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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
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1. ABSTRACT

Title

Pregnancy Registry to collect Long-Term Safety Data from Women treated with HyQvia

Date of the abstract: 10 November 2020

Name and affiliation of main author: [redacted], Takeda

Keywords

Immune globulin, recombinant human hyaluronidase (rHuPH20), pregnancy, safety

Rationale and background

Immunoglobulin (IG) replacement therapy has been well established as an effective treatment for patients with primary immunodeficiency disease (PID) to prevent or reduce the severity of infections. IG can be administered using an intravenous (IV) route or subcutaneous (SC) route. SC treatment has been shown to be as effective as IV treatment and is associated with fewer systemic adverse reactions. HyQvia (Immune Globulin (Human) 10% with rHuPH20) (European Union [EU]: Baxalta Innovations GmbH, now part of Shire, Vienna, Austria; United States [US]: Baxalta US Inc., now part of Shire, Lexington, MA) is a dual vial unit for SC use, consisting of one vial of Immune Globulin Infusion 10% (Human) and one vial of recombinant human hyaluronidase (rHuPH20).

The Immune Globulin Infusion 10% (Human) component provides the therapeutic effect of this medicinal product. Recombinant human hyaluronidase (rHuPH20) facilitates the dispersion and absorption of The Immune Globulin Infusion 10% (Human). rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan. Hyaluronan is a polysaccharide found in the intercellular matrix of connective tissue and causes resistance to bulk fluid flow through subcutaneous tissue. It is degraded by naturally occurring hyaluronidase and has a very fast natural turnover in subcutaneous tissue. As a permeation enhancer, rHuPH20 temporarily accelerates the break-down of hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates more rapid dispersion and absorption and improved bioavailability of the IG 10%. Several studies have demonstrated the safety and efficacy of recombinant human hyaluronidase in facilitating the absorption and dispersion of medications in human SC tissues.

In the EU, HyQvia is indicated for replacement treatment in adults, children and adolescents (0-18 years) in PID with impaired antibody production and in secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF= failure to mount at least a 2-fold

rise in IgG antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines) or serum IgG level of <4 g/l. In the US, HyQvia is indicated for the treatment of primary immunodeficiency in adults, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

To date, there are no clinical studies conducted with HyQvia in pregnant women. In the EU, HyQvia should only be given with caution to pregnant women. In the US, HyQvia should be given to a pregnant only if clearly indicated. There are no safety data on the use of HyQvia in breastfeeding women and no human safety data on the development of the reproductive system. This pregnancy registry with regular assessment of antibodies against rHuPH20 was a commitment to the Committee for Medicinal Products for Human Use (CHMP) and the Food and Drug Administration (FDA). The CHMP stated in the final assessment report dated 21 March 2013 that further investigations were needed to evaluate safety concerns in women who become pregnant during or after treatment with HyQvia as well as the physical and neurological development of the infant during the first 2 years of life.

Research question and objectives

Primary objective

To collect and assess clinical safety data regarding the possible effects of HyQvia over the course of and about the outcome of pregnancy, and on the growth and development of the fetus/infant.

Secondary objective

To collect any laboratory safety data and additional safety assessments obtained during the clinical management of the pregnancy or in the evaluation of the fetus in utero and the infant post-partum.

Study design

This study was a non-interventional, prospective, uncontrolled, two-arm, open-label, multicenter post-authorization pregnancy registry of women treated with HyQvia.

- Study Arm 1 (Alternative Product Arm): subjects who stopped HyQvia treatment (if the subjects were still treated) and a licensed human normal immunoglobulin other than HyQvia for IV or SC infusion or an alternative treatment were administered, as determined by the treating physician. Subjects in countries where HyQvia treatment during pregnancy was not indicated were enrolled in Study Arm 1. The date and gestational age were collected for any subject in the Alternative Product Arm who restarted HyQvia.

- Study Arm 2 (HyQvia Arm): subjects who continued to receive HyQvia according to their treatment regimen.

Female patients treated with HyQvia were to notify their treating physician immediately of the pregnancy.

The overall duration of the study was planned to be approximately 6 years from study initiation to end of data collection. The enrollment was open for approximately 3.5 years with first site initiation (SIV) on 25 March 2015 and the last subject in on 29 December 2017. First subject (mother) was enrolled on 04 December 2015. First infant was enrolled on 20 January 2017 and last infant last visit was on 17 December 2019.

Each mother was to be followed from enrollment through delivery/end of pregnancy until the study completion visit which should take place within 6 months of delivery/end of pregnancy. The participation period for the infant was from enrollment until the age of 2 years to assess the development, unless prematurely discontinued. Visits to the investigator and all other medical care were performed as per the standard of care for the site and for the subject's healthcare. The mothers, regardless of which Arm they were enrolled in, were invited to return approximately every 3 months to the site for blood samples to be taken to assess antibodies against rHuPH20.

Subjects and study size, including dropouts

Inclusion criteria

Subjects who met all of the following criteria were eligible for this study:

- For the expectant mother only: Subject became pregnant during or after treatment with HyQvia
- Subject/subject's legally authorized representative was willing to sign informed consent form (ICF)

Exclusion criteria

There were no applicable exclusion criteria for this registry.

Any subject who provided informed consent (i.e., signed and dated the ICF, and if applicable, the assent form) was considered enrolled in this registry. An enrollment/screening log was maintained by each participating site to record all enrolled subjects and to document the reasons for screen failure. All screening data were collected and reported in the case report forms (CRFs), regardless of screening outcome. If a subject was to be re-screened, the End of Study (EOS) CRF was completed, and a new ICF, new Subject Identification Code (SIC) and new CRF were created for that subject.

Any subject could voluntarily withdraw (i.e., reduced the degree of participation of the study) consent and discontinue participation in the study. The reasons for withdrawal were recorded on the EOS CRF. The data collected on withdrawn subjects were used in the analysis and included in the clinical study report. Discontinuation (i.e., complete withdrawal from study participation) could have been due to dropout (i.e., active discontinuation by subjects) or loss of follow-up (i.e., discontinuation by subjects without notice or action).

Stopping rules were not established for this study as mothers were treated with a licensed human normal IG or an alternative treatment, according to the routine standard of care at the study site, for the duration of the study.

Variables and data sources

- HyQvia treatment history
- Planned HyQvia treatment
- Actual HyQvia treatment during the study
- Changes in HyQvia treatment during the study
- Demographics and subjects' characteristics
- Medical and surgical history
- Family, pregnancy and obstetrical history
- Current pregnancy
- Pregnancy outcome
- Infant information at birth and at follow-up
- Concomitant medication, non-drug therapy/procedure
- Physical examinations
- Vital signs
- Clinical laboratory parameters: anti-rHuPH20 antibodies, hematology, urinalysis, antenatal diagnostics
- Adverse events (AEs) and serious adverse events (SAEs)

Results

Mothers

A total of 9 mothers who had/was exposed to HyQvia treatment before or during pregnancy were enrolled in this study (4 mothers were enrolled before delivery and 5 mothers were enrolled after delivery). Seven mothers were included in the HyQvia Arm and 2 mothers were included in the Alternative Product Arm. The mean age of mothers was 33.7 years overall at time of enrollment, 33.9 years in HyQvia Arm, and 33.0 years in Alternative Product Arm. The majority of mothers registered ethnicity as non-Hispanic/Latino (88.9%) overall, in HyQvia Arm (85.7%), and in Alternative Product Arm (100.0%). The mean pre-pregnancy weight was higher in HyQvia Arm than in Alternative Product Arm (69.3 kg vs. 60.0 kg). Similar distribution of age, ethnicity and race was observed between HyQvia Arm and Alternative Product Arm. Of the 9 enrolled mothers, 7 were included in the Retrospective cohort (5 in HyQvia Arm and 2 in Alternative Product Arm), and 2 were included in the Prospective cohort (all in HyQvia Arm).

Medical history

All enrolled mothers (n=9) had at least one medical history prior to the date of Last Menstrual Period (LMP), with 60 medical conditions/surgeries reported. Respiratory was the most common medical conditions/surgeries overall (18.3%), and in HyQvia Arm (19.6%). In Alternative Product Arm, hematopoietic/lymphatic was the most common medical history (21.4%). Eight (88.9%) mothers had CVID and 1 (14.3%) mother had hyper IgM syndrome as a PID type.

Family, pregnancy and obstetrical history

Among the 9 mothers enrolled, no family history of consanguinity between parents was reported (100.0%). Six mothers (66.7%) had previous pregnancies, of these, 4 (66.7%) mothers had normal live births, 1 (16.7%) mother had an abnormal live birth, and 1 mother had an induced termination (n=1, 16.7%). Of the 6 mothers with previous pregnancies, 3 (50.0%) mothers had obstetrical complications during previous pregnancies, while the status was unknown in 1 (16.7%) mother. No fetal/neonatal abnormalities in the previous pregnancies were observed (n=6, 100.0%). Of the 9 mothers enrolled, 1 (11.1%) mother had family history of congenital abnormalities/birth defects (no history: n=4, 44.4%; unknown: n=4, 44.4%), 1 (11.1%) mother had family history of adverse fetal outcome (no history: n=5, 55.6%; unknown: n=3, 33.3%), and no mother had family history of psychomotor retardation (no history: n=6, 66.7%; unknown: n=3, 33.3%).

HyQvia treatment history

Overall, the pre-study mean rHuPH20 volume and total IG dose in the HyQvia treatment history were 14.64 mL per month and 30.8 grams/month, respectively. A higher pre-study mean dose volume of rHuPH20 and IG dose were observed in the HyQvia Arm than in Alternative Product Arm (rHuPH20: 16.00 mL vs. 11.25 mL; IG: 35.0 grams/month vs. 22.5 grams/month). Overall, mothers had a pre-study mean weight of 66.2 kg. Most mothers (62.5%) received treatment at 4-week interval with a mean treatment duration of 459.8 days before enrollment in the study. The pre-study mean weight was higher in HyQvia Arm than Alternative Product Arm (69.3 kg vs. 60.0 kg). In HyQvia Arm, 4 (57.1%) mothers had information on treatment duration with a mean (SD) duration of 540.0 (265.91) days.

Planned HyQvia treatment

Overall, the mean (SD) planned monthly IG dose was 31.7 (14.72) grams for the 6 (85.7%) mothers with available information in the HyQvia Arm. All mothers had a planned HyQvia treatment with 4-weeks (n=4, 57.1%) or 3-weeks (n=3, 42.9%) intervals. The mean (SD) body weight used for calculation was 72.6 (15.62) kg. The mean (SD) total volume of rHuPh20 was 10.8 (5.85) mL per administration (i.e. if a patient has more than 1 infusion site, per administration includes all infusion sites together) in the 6 mothers with available information. The mean (SD) planned IG dose per 4 weeks was 0.469 (0.2052) g/kg (n=6). The mean (SD) planned number of infusion sites was 1.7 (0.49) sites per administration (n=7), with a mean (SD) planned maximum IG infusion rate of 230.0 (72.80) mL/h per administration (n=5).

Actual HyQvia treatment during the study

Overall, data on the actual HyQvia treatment was available for 6 (85.7%) mothers in the HyQvia Arm (4 mothers in the retrospective cohort and 2 mothers in the prospective cohort). These patients received a total of 26 infusions, with 96.2% of infusions being administered at home, and 3.8% being administered at the site. One mother reported receiving 10 infusions during the study, 1 mother reported receiving 6 infusions during the study, 1 mother reported receiving 5 infusions during the study, 1 mother reported receiving 3 infusions during the study and 2 mothers reported receiving 1 infusion during the study.

The mean maximum IG infusion rate was 273.3 mL/h (range 200-300, n=3). Among the 26 infusions with time of the previous infusion given, the most frequent infusion interval was 3 weeks (n=15 infusions in 3 mothers), followed by 4 weeks (n=7 infusions in 3 mothers). The mean administered volume of IG was 305.0 mL (range 100-500mL, n=5 mothers). Overall, 100% (n=26) of infusions were administered as planned. The mean actual administered volume of rHuPH20 during the study was 15.0 mL (range 5-20mL, n=15 infusions in 3 mothers). The mean number of infusion sites was 1.85 (range 1-2 sites, n=20 infusions sites in 5 mothers).

Changes in HyQvia treatment during the study

Overall, 2 mothers (in HyQvia Arm) had revised ongoing treatment due to low IG trough level (n=1) and 'other' (n=1) during the study conduct. Of the 2 mothers with revised ongoing treatment, 1 mother had new planned monthly IG dose of 30 g, new planned total volume rHuPH20 per administration of 15 mL, new planned IG dose of 0.405 g/kg/4 weeks, and new planned maximum IG infusion rate of 300 mL/h, the other mother had new planned monthly IG dose of 40 g, new planned total rHuPH20 volume per administration of 20 mL, new planned IG dose of 0.571 g/kg/4 weeks, and new planned maximum IG infusion rate of 200 mL/h.

One (50.0%) mother in the Alternative Product Arm had changes in HyQvia treatment. For this mother, HyQvia was restarted after delivery (date of delivery: [redacted]; date of HyQvia restarted: [redacted]) due to other unspecified reason.

Concomitant medications, non-drug therapies/procedures, clinical laboratory results, physical examinations

Overall, a total of 5 (55.6%) mothers had at least one concomitant medication (3 [42.9%] in HyQvia Arm and 2 [100.0%] in Alternative Product Arm). Of these, adrenergic in combination with corticosteroids or other drugs (excluding anticholinergics), glucocorticoids, human normal IG, iron bivalent, oral preparations, second-generation cephalosporins, thyroid hormones, and vitamin D and analogues were reported in 2 (22.2%) mothers, respectively. Other concomitant medications were reported in 1 mother (11.1%). No non-drug therapy or procedure data was available between the enrolled mothers. Antenatal diagnostic procedures, including ultrasound (n=3, 33.3%), serology (n=2, 22.2%), and nuchal translucency screen (n=1, 11.1%), were reported in 3 (33.3%) out of 9 enrolled mothers.

In HyQvia Arm (n=7), AE related laboratory results were observed in hemoglobin (n=3), erythrocytes (n=1), and hematocrit (n=1). No data on abnormal physical examination was recorded for mothers. In Alternative Product Arm (n=2), 1 mother reported 2 clinically significant laboratory results that constituted an AE, specifically alanine aminotransferase (n=1) and aspartate aminotransferase (n=1).

Safety outcomes

A total of 2 SAEs were reported in 1 mother in HyQvia Arm among the Prospective cohort, including blood and lymphatic system disorders (preferred term [PT]: thrombocytopenia; n=1) and pregnancy, puerperium and perinatal conditions (PT: pre-eclampsia; n=1).

Overall among the 9 enrolled mothers, 4 mothers had at least one AEs (3 in HyQvia Arm and 1 in Alternative Product Arm), and 1 mother had at least one SAE (in HyQvia Arm).

Non-serious AEs were reported in 4 mothers (3 in HyQvia Arm and 1 in Alternative Product Arm). Severe AE was reported in 1 mother (in HyQvia Arm).

Thirteen AEs were reported in 4 mothers. The number of reported AEs were 5 infections and infestations in 2 (22.2%) mothers (2 events in 1 [14.3%] mother in HyQvia Arm and 3 events in 1 [50.0%] mother in Alternative Product Arm), 3 blood and lymphatic system disorders in 2 (22.2%) mothers (3 events in 2 [28.6%] mothers in HyQvia Arm), 3 pregnancy, puerperium and perinatal conditions in 1 (11.1%) mother (3 events in 1 [14.3%] mother in HyQvia Arm), 1 investigations in 1 (11.1%) mother (1 event in 1 [50.0%] mother in Alternative Product Arm), and 1 neoplasms benign, malignant and unspecified (including cysts and polyps) in 1 (11.1%) mother (1 event in 1 [50.0%] mother in Alternative Product Arm). None of the AEs reported in the study were related to previous or current HyQvia treatment. No AE was related to alternative product treatment. None of the AEs reported were related to human normal IG treatment in the Alternative Product Arm.

No local and immunologic AEs (i.e., allergic conditions [10001708], allergies to foods, food additives, drugs and other chemicals [10001737], anaphylactic and anaphylactoid responses [10077535], angioedemas [10002425], atopic disorders [10052737], and urticarias [10046736]) was recorded for mothers.

Six of 9 mothers enrolled consented to anti-rHuPH20 antibody assessments in the registry, where 4 mothers had blood sample taken while 2 mothers did not have blood sample taken. Of the 4 (44.4% of all mothers) mothers had finally anti-rHuPH20 binding antibody assessments, 2 mothers with 2 anti-rHuPH20 binding antibody assessments in the HyQvia Arm, and 2 mothers with 3 anti-rHuPH20 binding antibody assessments in the Alternative Product Arm were recorded. All the anti-rHuPH20 binding antibody assessments were negative (titer <160). Since no mother had a positive titer of binding anti-rHuPh20 antibody, no neutralizing anti-rHuPH20 antibody was assessed in any mother.

Current pregnancy

Among the 9 enrolled mothers (4 mothers were enrolled before delivery and 5 mothers were enrolled after delivery), the mean time from the date of LMP to enrollment was 237.7 days. The mean age at conception was 33.3 years. Patients in Alternative Product Arm had longer LMP to enrollment time than HyQvia Arm (265.5 days vs. 223.8 days), while patients in HyQvia Arm had older conception age than Alternative Product Arm (34.3 years vs. 30.0 years). All mothers had 1 fetus at current pregnancy (7 in HyQvia Arm and 2 in Alternative Product Arm). One mother (in HyQvia Arm) had history of subfertility/infertility while no treatment was received for subfertility/infertility for the current pregnancy. Three (2 in HyQvia Arm and 1 in Alternative Product Arm) mothers had exposure for tobacco at peri-LMP during current pregnancy. Two mothers (1 in HyQvia Arm and 1 in Alternative Product Arm) had exposure to alcohol.

Pregnancy outcome and complications of pregnancy

Of the 8 pregnancies with known outcomes, there were 8 live births (6 in HyQvia Arm and 2 in Alternative Product Arm). One mother discontinued from the study prior to the expected delivery. Of the 8 living births, 7 live births were normal (5 in HyQvia Arm and 2 in Alternative Product Arm) and 1 (in HyQvia Arm) was reported abnormal (reason for abnormal classification was an elective cesarean section due to failure to progress in labor that the physician considered was not an AE) as per physician's evaluation. The mean duration of gestation was 277.6 days (286.0 days in HyQvia Arm and 265.0 days in Alternative Product Arm). Four (50.0%) mothers had vaginal delivery and 4 (50.0%) had cesarean section delivery. Seven out of 8 (87.5%) mothers had no labor or delivery complications, while 1 (12.5%) mother (in HyQvia Arm) had unspecified labor or delivery complications.

Infants

Overall, a total of 7 infants were enrolled in this study. One infant was not enrolled in the study because the mother did not sign the assent despite she was participating in the study. Of 7 infants, 5 infants were included in the HyQvia Arm and 2 were included in the Alternative Product Arm based on their mother's treatment arm. There was a similar distribution of males (42.9%) and females (57.1%). All infants were non-Hispanic/Latino and White/Caucasian. Of the 7 enrolled infants, 5 were included in the Retrospective cohort (3 in HyQvia Arm and 2 in Alternative Product Arm), and 2 were included in the Prospective cohort (all in HyQvia Arm).

Concomitant medications, non-drug therapies/procedures, clinical laboratory results, physical examinations

Overall, a total of 6 (85.7%) infants had at least one concomitant medication (4 in HyQvia Arm and 2 in Alternative Product Arm). Of these infants, 1 had an other non-therapeutic products and 1 had an other-therapeutic products, 1 had amoxicillin trihydrate; clavulanate potassium, 1 had bisulepin, 1 had other nasal preparations, 1 had cefixime, 1 had vaccines, and 2 had vitamin K. Of the 7 enrolled infants, 2 (28.6%) infants had data available on non-drug procedures. Of these, 1 (14.3%) infant received cleft lip surgery, and 1 (14.3%) infant received rehabilitation for talipes calcaneovalgus.

Of the 7 infants enrolled in the study, 1 clinically significant laboratory result for bilirubin due to newborn regular icterus (as reported by the site) was available in 1 infant in the HyQvia Arm and Retrospective cohort. Anti-rHuPH20 antibody assessment was not performed in infants.

Safety outcomes

Two SAEs were reported in 2 infants (both infants were in HyQvia Arm). Both SAEs were congenital, familial and genetic disorders, including cleft lip without cleft palate (n=1) and talipes calcaneovalgus (n=1). Both SAEs were assessed as not related to their mothers' previous and current HyQvia treatment by the investigators. Both SAEs were mild by severity. [redacted].

Overall among the 7 infants enrolled, 6 infants had at least one AE (5 infants in HyQvia Arm and 1 infant in Alternative Product Arm) during the mean 661.4 days follow-up period. Non-serious AEs were reported in 5 infants (4 infants in HyQvia Arm and 1 infant in Alternative Product Arm). No severe AE was recorded.

A total of 16 unrelated AEs was reported in 6 (85.7%) infants (14 events in 5 [100.0%] infants in HyQvia Arm and 2 events in 1 [50.0%] infant in Alternative Product Arm. The reported AEs included 5 infections and infestations in 3 (42.9%) infants (4 events in 2 [40.0%] infants in HyQvia Arm and 1 event in 1 [50.0%] infant in Alternative Product Arm), 2 congenital, familial and genetic disorders in 2 (28.6%) infants (2 events in 2 [40.0%] infants in HyQvia Arm), 2 injury, poisoning and procedural complications in 2 (28.6%) infants (1 event in 1 [20.0%] infants in HyQvia Arm and 1 event in 1 [50.0%] infants in Alternative Product Arm), 1 blood and lymphatic system disorders in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm), 1 gastrointestinal disorder in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm), 1 hepatobiliary disorders in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm), 1 investigations in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm), 1 metabolism and nutrition disorders in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm), 1 pregnancy, puerperium and perinatal conditions in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm), and 1 skin and subcutaneous tissue disorders in 1 (14.3%) infant (1 event in 1 [20.0%] infant in HyQvia Arm). Both infants (40%) with congenital, familial and genetic disorders were included in HyQvia Arm, including 1 cleft lip without cleft palate and 1 talipes calcaneovalgus. No AE in an infant was assessed as related to HyQvia treatment of the mother.

Neonatal assessment and status at birth

The mean gestational age for the 7 infants enrolled was 38.7 weeks (39.2 weeks in HyQvia Arm and 37.5 weeks in Alternative Product Arm), with a mean weight of 3.09 kg (3.19 kg in HyQvia Arm and 2.83 kg in Alternative Product Arm), mean length of 49.5 cm (50.0 cm in HyQvia Arm and 48.5 cm in Alternative Product Arm), and mean head circumference of 34.1 cm (35.0 cm in HyQvia Arm and 33.3 cm in Alternative Product Arm).

Normal weight, length, and head circumference assessments were observed in all infants. Seven infants had information on weight at screening with weight-for-age percentiles ranging from 6.8% to 82.4% (HyQvia Arm: n=5, ranging from 12.1% to 82.4%; Alternative Product Arm: n=2, ranging from 6.8% to 33.2%). Six infants had information on both weight and length at screening with length-for-age percentile ranging from 13.8% to 84.7% (HyQvia Arm: n=4, ranging from 28.8% to 84.7%; Alternative Product Arm: n=2, ranging from 13.8% to 43.3%) and weight-for-length percentile ranging from <0.01% to 72.2% (HyQvia Arm: n=4, ranging from <0.01% to 63.0%; Alternative Product Arm: n=2, ranging from 0.7% to 72.2%). Four infants had information on head circumference at screening with head circumference-for-age percentile ranging from 4.7% to 87.2% (HyQvia Arm: n=2, ranging from 50.8% to 87.2%; Alternative Arm: n=2, ranging from 4.7% to 48.0%). The mean Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores at 1 minute, 5 minutes, and 10 minutes were 9.4, 10.0, and 10.0, respectively. Normal APGAR scores assessment was observed in all infants. Two out of 7 (28.6%) infants (all in HyQvia Arm) had presence of congenital malformations/anomaly that both were assessed as mild in severity and were not related to their mother's previous and current HyQvia treatment.

Growth and development of infants

At approximately 6-month follow-up, no congenital malformations diagnosed that were not reported at birth or conditions that were noted since birth were reported. Of the infants with weight information (n=3, 42.9%), all had normal weight. Length and head circumference information was available in 2 (28.6%) infants, of these, all infants had normal length and head circumference. One infant had complete information on weight, length and head circumference at the 6-months follow-up (age: 191 days) with a weight-for-age percentile of 64.9%, weight-for-length percentile of 44.3%, length-for-age percentile of 84.7%, and a head circumference-for-age percentile of 89.2%. Information on breast feeding at of the 6-month follow-up was available in 2 (28.6%) infants, of these, 1 (50.0%) infant was breastfed for a duration of 27.0 weeks and was ongoing at this follow up visit, while the status was unknown in 1 (50.0%) infant. Information on illnesses since last visit was available in 2 (28.6%) infants with all infants reporting no illnesses since last visit. Of the 2 (28.6%) infants with drug therapy/non drug therapy/procedure data, no infant received at least one drug therapy/non drug therapy/procedure, while data was unknown in 1 (50.0%) infant. Information on developmental milestones was available in 2 (28.6%) infants with no evidence of missed developmental milestones (i.e., rolled over, attend to and reached for objects, sat up without support, turned to locate a voice, said his/her first words, stand without support/help) reported. Information on pulse rate, blood pressure, respiratory rate, and body temperature was missing in all infants.

At approximately 12-month follow-up, no congenital malformations diagnosed that were not reported at birth or conditions that were noted since birth were reported. Of the infants with weight information (n=2, 28.6%), all had normal weight. Length and head circumference information was available in 2 (28.6%) infants, of these, all infants had normal length and head circumference. Two infants had complete information on weight, length and head circumference at the 12-months follow-up (ages: 338 and 365 days) with weight-for-age percentiles ranging from <0.01% to 69.8%, weight-for-length percentiles ranging from 87.8% to 98.95%, length-for-age percentiles ranging from <0.01% to 22.6%, and head circumference-for-age percentiles ranging from <0.01% to 84.6%. Information on breastfeeding at the time of the 12-months follow-up was available for 1 (14.3%) infant, who was breastfed, but breastfeeding duration was not available. Information on any illness since last visit was available in 1 (14.3%) infants, of these, all infants had no illness since last visit. Of the 1 (14.3%) infant with drug therapy/non drug therapy/procedure data, data was unknown in this infant. Information on developmental milestones were available in 1 (14.3%) infant, no evidence of missed developmental milestones was reported. Information on pulse rate, blood pressure, respiratory rate, and body temperature was missing in all infants.

At approximately 18-months follow-up, no congenital malformations diagnosed that were not reported at birth or conditions that were noted since birth were reported. One (14.3%) infant had available information on weight, length and head circumference information with all parameters being normal. One infant had complete information on weight, length and head circumference at the 18-month follow-up (age: 549 days), with a weight-for-age percentile of 71.8%, weight-for-length percentile of 82.9%, length-for-age percentile of 39.9%, and a head circumference-for-age percentile of 70.7%. Breastfeeding information was available in 1 (14.3%) infant who was not breastfed. Information on illnesses since last visit was available in 1 (14.3%) infant where the infant had illness since last visit. One (14.3%) infant with information on drug therapy/non drug therapy/procedure had at least one drug therapy/non-drug therapy/procedure reported (n=1, 100.0%). Information on developmental milestones were available in 1 (14.3%) infant who had no evidence of missed developmental milestones. Information on pulse rate, blood pressure, respiratory rate, and body temperature was missing in all infants.

At approximately 24-months follow-up, no congenital malformations diagnosed that were not reported at birth or conditions that were noted since birth were reported. Weight, length and head circumference information was available in 1 (14.3%) infant who had normal weight, length and head circumference. Only one infant had complete information at the 24-month follow up (age: 722 days) with a weight-for-age percentile of 76.4%, weight-for-length percentile of 95.1%, length-for-age percentile of 16.2%, and a head circumference-for-age percentile of 98.0%. Breastfeeding information was available in 2 (28.6%) infants, of these, 1 (50.0%) infant was breastfed and 1 (50.0%) infant was not breastfed. Information on illness since last visit was available in 2 (28.6%) infants, of these, 1 (50.0%) infant had an illness since last visit.

Of the 2 (28.6%) infants with drug therapy/non drug therapy/procedure data, 1 infant did not receive drug therapy/non drug therapy/procedure and the data was unknown for the other infant. Two (28.6%) infants had available information on developmental milestones with one of them [redacted]) reporting to have missed milestones at the 24-month follow-up. The infant that reported having missed milestones, did reach 'sat up without support', 'turned to locate voice', and 'stand without support/help' milestones, and had unknown information on the milestones of rolled over, attend to and reached object, and said first words. None of the infants had available data on pulse rate, blood pressure, respiratory rate, and body temperature.

Discussion

There were 9 mothers who had become pregnant during or after treatment with HyQvia enrolled in this study. Seven mothers were included in the HyQvia Arm and 2 were included in the Alternative Product Arm. A total of 7 infants were enrolled in this study, where 5 infants were included in the HyQvia Arm and 2 were included in the Alternative Product Arm.

This registry observed more AEs in the HyQvia Arm (mothers: 8 AEs in 3 mothers; infants: 14 AEs in 5 infants) than in the Alternative Product Arm (mothers: 5 AEs in 1 mother; infants: 2 AEs in 1 infant) among mothers and infants, which could be in part due to a higher number of mothers and infants being enrolled in the HyQvia Arm than in the Alternative Product Arm (7 mothers vs. 2 mothers; 5 infants vs. 2 infants). All AEs were reported as not related to previous or current HyQvia treatment. The AEs reported in HyQvia Arm of the registry (all observed in ≥10% of mothers) (i.e., anemia of pregnancy, pre-eclampsia, thrombocytopenia, bronchitis, influenza, urinary tract infection, and uterine contractions during pregnancy) were not consistent with the most common adverse reactions (>5%) observed in clinical trials (i.e., local reactions, headache, antibody formation against rHuPH20, fatigue, nausea, pyrexia, and vomiting). No anti-rHuPH20 binding or neutralizing antibodies were developed therefore the effect of anti-rHuPH20 antibodies on fetal development and pregnancy outcome cannot be evaluated. No local and immunologic AEs were reported in this registry.

The 2 birth defects (28.6% of enrolled infants) reported in this registry were in infants on the HyQvia Arm, including one infant with cleft lip without cleft palate (14.3% of enrolled infants) and one infant with talipes calcaneovalgus (14.3% of enrolled infants). The cleft lip event was resolved with surgery and the talipes calcaneovalgus event did not require surgery during the first 2 years of life. These 2 birth defects are not known to be associated with one another, were assessed as mild in severity and were not related to their mother's previous and current HyQvia treatment.

Cleft lip without cleft palate in this study occurred in 1 out of 7 live births; whereas in the general US population cleft lip without cleft palate occurs in 1 out of every 2,807 live births according to the CDC statistics. Similarly, talipes calcaneovalgus in this study were reported in 1 out of 7 infants; whereas in the literature talipes calcaneovalgus occurs in 4.2 per 10,000 live births in South American hospitals. During a one-year screening period in a Swedish hospital a foot deformity was noted in 100 of 2,401 newborn (4.2 percent) and talipes calcaneovalgus was diagnosed in 18 newborns. According to the CDC statistics the rate of talipes calcaneovalgus in live birth is not available. However, any comparison should be taken with caution considering the small number of subjects enrolled in this study and the fact that the occurrence of cleft lip and the foot deformity in patients with PID is unknown and the comparison was made to the general population.

Risk factors associated to cleft lip without cleft palate and talipes calcaneovalgus should also be considered in this study. Cleft lip has been associated in previous studies with smoking during pregnancy, diabetes before pregnancy, and exposure to epilepsy-related treatment during the first trimester. Similarly, risk factors for talipes include smoking and genetic predisposition, although the etiology remains poorly understood. Overall, the known risk factors associated with cleft lip or talipes regarding smoking and family history for congenital anomalies/birth defects were not presented for the mothers of the 2 infants with birth defects in this registry, although the mother of the infant with cleft lip had reported a congenital double kidney abnormality. The investigators assessed the two birth defects as not related to the mother's previous or current HyQvia treatment. Both infants' mother consented to anti-rHuPH20 antibody assessments. The mother of the infant with cleft lip without cleft palate (SID: [redacted]) had no binding anti-rHuPH20 antibody titer. Although the mother of the infant with talipes calcaneovalgus (SID: [redacted]) also consented to anti-rHuPH20 antibody assessment, the blood samples were not collected by the site therefore anti-rHuPH20 data was not available.

In conclusion, the AEs reported in HyQvia Arm of the registry were not consistent with the most common adverse reactions observed in clinical trials with HyQvia. None of the AEs reported in the study were assessed as related to previous or current HyQvia treatment in the mother, or caused HyQvia treatment changes (i.e., dose reduction, interruption, withdrawal). No anti-rHuPH20 binding or neutralizing antibodies, or local and immunologic AEs were reported in this registry. Five mothers continued HyQvia treatment during the pregnancy (2 mothers enrolled before delivery and 3 mothers enrolled after delivery with ongoing HyQvia treatment at the screening visit) and all had live births, with normal APGAR scores. Five mothers in the Retrospective cohort were enrolled after the delivery and therefore no data on anti-rHuPH20 antibodies during the pregnancy was available in these mothers. HyQvia given during pregnancy was not associated with labor and delivery complications. Two minor birth defects, i.e. cleft lip without cleft palate and talipes calcaneovalgus, were reported in 2 infants in the HyQvia Arm.

These 2 birth defects were not known to be related to one another, they were assessed as unrelated to HyQvia treatment and, given the small sample size in this study, these events could be attributed to chance. The mothers of these infants did not report any known risk factors associated with cleft lip or talipes, although the mother of the infant with cleft lip, had reported a congenital double kidney abnormality. Considering the small sample size and limited data collection in this study, the results should be interpreted with caution.

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