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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

1. ABSTRACT

Title

Non-Interventional Post-Authorization Safety Study on the Long-Term Safety of HyQvia in Subjects Treated with HyQvia

Keywords

Immune globulin, recombinant human hyaluronidase (rHuPH20), safety

Rationale and Background

This post-authorization safety study (PASS) with regular assessment of anti-rHuPH20 antibodies was a request of the Committee for Medicinal Products for Human Use (CHMP) in the course of the HyQvia Marketing Authorization Procedure. Further data were collected to evaluate long-term local and systemic effects of HyQvia in subjects treated with HyQvia.

Research Question and Objectives

The purpose of the study was to acquire additional data (including the assessment of anti-rHuPH20 antibodies) on the long-term safety of HyQvia and to assess the prescribed treatment regimens and treatment administration in routine clinical practice. The primary objective was to collect and assess safety data, in particular the occurrence of long-term changes in incidence and severity of related adverse events (AEs) in patients treated with HyQvia. Secondary objectives were to collect data on the prescribed treatment regimen, anti-rHuPH20 antibodies and, as available, other laboratory safety assessments, total immunoglobulin G (IgG), further safety assessments that were obtained during the routine clinical management of the subjects, treatment administration, and health-related quality of life (HRQoL) and health resource use (HRU) assessments (optional).

Study Design

This was a non-interventional, prospective, uncontrolled, multi-center, open-label, PASS in the European Economic Area (EEA).

Setting

Adult patients (≥18 years) who were prescribed treatment with HyQvia were enrolled in the EEA. Subjects were treated with HyQvia, a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial (rHuPH20). Treatment regimens were prescribed at the discretion of the attending physician in accordance with routine clinical practice. Visits to the investigator and all other medical care were performed as were standard for the site and subject's healthcare.

In addition, however, the subject was asked to provide additional blood samples at the time of routine laboratory assessments approximately every 3 months, but no more often than 4 times a year, for the measurement of anti-rHuPH20 antibodies, as requested by the CHMP. If testing for anti-rHuPH20 antibodies was not done for any reason, all other laboratory data were collected as available.

The overall duration of the study was approximately 6 years from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period was approximately 3 years from 17 Jul 2014 to 23 Feb 2017. The subject participation period was approximately 3 to 6 years from enrollment to subject completion (ie, last study visit on 26 Feb 2020), depending on the time point of enrollment, unless prematurely discontinued.

Subjects and Study Size, Including Dropouts

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

- Subject required IG treatment
- Subject was ≥18 years old at the time of screening
- Subject had been prescribed treatment with HyQvia prior to enrollment
- Subject was willing and able to comply with the requirements of the protocol

Subjects who met ANY of the following criteria were not eligible for this study:

- Subject had known hypersensitivity to any of the components of the medicinal product
- Subject had participated in an interventional clinical study involving a medicinal product or device within 30 days prior to enrollment, or was scheduled to participate in an interventional clinical study involving a medicinal product or device during the course of the study
- Subject was a family member or employee of the investigator

No minimum sample size was specified for this study. It was anticipated that approximately 80 to 120 subjects would be eligible for enrollment.

Variables and Data Sources

Variables included anti-rHuPH20 antibodies (rHuPH20 binding antibodies in addition to neutralizing antibodies in samples with a titer ≥160), laboratory assessments such as hematology, clinical chemistry, urinalysis, seroconversion to hepatitis B virus, hepatitis C virus and human immunodeficiency virus, total IgG, pregnancy (if applicable), further safety data (eg, AEs and serious AEs [SAEs]), treatment regimen, product administration details, and HRQoL and HRU.

Source data comprised hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subject diaries, home treatment records or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, medical imaging data (eg, microfiches, photographic negatives, microfilm or magnetic media, X-rays), subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

Results

Participants

A total of 111 subjects were enrolled in the study, of whom 106 had reported data on at least 1 dose of HyQvia and were included in the safety population. The subjects were enrolled at 17 sites from 6 countries in the EEA (ie, Germany, Netherlands, Denmark, Ireland, Italy, and Czech Republic). The median follow-up time was 3.17 years (range 0.02–5.22). Half (50.5%) of subjects discontinued the study prematurely, primarily due to subject withdrawal (n=18), lost to follow-up (n=14), and AEs (n=13). Subjects were followed for a total of 302.35 person-years during the study.

The mean age of the study population was 46.2 (standard deviation [SD]=14.69) years at informed consent, and 14.2% (n=15) of the subjects were 65 years or older. Over half of subjects were female (n=60, 56.6%), of whom 56.7% were of childbearing potential. Nearly all subjects identified as Caucasian/White race (98.1%) and Non-Hispanic or Latino ethnicity (93.4%). The mean weight was 77.1 kilograms (SD=17.57). The subjects were slightly overweight, the mean body mass index was 26.2 (SD=5.39). Most subjects reported a history of respiratory and hematopoietic/lymphatic medical conditions/surgeries of moderate severity. All subjects but one had previous IG treatment. Treatment with HyQvia was indicated for primary immunodeficiency (PID) in 91.5% of subjects, secondary immunodeficiency (SID) in 6.6% of subjects, and immunomodulatory therapy in 1.9% of subjects. The most commonly prescribed concomitant antibiotics were macrolides (35.2%). Over 90% of subjects had an overall normal result recorded on their physical examination at baseline.

Safety

One subject had 1 treatment emergent, non-fatal SAE assessed as probably related to HyQvia by the investigator, resulting in an incidence proportion of related SAEs of 0.94% (95% confidence interval [CI]: 0.17, 5.15), an incidence rate of related SAEs of <0.01 per person-year (95% CI: 0.00, 0.02), and an event rate of related SAEs of 0.03 per 100 infusions (95% CI: 0.00, 0.17). The subject was [redacted] years old, male, and had an indication for HyQvia of PID.

The SAE was toxic erythema of the abdomen skin. The immunological investigation including the measurement of C3 and C4 levels did not reveal any abnormality. Anti-rHuPH20 antibody titers were repeatedly negative. The skin biopsy showed toxic vasculopathy without any sign of increased complement deposition or activity. The SAE occurred during the first year of follow-up after multiple uneventful doses of HyQvia. The investigator reported that erysipelas, which was reported as an initial diagnosis for the subject's skin lesion and treated with antibiotics, may have been a co-factor that more plausibly explained the SAE.

A total of 82 treatment emergent SAEs were reported in 36 subjects within the safety population. The overall incidence proportion of treatment emergent SAEs was 33.96% (95% CI: 25.65, 43.40); the incidence rate was 0.27 per person-year (95% CI: 0.22, 0.34), and the event rate was 2.44 per 100 infusions (95% CI: 1.94, 3.03). Subjects aged 30–<40 years had a significantly lower incidence rate of treatment emergent SAEs than subjects aged 18–<30 years and subjects aged 65 years and over. No substantial differences in SAE incidence were observed by gender or between subjects with PID and SID, though the size of the indication subgroups varied widely (N=97 vs. 7, respectively). The annual SAE rate per 100 subjects was substantially lower in the year of study completion/discontinuation than in Year 2 (12.26 [95% CI: 6.53, 20.97] vs 36.00 [95% CI: 23.72, 52.38]). Annual per-subject event rates were highest for SAEs classified as moderate in severity during Year 1 to Year 3 and severe in Year 4 and the year of study completion/discontinuation.

The overall incidence rate of all treatment emergent non-serious AEs, excluding infections, was 2.39 per person-year (95% CI: 2.22, 2.58). The event rate was 21.53 per 100 infusions (95% CI: 19.99, 23.16). When including infections, the incidence rate of treatment emergent non-serious AEs was 3.60 per person-year (95% CI: 3.39, 3.82), and the event rate was 32.38 per 100 infusions (95% CI: 30.49, 34.36). Results for non-serious AEs related to HyQvia were almost identical whether excluding or including infections. The incidence rate of related non-serious AEs was 0.98 per person-year (95% CI: 0.87, 1.10) when excluding infections and 0.99 per person-year (95% CI: 0.88, 1.10) when including infections; the event rates were 8.83 per 100 infusions (95% CI: 7.86, 9.90) and 8.86 per 100 infusions (95% CI: 7.88, 9.93), respectively. Subjects in the 40–<50 age group had higher incidence rates and event rates of related non-serious AEs compared to all other age groups, as did males compared to females. The annual per-subject related non-serious AE rate peaked in Year 2 of follow-up (114.67 per 100 subjects [95% CI: 91.72, 141.61]) before declining annually in subsequent years. The highest annual per-subject event rates were observed for mild AEs in each year. No related non-serious AEs were classified as severe.

Overall, the incidence rate of treatment emergent infections was 1.32 per person-year (95% CI: 1.19, 1.45). The annual per-subject event rate of treatment emergent infections was comparable in Year 1 (150.00 per 100 subjects, 95% CI: 125.50, 177.88) and Year 2 (152.00 per 100 subjects, 95% CI: 125.38, 182.60), then declined each year after Year 2. In each year of follow-up, the highest annual event rates of infections that were observed for AEs classified as mild in severity.

No treatment emergent local AEs suspected to be immunologic were reported. One subject presented with 1 treatment emergent event that was flagged as a temporally and/or causally associated systemic allergic AE. This same case was classified as a new onset of an AE that was potentially immunologically mediated. The subject was [redacted] years old, female, and had an indication for HyQvia of SID. The event was a mild allergic reaction tingling of the tongue and throat, which resolved after treatment discontinuation.

For treatment emergent gastrointestinal (GI) symptoms related to HyQvia, an overall incidence rate of 0.06 per person-year (95% CI: 0.03, 0.09) and event rate of 0.51 per 100 infusions (95% CI: 0.29, 0.81) was observed. All related GI symptoms were reported in Year 1 with a per-subject event rate of 13.64 per 100 subjects (95% CI: 7.05, 23.82) or the year of study completion/discontinuation (4.72 per 100 subjects, 95% CI: 1.53, 11.01). The majority of events were mild in Year 1 and either mild or moderate in the year of completion/discontinuation.

Overall, 5 positive test results for binding rHuPH20 antibodies were observed in 3 subjects (2 subjects with PID and 1 subject with SID). Two subjects presented with 1 positive test in Year 1 (4.8%), and 1 subject presented with 1 positive test in Year 2 (2.3%) and 2 positive tests in Year 3 (3.1%). With a total of 137.96 person-years of follow-up from the first reported HyQvia infusion to the date of the last blood sample collection for rHuPh20 antibody assessment, the overall incidence rate was 0.04 per person-year (95% CI: 0.01, 0.08). Event rates were 4.72 per 100 subjects (95% CI: 1.53, 11.01) and 0.20 per 100 infusions (95% CI: 0.06, 0.46). No subjects presented with rHuPH20-reactive neutralizing antibodies during the study.

For treatment emergent local and systemic AEs, related to HyQvia, incidence rates per person-year were 0.57 (95% CI: 0.49, 0.66) and 0.42 (95% CI: 0.35, 0.50), respectively; event rates were 5.14 per 100 infusions (95% CI: 4.41, 5.97) and 3.75 per 100 infusions (95% CI: 3.12, 4.46), respectively. The annual per-subject rates of related local AEs per-subject were significantly lower in the second half of follow-up, with an event rate of 0.00 per 100 subjects (95% CI: 0.00, 122.96) in Year 5. Annual per-subject event rates of related systemic AEs decreased annually from a high of 42.05 per 100 subjects (95% CI: 29.60, 57.95) in Year 1 to 10.71 per 100 subjects (95% CI: 2.21, 31.31) in Year 4 and 0.00 per 100 subjects (95% CI: 0.00, 122.96) in Year 5, though the overall change was not significant. For both safety outcomes, the highest annual per-subject event rates in each year were observed for AEs classified as mild in severity.

Treatment Regimen

The total duration of exposure to HyQvia was 302.35 person-years. The total mean duration of HyQvia exposure was 2.85 (SD=1.495) years, with a range of 0.02–5.22 years. Of the 3363 HyQvia infusions reported during the study, the most common infusion interval was 4 weeks (n=1411, 42.0%), with a total observation time of 113.65 person-years. Overall, 94.2% of HyQvia infusions were administered at home.

The mean planned IG dose per 4 weeks was 0.5 (SD=0.17) g/kg/4 weeks at enrollment, and the mean planned volume of rHuPH20 per administration was 18.4 (SD=12.21) mL at enrollment, with no substantial changes in planned dose observed over the follow-up years. The actual mean administered IG dose per 4 weeks was 362.1 (SD=216.46) mg/kg/4 weeks overall and increased annually from 334.1 (SD=218.03) mg/kg/4 weeks at first treatment to 405.4 (SD=251.95) mg/kg/4 weeks after Year 3. The mean administered volume of rHuPH20 was 15.99 (SD=5.162) mL during the study.

The mean infusion duration was 2.7 (SD=0.70) hours by using a mean number of infusion sites of 1.1 (SD=0.35). The actual mean maximum IG infusion rate was 238.7 (SD=65.53) mL/h during the study. The infusion rate was changed or infusion was interrupted due to an AE in 0.4% (n=15) of all infusions reported during the study. Most of the changes/ interruptions were observed in the first year of HyQvia treatment. Of the 0.6% of all doses not administered as planned (n=20), 4 were due to AEs in the first and second years following the first reported HyQvia treatment.

Health-Related Quality of Life and Health Resource Utilization

Results from the Short Form-36 version 2 indicated both physical and mental health component summary scores were stable over time. Mean global satisfaction scores for HyQvia treatment increased over time from 72.1 (SD=18.93) at baseline to 76.9 (SD=22.43) at Year 4. Euro Qol-5 Dimension (EQ-5D) results showed that the proportion of subjects with some problems in mobility, self-care, usual activities, and pain/discomfort slightly decreased over time from baseline to the completion visit, while the proportion of subjects reporting some problems in anxiety/depression increased between baseline and study completion. Of those who completed the EQ-5D visual analogue scale, mean scores were slightly higher upon study completion (66.5 [SD=18.56]) than at baseline (65.0 [SD=20.56]). Lastly, results of the Treatment Satisfaction Questionnaire for Medication-9 pertaining to mean effectiveness scores, convenience scores, and global satisfaction scores did not differ substantially over the course of the study.

There were 33 subjects hospitalized (n=69 total all-cause hospitalizations) with an event rate of 0.22 per person-year (95% CI: 0.17, 0.28); 32 hospitalizations were due to infections. Thirty-two subjects spent 807 days in the hospital for all-cause hospitalizations (n=68), yielding a rate of 2.59 per person-year (95% CI: 2.42, 2.78). One subject experienced 1 hospitalization for which the total number of days in the hospital could not be calculated. There were 33 subjects with 195 acute care visits, the event rate of which was 0.63 per person-year (95% CI: 0.54, 0.72). Nineteen subjects had 35 emergency room visits, corresponding to an event rate of 0.11 per person-year (95% CI: 0.08, 0.16). For the 27 subjects who missed 1996 days of school/work, the event rate of missed days was 6.41 per person-year (95% CI: 6.13, 6.70).

Discussion

The study findings presented in this report support the conclusion that long-term repeated self-administration of HyQvia is safe in adult patients with PID with up to 5.22 years of follow-up. The present study has been the longest follow-up with any subcutaneous IgG replacement treatment of PID to date, with 302.35 total person-years of exposure to HyQvia observed. All SAEs were reported unrelated to HyQvia with the exception of 1 non-fatal SAE. Incidence rates of related treatment emergent local and systemic AEs were low (local: 0.57 per person-year; systemic: 0.42 per person-year). The development of antibodies against rHuPH20 is rare, and no neutralizing antibodies were detected in the study, consistent with previous HyQvia studies. Although observed HyQvia doses were lower than in previous HyQvia trials, the incidence rate of treatment emergent infections was not higher than reported in published research (1.32 per person-year). There were no reports of anaphylaxis/anaphylactoid reactions requiring emergency treatment. The infusion rate was changed or the infusion was interrupted due to an AE in 0.4% of the reported infusions and gradually decreased over the years. These long-term safety data show that HyQvia can be administered safely at home. The most common dosing interval was 4 weekly, which is in line with product labeling. The results of this study confirm the known safety profile of HyQvia, and provide valuable insights into HyQvia treatment and product administration in European settings.

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