) was enrolled when the condition of the fetus had been assessed through prenatal testing, or the outcome of pregnancy was known prior to enrollment. One of the SAEs (cleft lip) was in the prospective cohort and one SAE (talipes calcaneovalgus) was in the retrospective cohort. However, during interactive review, the Sponsor noted that the SAE (cleft lip) in the prospective cohort was referred late in pregnancy. Subjects were categorized by self-reporting and the availability of medical records. Because of the possibility for detection of cleft lip by ultrasound, the Sponsor maintained selection bias may be a contributor to both subjects' enrollment in the study, which is worth considering.

Talipes Calcaneovalgus can be secondary to positional abnormalities that improve with time. However, the subject's talipes calcaneovalgus was ongoing at time of study completion (approximately 2 years and 9 months after birth), which suggests a structural deformity.

The role that Hyqvia played in the development of the congenital abnormalities is not clear. As discussed in Section 11.6, we recommend a PMC for further evaluation of outcomes after exposure to Hyqvia during pregnancy.

6.4.11.2 Analyses of Secondary Endpoints

Adverse Events in Mothers

Hyqvia Arm

Two subjects in the Hyqvia arm had emergency cesarean sections due to failure to progress. One mother (17%) had an unspecified labor or delivery complication.

In the Hyqvia arm, 8 adverse events were reported in 3 mothers. Events included the following (percentages indicate the percentage of subjects with each reported AE):

- 2 events of anemia during pregnancy in 2 subjects (29%)
- 1 Thrombocytopenia (14%)
- 1 influenza (14.3%)
- 1 urinary tract infection (14.3%)
- 2 pre-eclampsia events in 1 subject (14%)
- 1 uterine contraction during pregnancy (14%)

Alternative Treatment Arm

In the alternative treatment arm, 5 AEs were reported in 1 (50%) mother. Events included the following (percentages indicate the percentage of subjects with each reported AE):

- 1 bronchitis (50%)
- 1 genital herpes simplex (50%)
- 1 laryngitis (50%)
- 1 episode of increased hepatic enzyme (50%)
- 1 episode of anogenital warts (50%)

No AEs were related to Hyqvia among enrolled mothers.

Adverse Events in Infants
Seventeen AEs were reported in 6 infants. None of the AEs in the infants were thought to be related to the mother's Hyqvia treatment by the sponsor/investigators.

Hyqvia Arm
In the Hyqvia arm, all subjects (n=5, 100%) had an AE. The AEs included:

- 4 infections and infestations (bronchitis, otitis media, pharyngitis, upper respiratory tract infection)
- 2 congenital, familial and genetic disorders (cleft lip and talipes)
- 1 head injury
- 1 neutropenia
- 1 diarrhea
- 1 jaundice
- 1 decreased weight
- 1 lactose intolerance
- 1 atopic dermatitis

Alternative Treatment Arm
In the alternative product arm, 2 adverse events were reported in 1 (50%) infant:

- 1 rhinitis
- 1 fall

Infant Growth and Development
At 6 months, one infant (50%) was breastfed, and another infant had unknown breastfeeding status. All (n=3) of the infants with weight information, had normal weights. All infants with length, and head circumference (n=2) had normal values.

After 12 months, two subjects had weight, length, and head circumference data available, and all of these values were reported as normal.

At 24 months, one subject had reached all developmental milestones, another subject had reached some milestones with some missing data.

Clinical Reviewer Comment: *As discussed in Section 6.4.11.1, the rate of congenital malformations in the Hyqvia arm is concerning. Otherwise, the adverse events reported in both infants and mothers were not concerning, although the study is limited by the small population size.*

6.4.11.3 Subpopulation Analyses

Given the small study size population, no subpopulation analyses were feasible.

6.4.11.4 Dropouts and/or Discontinuations

Two mothers who enrolled in the study did not have their infants participate in the study. One of the mothers, who was being treated with Hyqvia, had normal antenatal testing. The other mother, also being treated with Hyqvia, did not have available data on antenatal diagnostic procedures.

6.4.12 Safety Analyses

6.4.12.3 Deaths

No deaths were reported in this registry.

6.4.12.4 Nonfatal Serious Adverse Events

Please see Section 6.4.11.1 for analyses of SAEs (the primary endpoint).

6.4.12.5 Adverse Events of Special Interest (AESI)

Four mothers had blood samples taken for anti-rHuPH20 antibody assessment in the registry. Two mothers (2 assessments) in the Hyqvia arm and 2 mothers (3 assessments) in the alternative treatment arm were assessed for anti-rHuPH20 antibodies. All assessments were negative (titer <160).

Clinical Reviewer Comment*: Because anti-rHuPH20 antibodies were not observed, this study cannot demonstrate if pregnancy course or outcomes could be affected by the development of anti-rHuPH20 antibodies. Additionally, this study is not large enough to demonstrate whether the risk of antibody development is higher or lower in pregnant patients. More data should be obtained about Hyqvia treatment in pregnancy.*

6.4.12.6 Clinical Test Results

Overall, 3 (33%) mothers enrolled had available information on 20 clinically significant lab parameters.

In the Hyqvia arm (n=7), 2 mothers had 5 clinically significant lab findings that were AEs. These adverse events included abnormal values for hemoglobin, erythrocytes, and hematocrit.

In the alternative treatment arm (n=2), 1 mother had 2 clinically significant lab results that were AEs. These adverse events included abnormal values for alanine aminotransferase (1 AE) and aspartate aminotransferase (1 AE). One mother had 18 clinically significant lab findings due to pre-existing disease (haptoglobin, erythrocyte sedimentation rate, erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, platelets, complement C3a, complement C4a, immunoglobulin A, immunoglobulin G, n-terminal pro B-type natriuretic peptide, leukocyte esterase, microscopic examination, occult blood, and protein).

Clinical Reviewer Comment: *None of these lab abnormalities were thought to be related to Hyqvia treatment by this reviewer.*

6.4.13 Study Summary and Conclusions

A concerning safety signal regarding Hyqvia use in pregnancy was identified. Two of the 5 infants (40%) born to mothers taking Hyqvia during pregnancy had congenital malformations (one cleft lip and another talipes calcaneovalgus). Hyqvia contains recombinant human hyaluronidase, which alters the permeability of connective tissue. This reviewer believes it is plausible that Hyqvia could affect the development of these congenital malformations. Because of the potential for selection bias, the significance of these findings is not clear. Further study is warranted, and a PMC is recommended as discussed in Section 11.6.

No subjects were positive for anti-rHuPH20 during the study. However, only two mothers in the Hyqvia arm and two mothers in the alternative treatment arm were assessed for anti-rHuPH20. Because of the small sample size, the findings regarding antibody development are uninterpretable.

6.5 Trial #5, Study 161504

"Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects with Primary Immunodeficiency Diseases."

6.5.1 Objectives (Primary, Secondary, etc)

Primary Objective: To assess the safety of Hyqvia in pediatric subjects with PI.

Secondary Objective: To further assess safety, including immunogenicity, tolerability, and product characteristics (i.e., IgG trough levels) of Hyqvia in pediatric subjects with PI.

Tertiary Objectives: Additional safety and efficacy assessments.

6.5.2 Design Overview

This study was a Phase 4, multi-center, post-authorization, prospective, non-controlled study on the safety, tolerability, and immunogenicity of Hyqvia in pediatric subjects with PI in Europe. The study was conducted from May 30, 2017 to January 15, 2021.

Clinical Reviewer Comment: *This is an adequate design to study safety of Hyqvia in pediatric subjects*.

6.5.3 Population

Inclusion Criteria
Subjects had to meet all of the following criteria to enroll in the study:

- Documented diagnosis of primary humoral immunodeficiency involving a defect in antibody formation and requiring treatment with immunoglobulin replacement
- Subject was 2 to less than 18 years of age at screening
- Receiving a consistent dose of IgG for at least 3 months prior to screening
- Serum trough level of IgG >5 g/L
- If a female that could bear children, the subject had to have a negative pregnancy test and comply with birth control measures for the duration of the study
- The subject or legally authorized representative was willing and able to comply with the protocol requirements

Exclusion Criteria
Subjects who met any of the below criteria were excluded from participating in the study:

- Known history or positive at screening of any of the following: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), human immunodeficiency virus (HIV) type 1/2
- Abnormal labs including persistent alanine aminotransferase and aspartate amino transferase greater than 2.5 times the upper limit of normal and persistent severe neutropenia with an absolute neutrophil count ≤ 500/mm^3

- Anemia that would have prevented blood draws per the institutional rules
- Hypersensitivity or persistent reactions (urticaria, difficulty breathing, severe hypotension, anaphylaxis) after intravenous immunoglobulin, subcutaneous immunoglobulin, or immune serum globulin infusions
- Severe IgA deficiency (<7.0 mg/dL) with known anti-IgA antibodies and a history of hypersensitivity
- Known allergy to hyaluronidase
- Active infection, being treated with antibiotics
- Bleeding disorder, platelet count <20,000/µL, or in the opinion of the investigator had a significant risk of bleeding or bruising with subcutaneous therapy
- Severe dermatitis that limited adequate sites to safely administer the product in the opinion of the investigator
- The subject was scheduled to participate in another clinical study involving an investigational product or device, or had participated in such a study within 30 days prior to enrollment
- Subject was a family member or employee of the investigator
- If female, subject was lactating or pregnant

Clinical Reviewer Comment*: Eligibility criteria were appropriate. All subjects were on stable doses of IG for at least 3 months. Therefore, no subjects were treatment naïve. This conforms with other development programs for similar products, but likely results in an overestimation of safety and tolerability.*

6.5.4 Study Treatments or Agents Mandated by the Protocol

Epoch 1 (ramp up):

- Treatment interval of 1 week, followed by 1 treatment interval of 2 weeks, then 1 treatment interval of 3 weeks (if the treatment was expected to be given every 4 weeks)

Epoch 2

- Epoch 1 was followed by Epoch 2 with the following treatment intervals for Hyqvia
    - For IV pre-treated subjects: treatment was every 3 or 4 weeks, depending on the previous IV dosing schedule
    - For SC-pre-treated subjects: treatment was every 3 or 4 weeks, at the discretion of the subject and the investigator
    - Alternative treatment intervals (for example every 2 weeks) were considered at the discretion of the investigator after discussing with the sponsor
- Subjects stayed in Epoch 2 for one year. The next step depended on the anti-rHuPH20 antibody titer as follows:
    - If the anti-rHuPH20 antibody titer was <160 during the entire study, the next visit was the study completion visit
    - If the anti-rHuPH20 antibody titer was ≥ 160 during the study, the subject continued in Epoch 2 for an additional 2 years of Hyqvia treatment

Epoch 3

- Epoch 3 (safety follow-up) was planned as a one-year safety follow-up, if needed

- Subjects would be enrolled if they had anti-rHuPH20 antibody titer ≥ 160 during Epoch 1 or 2 and had either a related serious adverse event (SAE) or a related severe adverse event (AE). Subjects without an anti-rHuPH20 antibody titer ≥ 160, but who experienced a related SAE or severe AE, could be enrolled in Epoch 3, terminated from the study, or continued in Epoch 1 or 2 with possible changes including decreasing the infusion rate or providing medication.
- Subjects would be treated with KIOVIG IV (IGIV 10%) or Cuvitru subcutaneously (IGSC 20%), at the discretion of the investigator and subject. If subjects had anti-rHuPH20 antibody titer ≥ 160 entering Epoch 3, anti-rHuPH20 antibody testing would be done approximately every 3 months for 1 year.

6.5.5 Directions for Use

Infusion Rate:
Epoch 1 (ramp up)

- If body weight <40 kg: 5 mL/h/site (at start) to 80 mL/h/site (maximum, if tolerated)
- If body weight ≥ 40 kg: 10 mL/h/site (at start) to 240 mL/h/site (maximum, if tolerated)

Epoch 2 (final dosing)

- If body weight <40 kg: 10 mL/h/site (at start) to 160 mL/h/site (maximum, if tolerated)
- If body weight ≥ 40 kg: 10 mL/h/site (at start) to 300 mL/h/site (maximum, if tolerated)

If infusions were tolerated after 2 Hyqvia infusions at the dose for the final infusion interval, then the investigator could use his/her discretion to choose an infusion rate.

Please see Section 6.1.5 of this document for further details about product storage and administration.

Epoch 3 (safety follow-up)

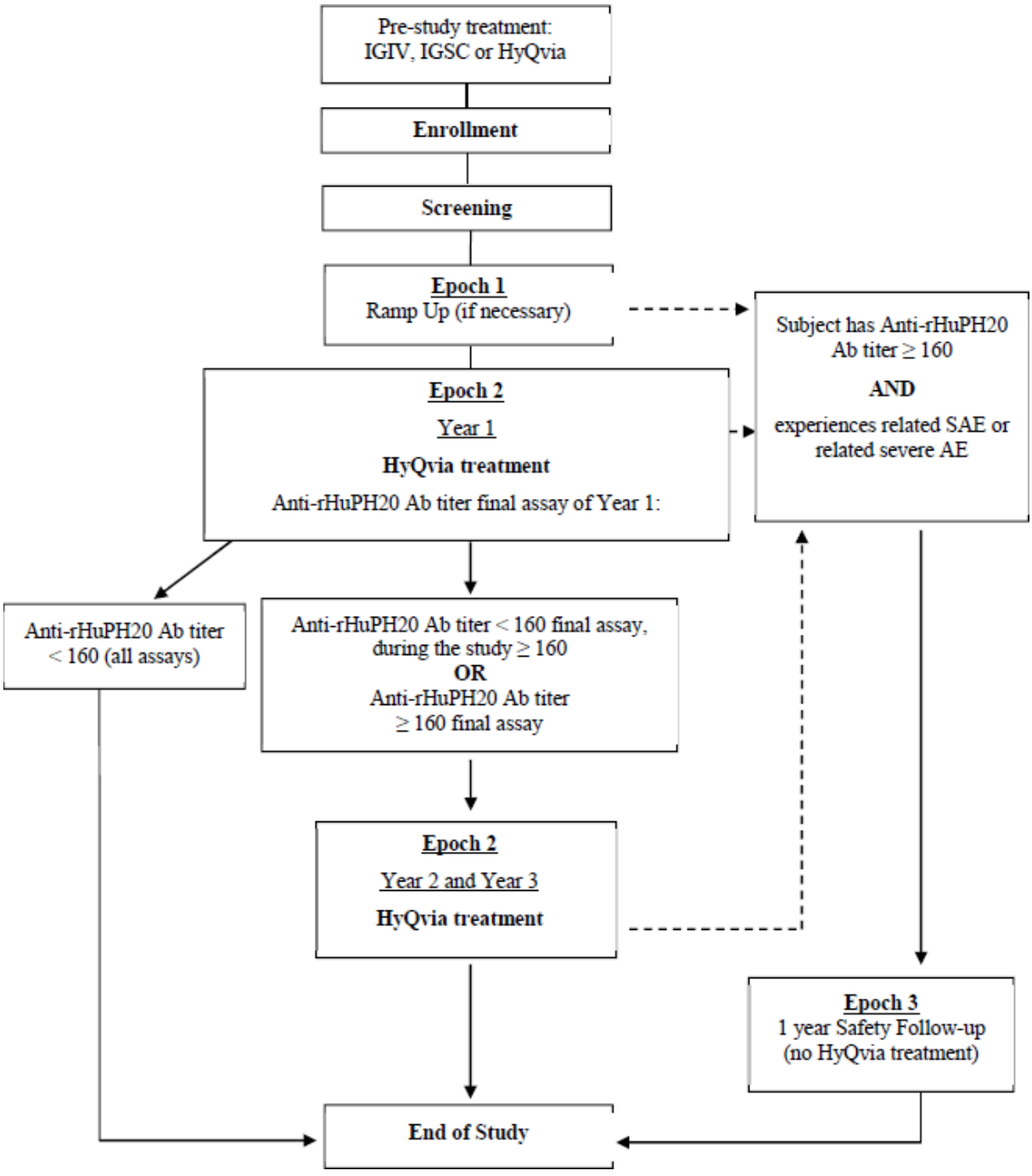
- Kiovig (IGI 10%, IGIV 10%)
    - Intravenous injection, every 3 to 4 weeks
    - Planned weekly dose target was 100% (+/- 5%) of the dose used in the previous Epoch
- Cuvitru (IGSC 20%)
    - Subcutaneous injection, per investigator discretion given from daily to every 2 weeks
    - Planned weekly dose target was 100% (+/- 5%) of the dose used in the previous Epoch

6.5.6 Sites and Centers

This was a multicenter study completed in the European Economic Area.

6.5.7 Surveillance/Monitoring

Figure 2: Study Schematic, Study 161504



Abbreviations: IGIV= intravenous immunoglobulin; IGSC= subcutaneous immunoglobulin; rHuPH20= recombinant human hyaluronidase; SAE= severe adverse event; AE= adverse event; Ab= antibody
Source: replicated from sBLA 125402/818, Clinical Study Report Study 161504, page 32.

6.5.8 Endpoints and Criteria for Study Success

Primary Endpoints

- Number and rate per infusion (excluding infections) of all severe related Adverse Events (AEs)
- Number and rate per infusion (excluding infections) of related Serious Adverse Events (SAEs)

Secondary Endpoints

Efficacy

- Trough levels of IgG (in Epoch 1 and 2)
    - IgG total and subclass trough levels
    - Trough levels of specific antibodies to clinically relevant pathogens (*Clostridium tetani* toxoid, *Haemophilus influenzae*, and Hepatitis B Virus)

Safety and Tolerability

- Proportion of subjects who had a treatment interval of 3 or 4 weeks in Epoch 2
- Proportion of subjects who maintained a treatment interval of 3 or 4 weeks for 12 months in Epoch 2
- Number and rate per infusion (excluding infections) of local AEs and adverse reactions (ARs)
- Number and rate per infusion (excluding infections) of systemic AEs and ARs
- Number and rate per infusion (excluding infections) of all AEs and all ARs
- Number and rate per infusion (excluding infections) of all related and/or temporally associated AEs
- Number and rate per infusion (excluding infections) of all SAEs
- Number/proportion of subjects who have anti-rHuPH20 antibody (neutralizing or binding) titer ≥ 160
- Clinical lab values (raw and change from baseline) and vital signs (raw and change from baseline)

Mode of Product Administration

For Study Epochs 1 and 2:

- Infusions
    - Number per month
    - Number of infusion sites (needle sticks) per infusion and per month
    - Duration of infusion
    - Maximum infusion rate/site
    - Infusion volume/site
    - Number/proportion of infusions that are discontinued, slowed, or interrupted due to an AE
- Number of weeks to reach final dose interval

Health-Related Quality of Life

- Treatment preference questionnaire
- Treatment satisfaction questionnaire for medication (TSQM-9)
- Health-related Quality of Life Questionnaire: Pediatric Quality of Life, European Quality of Life 5 Dimension

Tertiary Outcome Measures

Infections

- Number of Acute Serious Bacterial Infections (ASBI)
- Number of all infections

Healthcare Resource Utilization Endpoints

- Days not able to go to school or work or perform normal daily activities because of infection or illness
- Days on antibiotics
- Number of hospitalizations, indication for hospitalization (infection/non-infection) and days hospitalized
- Number of acute physician visits (office and emergency room) due to infection or other illness

6.5.9 Statistical Considerations & Statistical Analysis Plan

Statistical hypothesis testing was not planned for in the study design. Demographic, baseline characteristics, and subject disposition were to be summarized.

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

The analysis sets include the following:

The **Screened Set** includes all subjects who signed the informed consent, including both screen successes and failures. No statistical analysis used this set.

The **Enrolled Set** included all subjects who provided informed consent and met eligibility criteria.

The **Full Analysis Set** was equivalent to the Enrolled Set. This analysis set was used only for efficacy analysis.

The **Safety Analysis Set** included all subjects in the Enrolled Set/Full Analysis Set that received at least one dose of Hyqvia. Safety analyses were done using this set. For this study, all subjects in the Full Analysis Set are in the Safety Analysis Set.

6.5.10.1.1 Demographics

Table 9: Demographic Data, Study 161504

Subject Characteristic	**Statistic**	**All Subjects (N= 42)**
Age (years)	Mean (SD)	11 (4.1)
--	Min, Max	3, 17
Age Group n(%)	2 to <6 years	6 (14%)
--	6 to <12 years	15 (36%)
--	12 to <18 years	21 (50%)
Sex n(%)	Male	34 (81%)

--	Female	8 (19%)
Ethnicity n(%)	Hispanic or Latino	0
--	Not Hispanic or Latino	42 (100%)
--	Not Reported	0
Race (n%)	American Indian or Alaska Native	0
--	Asian	0
--	Native Hawaiian or Other Pacific Islanders	0
--	White	41 (98%)
--	Not Applicable – Not Collected per Local Regulations	1 (2%)
Height (cm)	Mean (SD)	148 (25.2)
--	Median	151
--	Min, Max	100, 195
Weight (kg)	Mean (SD)	45 (21)
--	Median	41
--	Min, Max	14, 98
BMI (kg/m^2)	Mean (SD)	20 (4.6)
--	Median	19
--	Min, Max	12, 33

Abbreviations: BMI= body mass index; max= maximum; min= minimum; SD= standard deviation; cm= centimeter; kg= kilogram; m= meter
Source: Original sBLA 125402/818; Clinical Study Report 161504 dated October 14, 2021, p.71-72.

Clinical Reviewer Comment*: All subjects who had information on race were white and non-Hispanic/Latino. This is not the expected make-up of subjects enrolled in the United States. However, this reviewer does not expect the lack of diversity in race/ethnicity to have major implications for generalizability.*

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

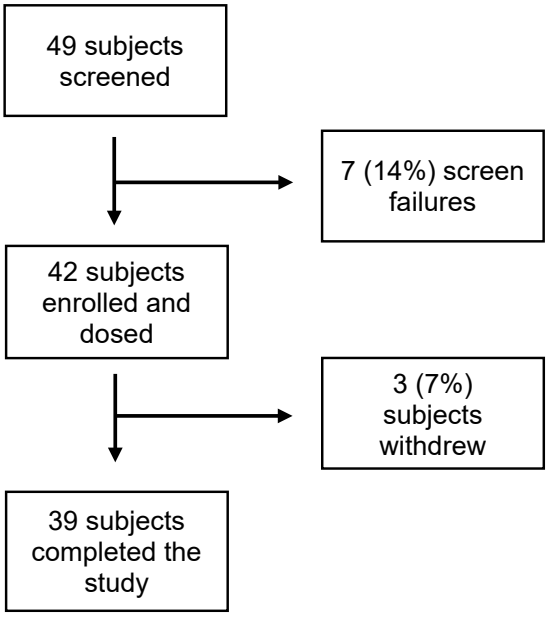
Table 10: Underlying Diagnosis for Primary Immunodeficiencies, Study 161504

Primary Immunodeficiency Diagnosis	**All Subjects** (N=42), n (%)
Agammaglobulinemia - AR	2 (5%)
Congenital Agammaglobulinemia - XLA	16 (38%)
Common Variable Immunodeficiency	18 (43%)
Severe Combined Immune Deficiency	1 (2%)
Activated Phosphokinase 3 Delta Receptor Syndrome (APDS)	1 (2%)
Nemo Immune deficiency	2 (5%)
PI3K-Delta Syndrome	1 (2%)

Abbreviations AR= Autosomal Recessive; PI3K= Phosphoinositide 3-kinase; XLA= X-linked Agammaglobulinemia
Source: Original sBLA 125402/818; Clinical Study Report 161504 dated October 14, 2021, p.73

6.5.10.1.3 Subject Disposition

Figure 3: Subject Disposition, Study 161504



Source: Adapted from sBLA 125402/818; Clinical Study Report 161504 dated October 14, 2021, p.66

6.5.11 Efficacy Analyses

6.5.11.1 Analyses of Primary Endpoint(s)

Two-hundred thirty TEAEs occurred in 38 (90%) subjects. Fifty-one AEs were assessed as either “possibly related” or “probably related” to Hyqvia in 16 subjects (38.1%).

There were 2 severe related TEAEs in 1 (2%) subject who had severe infusion site pain (resolved on the day of onset) and severe emotional distress (resolved in 3 days). The subject had a history of developmental delay, attention deficit hyperactivity disorder, anxiety, and self-harming. The subject continued the study in Epoch 3.

Forty local TEAEs in 14 (33%) subjects were thought to be possibly or probably related to the study drug.

Clinical Reviewer Comment: *Adverse events from Study 161504 were also analyzed pooled with data from 161503 and 160603. Please see section 8 for additional details.*

6.5.11.2 Analyses of Secondary Endpoints

Efficacy

- Total IgG trough levels were stable from baseline to Epoch 2 Month 12

- At the end of Epoch 2, all subjects had antibody levels above the minimal protective titer for *Clostridium tetani* toxoid, *Haemophilus influenzae B*, and Hepatitis B Virus (HBV)

One subject (161504-(b) (6) had a moderate systemic adverse event of decreased IgG levels. After increasing the dose of Hyqvia, the event was considered resolved in 124 days. The investigator assessed the event as related to inflammatory bowel disease, and not related to Hyqvia. This subject did not have any treatment-emergent serious bacterial infections.

Safety

- Most subjects (30, 71%) were treated every 4 weeks
- 35 subjects (83%) were treated with Hyqvia every 3 or 4 weeks for 12 months in Epoch 2
- 14 out of 42 (33%) of subjects experienced 41 local TEAEs (not including infections)

6.5.11.4 Dropouts and/or Discontinuations

Three subjects discontinued the study prematurely. All three subject's primary reasons for premature discontinuation were "withdrawal by the subject." One subject discontinued during Epoch 1, and the other 2 discontinued during Epoch 2. Of the Hyqvia new starters, 95.7% (22 of 23) subjects completed Epoch 2. Of the Hyqvia pre-treated subjects, 89.5% completed Epoch 2 (17 of 19).

6.5.11.5 Exploratory and Post Hoc Analyses

- One subject (2.4%) had 1 acute serious bacterial infection (ASBI) of bacterial pneumonia which resulted in hospitalization. This resulted in 0.02 ASBI events per subject and 0.02 events per subject-year.
- Mean number of days for which activities were impacted (i.e. subject could not go to school/work or complete normal activities for the day) was 10 days (range 0 to 53 days, SD= 13.9 days). For subjects started on Hyqvia for the study the mean was 8 days (range 0 to 53 days, SD= 14.3 days) and for subjects who were pre-treated with Hyqvia it was a mean of 12 days (range 0 to 44 days, SD= 13.5 days).
- Twenty-three of the 42 (55%) subjects received antibiotic therapy. Out of those 23 subjects, a mean of 2.2 antibiotic courses were reported per subject. Subjects who took antibiotics, were on a mean of 146.1 days of antibiotics (range 2- 549 days, SD= 202.64 days).
- There were nine hospitalizations during the study in seven subjects. Each hospitalization was a mean of 5 (SD= 2.2) days (range 2, 8). Four of these hospitalizations (57%) were due to infection. The rate of days hospitalized for any reason was 0.6 days per subject-year.

6.5.12 Safety Analyses

6.5.12.1 Methods

Treatment administration details were recorded by the legally authorized representative of the subject in the subject diary. Subjects were given tablets to assess patient reported outcomes (including patient questionnaires).

Physical exams, labs, and vital signs were assessed throughout the study.

6.5.12.2 Overview of Adverse Events

Adverse events were pooled with pediatric data from Study 160603 and 161503. Please see Section 8 for more details.

6.5.12.3 Deaths

No deaths were reported during this study.

6.5.12.4 Nonfatal Serious Adverse Events

Serious TEAEs

In 7 subjects (17%), there were 8 serious TEAEs (including infections). Excluding infections, there were 4 serious TEAEs in 3 (7%) subjects.
The serious TEAEs included:

- 2 gastrointestinal disorders in 2 (5%) subjects: dental caries (severe) and inflammatory bowel disease (moderate)
- 1 eye disorder in 1 (2%) subject: idiopathic orbital inflammation (severe)
- 1 general disorder in 1 subject (2%): pyrexia (mild)
- 4 infection/infestation in 4 (10%) subjects: acute sinusitis (mild), pharyngitis (moderate), pilonidal cyst (moderate), and pneumonia (moderate)

Idiopathic orbital inflammation and inflammatory bowel disease were not resolved. All other SAEs have resolved.

All SAEs were thought to be not related to the product.

Clinical Reviewer Comment*: Narrative summaries of all SAEs were reviewed and adjudicated as not related to the product by the reviewer.*

6.5.12.5 Adverse Events of Special Interest (AESI)

Anti-rHuPH20 titers ≥ 160 were not found in any subjects during the study. Therefore, no subjects were tested for neutralizing antibodies.

6.5.12.6 Clinical Test Results

Hematology and clinical chemistry lab values did not worsen to a ≥ Grade 3 value for any parameters.

6.5.12.7 Dropouts and/or Discontinuations

Three subjects withdrew early from the study.

6.5.13 Study Summary and Conclusions

Study 161504 provided supporting data for the safety and efficacy of Hyqvia in pediatric subjects. Forty-two subjects enrolled. There was a mean rate of 0.02 acute serious bacterial infections per subject-year. In 7 subjects (17%), there were 8 serious TEAEs. Excluding infections, there were 4 serious TEAEs in 3 (7%) subjects. All serious adverse events were thought not to be related to the product by the sponsor and the reviewer.

This study supports Hyqvia as a safe and effective treatment in pediatric subjects.

6.6 Trial #6, Study 161406 (Long-term safety)

Title: “Non-interventional post-marketing safety study on the long-term safety of Hyqvia”

This was a prospective, uncontrolled, open-label, observational, multicenter surveillance study to assess safety and tolerability data on adults treated with Hyqvia including assessment of anti-rHuPH20 antibodies. The study was conducted from November 12, 2015 to October 31, 2021.

6.6.1 Objectives (Primary, Secondary, etc)

The primary objective was to evaluate the long-term safety data in subjects taking Hyqvia.

The secondary objectives were to look at additional safety parameters including anti-rHuPH20 antibodies, other lab assessments, and quality of life and health resource use evaluations.

6.6.2 Design Overview

This was a prospective, uncontrolled, open-label, non-interventional, multicenter surveillance study to assess safety and tolerability in adults treated with Hyqvia including assessment of anti-rHuPH20 antibodies.

Clinical Reviewer Comment: *This study was completed to fulfill a PMC.*

6.6.3 Population

Inclusion
Subjects were included in the study if they were prescribed or had been taking Hyqvia, were 16 years of age or older, required treatment with immunoglobulins for Primary Immunodeficiency Disease, and were willing and able to fulfill the requirements of the study.

Exclusion
Subjects were excluded if they had a hypersensitivity to the product or any of its components, were related to or employed by the investigator, or if they were involved or planned to be involved in an interventional clinical study within 30 days prior to starting the study or during the study.

6.6.4 Study Treatments or Agents Mandated by the Protocol

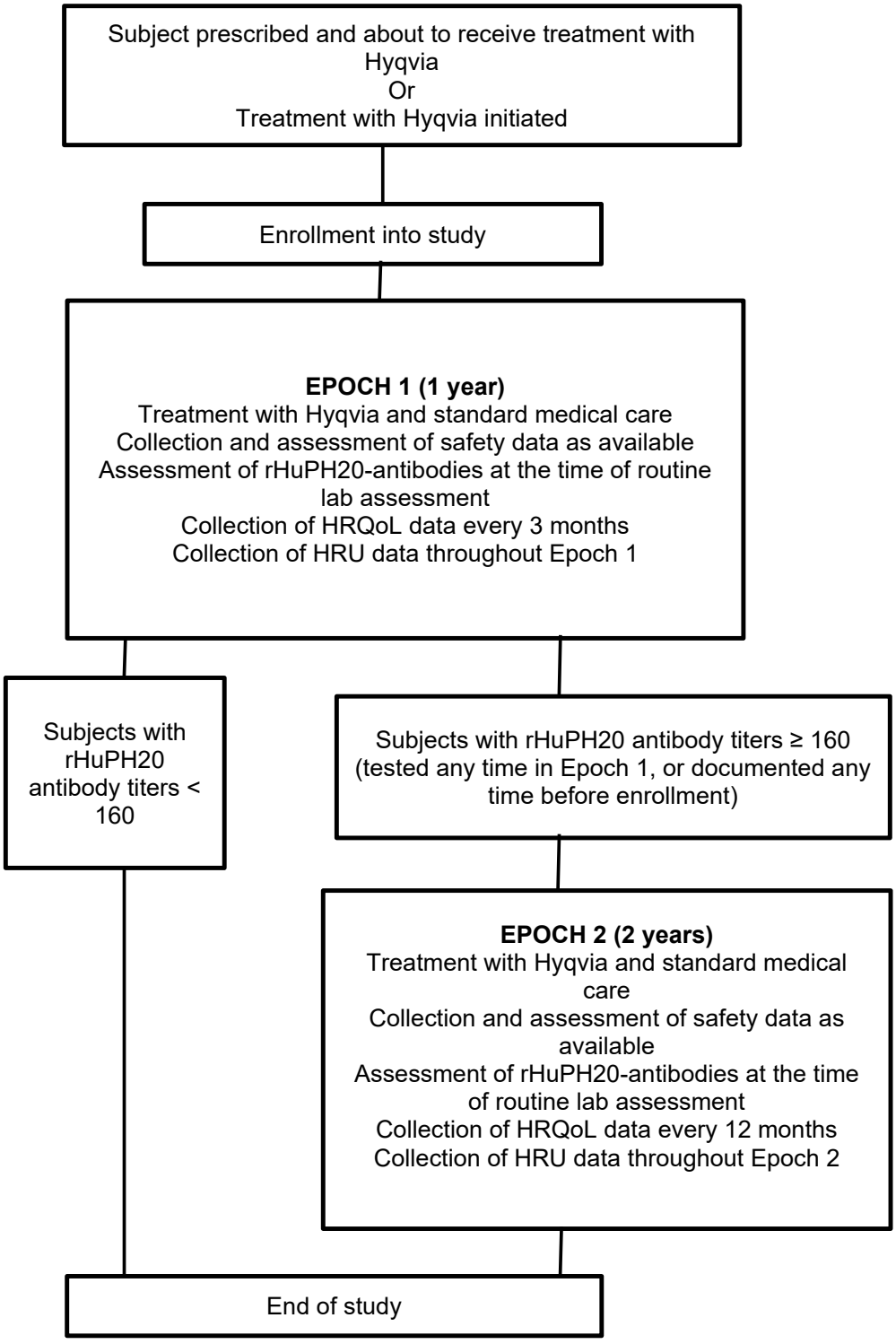
This was a non-interventional study.

6.6.6 Sites and Centers

Initially the study was planned to be conducted in all countries where Hyqvia is licensed. However, the study was conducted in 31 sites solely in the United States.

6.6.7 Surveillance/Monitoring

Figure 4: Study Schematic, Study 161406



Abbreviations: HRQoL=health related quality of life; HRU= health resource use; rHuPH20= recombinant human hyaluronidase
Source: Replicated from sBLA 125402/818; Clinical Study Report 161406 dated August 16, 2022. Page 38.

6.6.8 Endpoints and Criteria for Study Success

Safety Endpoints

- Related serious adverse events (SAEs) incidence
- SAE incidence overall
- Non-serious adverse event (AE) incidence: related/non-related; local/systemic
- Titer of rHuPH20 binding and neutralizing antibodies along with labs (i.e., clinical chemistry, total IgG, etc.)

Treatment Endpoints

- Dose
- Infusion interval:
    - Administration
    - Volume per infusion
    - Infusion rate, maximum
    - Infusion rate, mean
    - Infusion duration
    - Number of infusion sites per infusion

Health-Related Quality of life and Resource Use Endpoints

- Short Form-36, version 2
- 3—level version of EuroQoL 5-Dimension Questionnaire
- Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)
- Treatment Preference Questionnaire
- Health resource use information
    - Hospitalizations and length of stay
    - Acute care visits
    - Emergency room visits
    - Days missed from work/school

6.6.9 Statistical Considerations & Statistical Analysis Plan

No statistical hypotheses were tested.

6.6.10 Study Population and Disposition

6.6.10.1 Populations Enrolled/Analyzed

Full Analysis Set (FAS): The FAS included all subjects who met all eligibility criteria and gave their informed consent.

Safety Analysis Set (SAF): The SAF included all of the FAS subjects who had been given at least one dose of Hyqvia.

6.6.10.1.1 Demographics

Table 11: Demographic Data, Study 161406

Parameter	**Full Analysis Set** (n= 253)
Age at informed consent, years	--
Mean (SD)	54 (15.6)

Median (Q1, Q3)	57 (44, 66)
Min, Max	17, 86
Gender, n (%)	--
Male	53 (21%)
Female	200 (79%)
Female of childbearing potential, n (%)	45 (22%)
Race	--
American Indian or Alaskan Native	5 (2%)
Asian	1 (0.4%)
Black/African American	3 (1%)
Hispanic	0
Native Hawaiian or Other Pacific Islander	0
White	234 (92%)
Unknown/Not Available[a]	10 (4%)
Other	0
Ethnicity	--
Hispanic or Latino	11 (4%)
Non-Hispanic or Latino	240 (95%)
Not applicable [b]	2 (1%)
Missing/Unknown	0
PI type	--
Agammaglobulinemia	3 (1%)
CD4 lymphocytopenia	1 (0.4%)
Common Variable Immunodeficiency	182 (72%)
Hypogammaglobulinemia	38 (15%)
IgG Subclass Deficiency	3 (1%)
Selective IgM Deficiency	2 (1%)
Specific Antibody Deficiency	22 (9%)
X-linked Agammaglobulinemia	1 (0.4%)
Unknown	1 (0.4%)

PI= Primary Immunodeficiency Diseases

a. In countries where race was not recorded
b. In countries where ethnicity was not recorded

Source: Adapted from sBLA 125402/818; Clinical Study Report 161406, p. 67

6.6.10.1.3 Subject Disposition

Overall, 253 subjects were screen and enrolled for this study. No subjects were screen failures.

Table 12: Subject Disposition, Study 161406

Parameter	**Overall**	**Epoch 1**	**Epoch 2, Year 1**	**Epoch 2, Year 2**
Entered Study Period (FAS)	253	253	13	12
Completed	199 (79%)	190 (75%)	0	9 (75%)

Discontinued Study	54 (21%)	50 (20%)	1 (8%)	3 (25%)
Reason for discontinuation	--	--	--	--
Adverse event	2 (4%)	2 (4%)	0	0
Physician decision	1 (2%)	1 (2%)	0	0
Discontinuation by subject	20 (37%)	18 (36%)	1 (100%)	1 (33%)
Terminated by sponsor	0	0	0	0
Pregnancy	0	0	0	0
Lost to follow-up	21 (38%)	19 (38%)	0	2 (67%)
Death	2 (4%)	2 (4%)	0	0
Other	8 (15%)	8 (16%)	0	0

Abbreviations: FAS= Full Analysis Set
Source: Original sBLA 125402/818; Clinical Study Report 161406, p. 64

6.6.11 Efficacy Analyses

6.6.11.1 Analyses of Primary Endpoint(s)

The primary objective of this study was a safety evaluation. Please refer to the Safety Section (6.6.12) for analyses.

6.6.11.4 Dropouts and/or Discontinuations

Protocol Deviations

The Principal Investigator at one site did not sign the casebooks. Because of this, all of the data (n= 9 subjects) from this site were removed from all analyses. In addition, 2 subjects were excluded from the analyses because of protocol deviations (not signing the informed consent).

One subject had rHuPH20 antibody tests excluded because of unclear storage conditions.

Clinical Reviewer Comment: *Eleven subjects (4% of the study population) had data that were removed from analyses due to protocol deviations [unsigned informed consent (n=2) and a principal investigator not signing casebooks (n= 9)]. The sponsor submitted data for adverse events related to the subjects whose PI did not sign casebooks. The adverse events for these subjects were not of significant interest to report independently. No serious adverse events or serious bacterial infections were reported in this group of subjects.*

6.6.12 Safety Analyses

6.6.12.1 Methods

The Full Analysis Set was used for all analyses.

6.6.12.2 Overview of Adverse Events

Adverse Events
Of the total 253 subjects, 170 subjects (67%) had 945 adverse events (AEs) during the study. Of these events, 40 (16%) were mild; 90 (36%) were moderate, and 40 (16%) were severe. The most frequently reported AE was infections/infestations (n=111, 322 events). Other adverse events reported in more than 10% of subjects included: general disorders and administrative site conditions (n=51, 169 events); respiratory, thoracic, and mediastinal disorders (n=148, 87 events), gastrointestinal disorders (n= 39, 75 events), nervous system disorders (n= 36, 86 events), and musculoskeletal and connective tissue disorders (n=31, 49 events).

Fifty-four subjects (21%) had adverse events (286 events) related to Hyqvia treatment. Headache (n=13, 5%; 37 events), infusion site pain (n=12, 5%; 24 events), infusion site swelling (n=9, 4%; 23 events), and fatigue (n=9, 4%; 20 events) were common non-serious AEs related to Hyqvia.

Severe Adverse Events (non-serious)

Eighteen subjects had severe, non-serious adverse events.

In Epoch 2, one subject had a severe, non-serious AE, involving an episode of bronchitis. The episode was considered unlikely to be related to Hyqvia, and Hyqvia was continued unchanged.

Severe (non-serious) events considered possibly or probably related to Hyqvia include: fatigue, dizziness, headaches, and leukocytosis.

Clinical Reviewer Comment*: Narrative reports were reviewed for all severe, non-serious AEs without any additional concerns identified.*

6.6.12.3 Deaths

Two (4%) subjects died. Neither of these two subjects were positive for anti-rHuPH20 titers ≥ 160. Neither of these events (multiple organ dysfunction syndrome and chronic lymphocytic leukemia) were thought to be related to Hyqvia treatment.

Clinical Reviewer Comment: *Narrative reports for both deaths were reviewed. One death was a 76-year-old who died of multiple organ dysfunction syndrome in the context of atrial fibrillation, hypertension, congestive cardiac failure, cardiogenic shock, electrolyte abnormalities and interstitial lung disease 10 months after the last Hyqvia dose. The other death was an 87-year-old who died of complications of chronic lymphocytic leukemia. This reviewer agreed with the investigator's causality assessments.*

6.6.12.4 Nonfatal Serious Adverse Events

There were 61 serious adverse events (SAEs) in 37 (15%) subjects. Sixteen events (in 8 subjects, 3%) were moderate and 45 events were severe (in 29 subjects, 12%).

SAE in more than 1% of subjects included:

- Pneumonia in 6 subjects (2%); 8 events: 4 moderate, 4 severe
- Cellulitis in 3 subjects (1%); 4 events: 1 moderate, 2 severe.

SAE related to Hyqvia
Two subjects (1%) had serious AEs (2 events) at least possibly related to Hyqvia treatment: deep vein thrombosis and aseptic meningitis.

Clinical Reviewer Comment: *The adverse events were reviewed by preferred term and narrative reports were requested for concerning events. The SAEs at least possibly associated with Hyqvia (thrombosis and aseptic meningitis) are known risks associated with this class of product. SAEs in subjects who were anti-rHuPH20 positive are discussed in more detail in Section 6.6.12.5.*

6.6.12.5 Adverse Events of Special Interest (AESI)

Anti-rHuPH20 Antibodies

Out of the 253 enrolled subjects, 196 subjects were tested for anti-rHuPH20 antibodies at least once during the study. Fourteen subjects (7% of the 196 subjects tested) had positive anti-rHuPH20 antibody titers ≥ 160 in Epoch 1. None of the subjects developed neutralizing antibodies. Four subjects had antibody titers ≥ 10,000.

Of these 14 subjects, 13 were followed in Epoch 2. The subject who did not enter Epoch 2 did so because of “discontinuation by subject.” One subject (7.7%) discontinued in the first year of Epoch 2. The reason given was “discontinuation by subject.”

Nine subjects (75%) completed the 2 years in Epoch 2. The reasons for discontinuation in year two included “loss to follow-up” (n=2, 66.7%) and “discontinuation by subject” (n=1, 33.3%).

Baseline assessments of rHuPH20 antibodies were completed in 150 subjects. Of these 150 subjects, 8 subjects (5.3%) had positive rHuPH20-antibodies with a titer ≥ 160 at baseline. Six of those subjects with positive antibody titers at baseline had a history of Hyqvia use before enrolment. None of these subjects had neutralizing antibodies. One of the subjects had titers ≥ 10,000.

Adverse events in subjects who were +anti-rHuPH20
Five SAEs were observed in subjects after becoming positive for anti-rHuPH20 antibodies.

These SAEs were:

- 1 episode of cellulitis
- 1 episode of pneumonia
- 2 episodes of pancreatitis
- 1 episode of thrombosis

One episode of pancreatitis occurred in a 78-year-old with a history of gallstones and cholecystectomy. Hyqvia was continued unchanged.

The other episode of pancreatitis occurred in a 56-year-old with Sjogren’s syndrome and multiple medications (including prednisone, diltiazem, lisinopril, and mesalamine). Hyqvia was continued unchanged.

A 62-year-old female with a history of hypertension, fibromyalgia, asthma, neuropathy, kidney stones and attention deficit hyperactivity disorder reported chest pain, shortness of breath, and cough in July 2021. The subject was admitted for 5 days. All events were reported as resolved, but the outcome of embolism had an unknown outcome. The reporter considered the events (chest pain, thrombosis, dyspnea and cough) as unrelated to Hyqvia and did not provide an assessment for embolism. The sponsor considered a thromboembolic event unconfirmed and thought the patient's asthma and hypertension could have contributed to the subject's symptoms.

Clinical Reviewer Comment: *Two of the subjects enrolled in Epoch 2 were not taking Hyqvia during Epoch 2, although they were followed for safety. One subject discontinued Hyqvia because of "lack of efficacy." The other subject stopped Hyqvia secondary to a moderate severity adverse event of infusion bumps within 24 hours of an infusion. The event resolved without intervention.*

Narratives for all SAEs in subjects who were +anti-rHuPH20 were reviewed by this reviewer and thought not to be related to Hyqvia use. The occurrence of two episodes of pancreatitis in two separate subjects with anti-rHuPH20 antibodies represents an increased frequency of this SAE. However, both subjects have alternative explanations for the occurrence of pancreatitis. In addition, subjects tolerated continued dosing of Hyqvia without repeat episodes of pancreatitis reported, which this reviewer considers reassuring.

This reviewer does not consider the occurrence of a single episode of thromboembolism in a 62- year-old female with multiple medical conditions in the context of the Coronavirus-19 pandemic as a new safety signal. Hyqvia carries a boxed warning that thrombosis may occur with immune globulin products. There is no evidence that the presence of anti-rHuPH20 antibodies increased this subject's risk for thrombosis.

AEs were reviewed for each subject who became positive for anti-rHuPH20 and compared before/after testing positive at a threshold of 160. No concerning patterns were observed.

6.6.12.6 Clinical Test Results

Nine cases (in 4 subjects) of clinically significant hematology test results were reported in Epoch 1 (2 abnormal platelet counts, 1 case for white blood cells count, differential count neutrophils, neutrophils/leukocytes, differential count lymphocytes, lymphocytes/leukocytes, differential count basophils, and differential count monocytes). One subject had 3 cases of clinically significant hematology test results during Epoch 2 – Year 1 (erythrocyte sedimentation rate, prothrombin time, and international normalized ratio). No clinically significant hematology abnormalities were reported in Epoch 2 – Year 2.

6.6.12.7 Dropouts and/or Discontinuations

The study screened and enrolled 253 subjects. Of these 253 subjects, 190 (75%) completed Epoch 1 and 50 subjects (20%) discontinued during Epoch 1. Two subjects (4%) died during Epoch 1. Two subjects (4%) withdrew from the study during Epoch 1 because of adverse events.

Fourteen subjects developed anti-rHuPH20 antibody titers ≥ 160 during the study (the screening period and/or Epoch 1). One subject who had positive antibody titers withdrew consent and did not enter Epoch 2.

Discontinuation of Hyqvia
During the follow-up period 2,230 infusions in 227 subjects were reported. Of these 227 subjects, 37 subjects (16%) discontinued Hyqvia permanently. Fourteen of these discontinuations occurred during Epoch 1. These subjects were asked to stay for safety and antibody testing follow-up.

The reasons for discontinuing Hyqvia treatment were: “other” (n=4); “administration complexity” (n=4); and “systemic AEs” (n=3).

The reasons for discontinuation related to systemic adverse events included:

- an episode of weakness, chills, and vomiting (mild and probably related to study treatment)
- an episode of abdominal pain at the infusion site with a swollen abdomen and a sinus infection. The episode was characterized at moderate intensity. The AEs of swollen abdomen and abdominal pain were thought to be possibly related and the sinus infection was thought unlikely to be related to the study treatment.
- an episode of vomiting (moderate, probably related to the study treatment)

Clinical Reviewer Comment*: The frequency of discontinuation of the product likely reflects the availability of multiple treatment alternatives to Hyqvia, and is expected in clinical use. This reviewer believes that none of the adverse events leading to study/product discontinuation demonstrate a new safety concern.*

6.6.13 Study Summary and Conclusions

Out of 253 subjects were screened and enrolled, 196 subjects were tested at least once for anti-rHuPH20 antibodies. Fourteen subjects became positive for anti-rHuPH20 antibodies at a titer ≥ 160. Eight of these subjects had positive titers at baseline. Six of the eight subjects with a baseline positive anti-rHuPH20 antibody level, had a history of Hyqvia use.

The findings did not demonstrate concerning patterns of adverse events in subjects who developed anti-rHuPH20 antibodies. However, one of the concerns regarding anti-rHuPH20 was the possibility of reduced fertility which has not been assessed clinically. Additionally, data interpretation is limited by the small number of subjects who had anti-rHuPH20 antibodies in this study.

At the time of this memo, Agency review of this study is ongoing. Therefore, the PMC is not considered fulfilled.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Primary immunodeficiency (PI) in children 2 years of age and older.

7.1.1 Methods of Integration

Table 13: Studies in the Integrated Analysis of Efficacy

Study	General Description	General Methodology	Population Included
161503	Phase 3, open-label, prospective, multicenter study conducted in 17 study centers in the United States of IG 10% and rHuPH20 investigating efficacy, safety, tolerability, immunogenicity, pharmacokinetics and other parameters in pediatric patients with Primary Immunodeficiency (PI) Diseases. For a more complete description of the study please see section 6.1.	externally controlled (compared to historical benchmark)	The entire study population was used in this integrated analysis.
160603	Prospective, open-label, single-arm, Phase 3 study in 81 PI subjects at 14 centers in the US and one site in Canada of efficacy, tolerability, and pharmacokinetic comparison of IG 10% administer intravenously or SC with rHuPH20. For a more complete description of the study, please see section 6.2.	externally controlled (compared to historical benchmark)	Subjects less than 16 years of age were included in this analysis.

7.1.2 Demographics and Baseline Characteristics

Table 14: Demographic Data, Integrated Efficacy Analysis

Parameter	**Study 160603 + 161503** Subjects < 16 years, (N= 66)
Age (years)	--
Mean (SD)	9 (3.6)
Median	10
Min, Max	3, 15
Gender n (%)	--
Male	39 (59%)
Female	27 (41%)
Race n (%)	--

Black or African American	3 (4%)
White	61 (92%)
Other	1 (1%)
Multiple	1 (1%)
Asian	0
American Indian/Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Ethnicity n (%)	--
Hispanic or Latino	8 (12%)
Not Hispanic or Latino	58 (88%)
Height (cm)	--
Mean (SD)	135 (23)
Median	139
Min, Max	86, 175
Weight (kg)	--
Mean (SD)	39 (19.5)
Median	37
Min, Max	12, 93
BMI (kg/m^2)	--
Mean (SD)	20 (4.7)
Median	19
Min, Max	13, 35

Abbreviations: BMI= body mass index; max= maximum; min= minimum; SD= standard deviation; cm= centimeter; kg= kilogram; m= meter
Source: BLA 125402/818, Integrated Summary of Safety-2021Sept19, pages 4-5.

7.1.3 Subject Disposition

Please refer to Section 6.1.10.1.3 regarding Study 161503 and the original BLA Clinical Memo (125402) regarding the details for Study 160603.

7.1.4 Analysis of Primary Endpoint(s)

Hyqvia was effective in reducing the rate of Acute Serious Bacterial Infections (ASBIs), defined as bacterial pneumonia, visceral abscess, bacteremia/sepsis, bacterial meningitis, and osteomyelitis/septic arthritis, analyzed as rate per subject-year.

The 64 pediatric subjects (aged 2- less than16 years of age) in Study 161503 and 160603 had a mean rate of ASBIs per subject-year of 0.06 (upper 99% CI 0.18). This is well below the external comparison rate of 1.0 ASBI per subject-year that is considered as the threshold to establish efficacy. Among the 2 studies, 3 subjects (5%) had bacterial pneumonia.

7.1.5 Analysis of Secondary Endpoint(s)

7.1.6 Other Endpoints

Table 15: Healthcare Resource Utilization, Subjects 2-16 years of Age in Study 160603 and 161503

Parameter	**Mean rate per subject-year** (SE)	**95% CI of the rate**
Days hospitalized due to infections	0.2 (0.05)	(0.1, 0.3)
Number of acute physician visits due to infections	3 (0.3)	(2, 4)
Days not able to go to school/work or perform daily activities due to infections/illnesses	5 (0.9)	(3, 7)
Days on antibiotics	24 (3.9)	(17, 33)

SE= Standard Error of the Poisson Mean
CI= Confidence Interval
Source: Adapted from sBLA 125402/818; Integrated Summary of Efficacy, page 18.

7.1.11 Efficacy Conclusions

In a pediatric population, Hyqvia was effective in decreasing the rate of acute serious bacterial infections to below the threshold for efficacy as established in the FDA Guidance for IGIV products. Annualized rates for days hospitalized due to an infection, days of missed school/work or inability to perform daily activities due to infections, and days on antibiotics were within expectations compared to other labeled products.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Although the labeling changes were made based on Study 161503, to ensure complete safety assessments using all available data, integrated analyses were completed using multiple studies as indicated below to pool subjects enrolled who were less than 16 years of age. Pooled analyses are discussed below. For additional safety assessments not reviewed below, please refer to the individual study sections for more details.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 16: Studies in the Integrated Analysis of Safety

Study	**General Description**	**General Methodology**	**Population Included**
161503	Phase 3, open-label, prospective, multicenter study conducted in 17 study centers in the United States of IG 10% and rHuPH20 investigating efficacy, safety, tolerability,	externally controlled (compared to historical benchmark)	The entire study population was used in this integrated analysis.

	immunogenicity, pharmacokinetics and other parameters in pediatric patients with Primary Immunodeficiency (PI) Diseases. For a more complete description of the study please see section 6.1.		
160603	Prospective, open-label, single-arm, Phase 3 study in 81 PI subjects at 14 centers in the US and one site in Canada of efficacy, tolerability, and pharmacokinetic comparison of IG 10% administer intravenously or SC with rHuPH20. For a more complete description of the study, please see section 6.2.	externally controlled (compared to historical benchmark)	Subjects less than 16 years of age were included in this analysis.
161504	Phase 4, multi-center, post-authorization, prospective, non-controlled study on the safety, tolerability, and immunogenicity of Hyqvia in pediatric subjects with PI in Europe. For a more complete description of the study, please see section 6.5	non-controlled	Subjects less than 16 years of age were included in this analysis.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 17: Demographic Data, Integrated Analysis of Safety

Parameter	**Study 160603 + 161503 + 161504** Subjects < 16 years (N=102)
Age (years)	--
Mean (SD)	10 (3.6)
Median	10
Min, Max	3, 15
Gender n (%)	--
Male	68 (67%)
Female	34 (33%)
Race n (%)	--
Black or African American	3 (3%)
White	96 (94%)
Other	1 (1%)

Multiple	1 (1%)
Not collected per local regulations	1 (1%)
Ethnicity n (%)	--
Hispanic or Latino	8 (8%)
Not Hispanic or Latino	94 (92%)
Height (cm)	--
Mean (SD)	138 (23.6)
Median	140
Min, Max	86, 184
Weight (kg)	--
Mean (SD)	40 (19.2)
Median	38
Min, Max	12, 98
BMI (kg/m^2)	--
Mean (SD)	19 (4.6)
Median	18
Min, Max	12, 35

Abbreviations: BMI= body mass index; max= maximum; min= minimum; SD= standard deviation; cm= centimeter; kg= kilogram; m= meter
Source: adapted from sBLA 125402/818 st00856-pid-ir13-demog, page 1-2.

Clinical Reviewer Comment*: Of note, these pediatric data include only subjects who were less than 16 years of age. Study 161504 included subjects up to 18 years of age, and therefore some subjects were excluded from this integrated analysis.*

As discussed previously, the study population is 94% white, which is not typical for PI in the United States. However, this reviewer does not expect the safety profile or efficacy to vary between race and ethnic groups, although that expectation cannot be verified in these trials because of the lack of diversity in the study population.

8.2.3 Categorization of Adverse Events

All adverse events that occurred within 72 hours of the infusion were assessed as temporally associated adverse events.

8.4 Safety Results

8.4.1 Deaths

Two adult subjects died in Study 161406. Please refer to section 6.6.12.3 for further details.

No deaths were reported in Studies 160603, 161503, and 161504.

8.4.3 Study Dropouts/Discontinuations

Table 18: Subject Disposition, Integrated Safety Analysis

Parameter	**Study 160603 + 161503+ 161504**

	Subjects < 16 years of age N=104
Enrolled	104
Subjects completed	83 (80%)
Subjects ongoing at the time of data cut-off	1 (1%)
Subjects discontinued (n=20) due to:	--
Withdrawal by subject	13 (65%)
Adverse event	4 (20%)
Physician decision	1 (5%)
Subject missed 2 consecutive administrations of IP	1 (5%)
Other	1 (5%)

Abbreviations: IP= Investigational Product
Source: adapted from sBLA 125402/818 st00856-pid-ir13-dispo, page 1.

Clinical Reviewer Comment*: Of the pediatric subjects who enrolled in these studies, approximately 20% withdrew or were discontinued from the study. This represents a relatively high proportion of study withdrawals. Of the subjects who withdrew, 20% withdrew secondary to adverse events.*

8.4.6 Systemic Adverse Events

Table 19: Most frequent systemic adverse reactions (within 72 hours of an infusion) reported in greater than 5% of subjects during treatment with Hyqvia, (rate per subject)

Adverse Reaction	**Pediatrics** <16 years old, n=101	**Adults** 16 years and older, n= 62
Headache	30 (30%)	22 (35%)
Pyrexia	15 (15%)	8 (13%)
Vomiting	15 (15%)	2 (4%)
Fatigue	12 (12%)	11 (18%)
Abdominal pain	9 (9%)	4 (6%)
Diarrhea	7 (7%)	6 (10%)
Nausea	7 (7%)	14 (22%)
Upper respiratory tract infection	7 (7%)	9 (14%)
Cough	6 (6%)	2 (3%)
Rash	6 (6%)	4 (6%)
Sinusitis	6 (6%)	3 (5%)
Chills	5 (5%)	5 (8%)
Dizziness	5 (5%)	5 (8%)
Pain in extremity	4 (4%)	5 (8%)
Gastroenteritis	3 (3%)	4 (6%)
Asthma	3 (3%)	4 (6%)
Arthralgia	2 (2%)	7 (11%)
Contusion	2 (2%)	4 (6%)
Contact dermatitis	2 (2%)	4 (6%)
Migraine	2 (2%)	5 (8%)

Erythema	1 (1%)	5 (8%)
Pain	1 (1%)	5 (8%)
Bronchitis	1 (1%)	4 (6%)
Asthenia	-	4 (6%)
Local swelling	-	4 (6%)

Source: constructed from data submitted to BLA 125402 from Studies 160603, 161503, and 161504.
*Any AE in either children or adults with rates > 5% are included in the above table. The order of the AEs is based on the frequency in the pediatric population.

Table 20: Most frequent systemic adverse reactions (within 72 hours of an infusion) reported in greater than 5% of infusions during treatment with Hyqvia, (rate per infusion)

Adverse Reaction	**Pediatrics** <16 years of age, N=1724	**Adults** 16 years and above, N=1023
Headache	79 (5%)	27 (3%)

Source: adapted from the response to Information Request submitted to BLA 125402/818.17 and from data submitted to BLA 125402 from Study 160603, 161503, and 161504.

Table 21: Most frequent systemic adverse reactions (by number of subjects), by age range

Adverse Reaction	**2 to <6 years** (n=18)	**6 to < 12 years** (n= 47)	**12 to <16 years** (n=36)
Headache	7 (39%)	17 (36%)	6 (17%)
Pyrexia	5 (28%)	7 (15%)	3 (8%)
Vomiting	3 (17%)	8 (17%)	4 (11%)
Upper respiratory tract infection	2 (11%)	3 (6%)	2 (6%)
Fatigue	2 (11%)	4 (8%)	6 (17%)

Source: made from data submitted to BLA 125402 from Study 160603, 161503, and 161504.

8.4.7 Local Reactogenicity

Table 22: Most frequent local adverse reactions (within 72 hours of an infusion) reported in greater than 5% of subjects during treatment with Hyqvia, (rate per subject)

Adverse Reaction	**Pediatrics** <16 years old, n=101	**Adults** 16 years and older, n= 62
Infusion site pain	39 (39%)	30 (48%)
Infusion site pruritis	19 (19%)	5 (8%)
Infusion site erythema	17 (17%)	13 (21%)
Infusion site extravasation	13 (13%)	2 (3%)
Infusion site swelling	12 (12%)	7 (11%)
Infusion site discomfort	4 (4%)	7 (11%)
Infusion site hematoma	2 (2%)	6 (10%)
Infusion site edema	1 (1%)	6 (10%)

Source: made from data submitted to BLA 125402 from Study 160603, 161503, and 161504.

Table 23: Most frequent local adverse reactions (within 72 hours of an infusion) reported in greater than 5% of infusions during treatment with Hyqvia, (rate per infusion)

Adverse Reaction	**Pediatrics** <16 years of age, N=1724	**Adults** 16 years and above, N=1023
Infusion site erythema	41 (2%)	46 (5%)
Infusion site pain	97 (6%)	111 (11%)

Source: adapted from the response to Information Request submitted to BLA 125402/818.17 and from data submitted to BLA 125402 from Study 160603, 161503, and 161504.

Table 24: Most frequent local adverse reactions by number of subjects, by age range

Adverse Reaction	**2 to <6 years** (n=18)	**6 to < 12 years** (n= 47)	**12 to <16 years** (n=36)
Infusion site pain	5 (28%)	20 (42%)	14 (39%)
Infusion site erythema	4 (22%)	12 (25%)	1 (3%)
Infusion site extravasation	3 (17%)	6 (13%)	4 (11%)
Infusion site pruritis	2 (11%)	12 (25%)	5 (14%)
Infusion site swelling	2 (11%)	7 (15%)	3 (8%)

Source: made from data submitted to BLA 125402 from Study 160603, 161503, and 161504.

8.6 Safety Conclusions

The safety profile of Hyqvia is acceptable for pediatric subjects with PI and similar to the safety profile of Hyqvia in adults.

There was a safety signal in the pregnancy registry (Study 161301) with an increased frequency of congenital abnormalities (2 out of 5) in infants born to mothers taking Hyqvia during pregnancy. Although selection bias may be influencing these findings, further study is recommended. Please refer to Section 6.4.11.1 and Section 11.6 for additional details.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

There are insufficient data to conduct sub-group analyses.

9.1.1 Human Reproduction and Pregnancy Data

Please see Section 6.4, Study 161301.

9.1.2 Use During Lactation

In study 161301, there were inadequate data regarding Hyqvia use during breastfeeding to assess safety of breastfeeding when mothers are taking Hyqvia.

9.1.3 Pediatric Use and PREA Considerations

At the time of the original BLA approval (September 12, 2014), a post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) was issued. On March 8, 2022, the applicant submitted an efficacy supplement to support the addition of the pediatric population to the indication of PI (originally approved for adults only). Based on the review of the data submitted, the Division determined that the PREA post-marketing requirement was fulfilled. The assessment was presented to the Pediatric Review Committee (PeRC) on March 7, 2023. The PeRC agreed with the assessment and fulfillment of the PREA PMR.

9.1.4 Immunocompromised Patients

Hyqvia is indicated for primary immunodeficiency.

10. CONCLUSIONS

The applicant conducted a pediatric PK, efficacy, and safety study in children 2- less than 16 years of age to fulfill their PREA PMR obligation. The clinical study (Study 161503) was completed in accordance with FDA guidance “Safety, efficacy and PK studies to support marketing of IGIV (human) as replacement therapy for Primary Humoral Immunodeficiency” and the protocol was agreed upon with the Agency. In addition, a pediatric study (Study 161504) and pediatric data from the pivotal study (Study 160603) were reviewed and found to support the safety and efficacy of Hyqvia in a pediatric population with PI. These data are sufficient to fulfill the PREA PMR and expand the labeled indication to include children with PI who are at least 2 years of age.

A safety signal was identified in pregnant subjects taking Hyqvia. Infants born to mothers taking Hyqvia during pregnancy had a 40% (2 out of 5) rate of congenital abnormalities, which is considerably higher than expected. Although selection bias may have contributed to this finding, the Agency is concerned that there is a mechanistic rationale and that it is possible that hyaluronidase exposure in a developing fetus could cause congenital abnormalities. The prescribing information on pregnancy was updated and a new PMC was issued to further investigate this potential signal.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 25: Risk-Benefit

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary immunodeficiency (PI) represents a heterogeneous group of disorders resulting from inherited defects of the immune system. • Patients with PI are at increased risk for recurrent, severe infections	• PI diseases are serious, chronic conditions associated with considerable morbidity and mortality. • Immunoglobulin replacement therapy (administered either intravenously or subcutaneously) has been shown to reduce the incidence of serious infections through provision of passive immunity and prolong life span.
Unmet Medical Need	• Numerous marketed immunoglobulin products (both intravenous and subcutaneous forms) have demonstrated efficacy with serious bacterial infection rates less than 1.0 per subject-year.	• Currently, there is not an unmet medical need. • However, given potential for supply chain disruptions and shortages, there is a public health benefit for having additional immunoglobulin replacement products on the market.
Clinical Benefit	• Two pediatric studies (Study 161503 and Study 161504) were submitted to support the safety and efficacy of Hyqvia to treat PI in a pediatric population. In addition, data from pediatric subjects was analyzed from the pivotal study (Study 160603). • When pediatric (subjects 2 to less than 16 years of age) data were pooled from Study 161503 and Study 160603, subjects had a mean rate of 0.06 ASBI events per subject-year. • Study 161504 (whose primary endpoint was safety) showed a ASBI rate of 0.02 ASBI events per subject-year. • All data demonstrated the efficacy of Hyqvia in pediatric subjects with PI.	• The product is effective at preventing ASBIs in children 2-less than 16 years of age.
Risk	• In a pregnancy registry (Study 161301), 2 out of 5 (40%) infants born to mothers taking Hyqvia had congenital abnormalities. Of note, this is a small sample where selection bias is possible. • Antibodies to rHuPH20 (Recombinant Human Hyaluronidase) have been shown to develop. The potential exists for such antibodies to cross-react with endogenous PH20 which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may interfere with fertilization in humans. The clinical significance of these antibodies is not known, but studies have not shown adverse events associated with development of these antibodies to date, although lowered fertility was not assessed clinically. • The most frequent systemic adverse reactions (in > 5% of subjects) that were temporally associated with the product were: headache, fever, vomiting, fatigue, abdominal pain, diarrhea, nausea, upper respiratory tract infection, cough, rash, and sinusitis. • The most frequent local adverse reactions (in > 5% of subjects) that were temporally associated with the product were: infusion site reactions (pain, pruritis, erythema, extravasation, swelling). • There were no deaths reported in a pediatric population. Deaths in adults during a long-term study occurred, but were not attributable to the product.	• Although causality is not clear, infants born to mothers taking Hyqvia may be at increased risk for congenital abnormalities. Labeling changes and further study are warranted. • Risks of other safety findings were similar among pediatric and adult subjects.

Risk Management	• Subcutaneous immunoglobulin products carry an obligate boxed warning for thrombosis. • Warnings and Precautions for this class of products, include hypersensitivity, aseptic meningitis, spread of localized infections, transfusion-related acute lung injury (TRALI), transmitting infectious agents, acute intravascular hemolysis.	• Labeling, routine pharmacovigilance, and a PMC are appropriate • Patients should be monitored for signs and symptoms of hypersensitivity, thrombosis, aseptic meningitis, renal dysfunction, hemolysis, and TRALI

11.4 Recommendations on Regulatory Actions

The applicant has met the statutory standards and has provided substantial evidence of safety and effectiveness. The clinical review team recommends approval of the efficacy supplement to expand the indication for Hyqvia to patients 2 years old and above with PI and recommends considering the PREA PMR fulfilled. A PMC is recommended as discussed in Section 11.6 regarding concerns of an increased rate of congenital abnormalities found in infants whose mothers took Hyqvia during pregnancy.

11.5 Labeling Review and Recommendations

The primary changes to the label include:

- Updates to Indication and Usage (Section 1) to expand the age to patients with PI who are 2 years of age and older
- Updates to Section 6 (Adverse Reactions) to include data from a pediatric population
- Updates to Section 8 (Use in Specific Populations) to include updates from the pregnancy registry (including the reports of 2 congenital anomalies) and a pediatric population
- Updates to Section 12 (Clinical Pharmacology) to include a pediatric population
- Updates to Section 14 (Clinical Studies) to include a pediatric population

Please see the label for additional details.

11.6 Recommendations on Postmarketing Actions

This reviewer agrees with the Division of Pharmacovigilance and recommends a post-marketing commitment (PMC) to establish the safety of Hyqvia during pregnancy. Given the increased rate (40%) of congenital abnormalities found in infants whose mothers took Hyqvia during pregnancy (Study 161301), this reviewer is concerned regarding the safety of hyaluronidase use during pregnancy. Although selection bias may be contributing to this finding, this reviewer believes these data warrant further investigation. Because of ethical concerns regarding requesting a prospective study in subjects who are taking Hyqvia during pregnancy in the context of a safety signal and alternative products, the PMC will be for a retrospective study. The planned title for the study is “Maternal and infant characteristics and outcomes following exposure to HyQvia during pregnancy: a case series based on US claims data.”