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Human Medicines Division

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

HyQvia

Human normal immunoglobulin

Procedure no: EMA/PAM/0000332896

Note

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

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Abbreviations

AE	adverse event
BMI	Body Mass Index
b.w.	body weight
CVID	common variable immunodeficiency
FAS	full analysis set
fSCIG	facilitated subcutaneous immunoglobulin
IG	immunoglobulin
IVIG	intravenous immunoglobulin
Ig20Gly	Glycine-stabilized 20% human subcutaneous immunoglobulin solution
PID	primary immunodeficiency
PY	patient-year
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SCIG	subcutaneous immunoglobulin

1. Introduction

On 13 February 2026, the MAH submitted a completed paediatric study for HyQvia, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1 Information on the development program

The MAH stated that study PID-4001 (IG-TATRY) is a stand-alone study.

2.2 Information on the pharmaceutical formulation used in the study

HyQvia is 10% immunoglobulin (IG) with recombinant human hyaluronidase (rHuPH20). IG, 10% with rHuPH20 is a dual vial unit consisting of one vial of a liquid solution containing 100 mg/mL protein of which at least 98% is IgG and one vial of a liquid solution containing rHuPH20. HyQvia was administered in accordance with the Summary of Product Characteristics (SmPC; versions 03/2017; 07/2018, 01/2020 and Product Information (PIL) update 04/2020). There is no paediatric formulation for HyQvia.

Administration involved an initial dose of rHuPH20, followed by 10% IG. Dosing was based on body weight and adjusted to clinical response. No specific dose adjustments were required for the paediatric population.

2.3 Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- PID-4001 (IG-TATRY)

2.3.2. Clinical study

PID-4001 (IG-TATRY)

Description

Study PID-4001 (study acronym: IG-TATRY) was a retrospective, multicenter, observational study designed to document the management and clinical outcomes of Cuvitru (SCIG 20%) and HyQvia (fSCIG) use in paediatric patients (<18 years) with primary immunodeficiencies (PID) based on real-world data. This report focuses on participants that were treated with HyQvia (fSCIG). Data from patients' medical charts were collected during a period of 3 months between 28 January 2021 and 02 February 2022. Patients <18 years old with a diagnosis of PID (according to the criteria developed by the European Society for Immunodeficiencies [ESID]).

Methods

Study participants

A total of 28 patients treated with HyQvia participated in the study. Median IgG serum concentration was measured at four different time intervals after HyQvia administration: days 1-7 (2 measurements), 8–14 (12 measurements), 15–21 (10 measurements), and 22–28 (51 measurements).

Study design

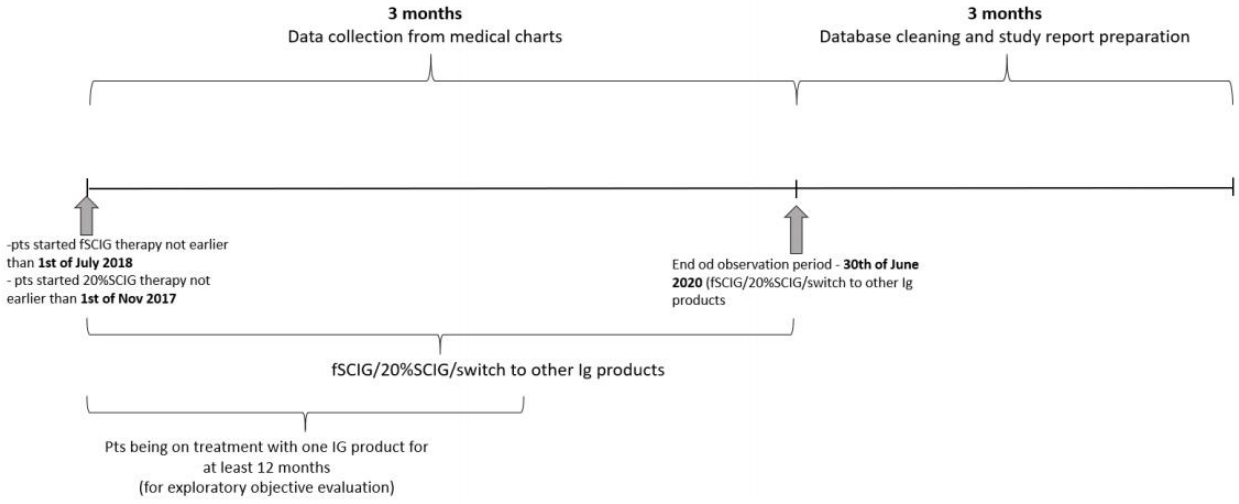
IG-TATRY is a retrospective, multicenter, observational study designed to document the management and clinical outcome of Cuvitru (SCIG 20%) and HyQvia (facilitated SCIG, fSCIG) use in paediatric patients with PID based on real-world data. Data collection from patient medical charts lasted for 3 months after the study initiation and followed by database cleaning, data analysis, and clinical study report (CSR) preparation.

This study is a 'non-interventional study' as defined in Directive 2001/20/EC (10) and follows the guidelines for GPP.

This means that:

- The assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice,
- No additional diagnostic or monitoring procedures shall be applied to the patients,
- Epidemiological methods shall be used for the analysis of collected data,
- SCIG 20%/fSCIG is prescribed in accordance with the terms of the marketing authorisation,
- The prescription of SCIG 20%/fSCIG is clearly separated from the decision to include the patient in the study.

Figure 1: Study design



Treatment

HyQvia was administered according to the summary of product characteristics. The HyQvia subgroup of the study included 28 paediatric patients (23 started on fSCIG and 5 switching from other therapies) aged <18 years. Full details are provided in the PID-4001 study report. The dose is calculated based on patient weight and clinical response. There is no dose adjustment for the paediatric population. Please refer to the currently approved Summary of Product Characteristics.

Objective(s)

The primary objectives of the study were:

• To determine treatment patterns: dose per month and per infusion, infusion volume per site and in total, treatment interval, infusion rate, site of injection, method of administration (pump/rapid push), length of needle, site of care (hospital/home), person who performs infusion – patient or parent/guardian, type of pump (if applicable),

• To determine clinical characteristics of paediatric patients with PID including PID diagnosis (PID type), reason to switch (if applicable), concomitant diseases, and concomitant medication.

The secondary objectives of the study were:

• To determine mean IgG through serum levels depending on the dose intervals,

• To determine the treatment pattern of IgG replacement therapy i.e. patient flow relating to the IgG product (SCIG 20%, fSCIG or other), and IgG replacement discontinuation or Interruption.

The exploratory objectives of the study were:

• To determine the number of serious bacterial infections (SBI) and the overall number of infections based on data collected from a subgroup of patients being on Ig treatment for at least 12 months,

• To assess the number of visits, hospitalisations or emergency room (ER) visits due to infection/symptoms exacerbation.

Outcomes/endpoints

Primary endpoints analysis

- The following data are summarised in tabular and graphical form to determine treatment patterns:
- Dose received monthly (g/kg),
- Infusion volume per site and in total,
- Treatment interval between doses,
- Infusion rate,
- Site of injection,
- Method of administration,
- Length of needle,
- Site of care,
- Person who performs infusion,
- Type of pump (if applicable)

Secondary endpoints analysis

- IgG level
- IgG replacement therapy

Sample size

There is no predefined sample size, and all data entered IG-TATRY study database were considered for analytical purposes. Alternative analyses may employ sample sizes based upon subpopulations.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Statistical significance level was set to level 0.05. P-values ≥0.001 are reported to 3 decimal places; p-values less than 0.001 are reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, are reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) are reported to 3 significant figures. For purpose of this analysis, treatment groups are defined based on first immunoglobulin replacement therapy – either HyQvia or Cuvitru or, when applicable patients after switching to medication. Further statistical analysis specifications are included in the Study report.

Results

Participant flow

A total of 28 paediatric patients treated with HyQvia were enrolled in the study. Of the 28 patients, 23 received HyQvia from the beginning and 5 patients changed treatment to HyQvia during the study. During the observation period, 2 patients transitioned to Cuvitru due to a limited availability of HyQvia and 3 patients discontinued the study early (n = 2 due to local side effects after transitioning to Cuvitru and n = 1 due to transition to a treatment center for adults). A total of 25 patients treated with HyQvia completed the study according to the protocol. All patients were included in the FAS analysis.

Recruitment

All patients or, when applicable, their legally acceptable representatives, signed an informed consent form (ICF) and data privacy authorisation prior to study enrollment. Patients who were enrolled in the HyQvia subgroup received treatment with fSCIG between 1 July 2018 and 30 June 2020.

Baseline data

In the full analysis set (FAS), the median age was 9.0 years old (the youngest participant was 14 months old and the oldest 17.0 years old). By age group, 21 (75%) participants were 12 years old or younger, and 7 (25%) participants were above 12 years old.

There were 22 (78.6%) male participants and 6 (21.4%) female participants. The median weight (n = 28) was 32.0 kg (range: 8.4 – 83.0) and the median z-score (n = 18) for weight deviation from the weight-for-age tables was 0.0 (range: - 1.7 – 2.4) (not applicable in the older group). The median height (n = 27) in the FAS was 137.5 cm (range: 74.0 – 180.0) and the median z-score (n = 27) for height deviation from the height-for-age tables was 0.1 (range: -1.6 – 2.6). Based on BMI (n = 27), 6 (22.2%) participants were overweight, and 21 (77.8%) participants had normal weight.

Number analysed

There is no predefined sample size, and all data entered into IG-TATRY study database were considered for analytical purposes. Alternative analyses may employ sample sizes based upon subpopulations. Statistical analysis was performed after closing the database. Due to the fact that the conducted study is a retrospective study, only one population was analysed.

Efficacy results

<u>Treatment patterns</u>

The full treatment details are provided in the PID-4001 study report, Section 7.3.

During the study, the median duration of HyQvia treatment was 15.1 months (range: 3.4 – 21.8). During the observation period, several patients changed their treatment. Change from HyQvia to Ig20Gly (Cuvitru) in 4 patients was due to limited availability of fSCIG, side effects or transition from paediatric to adult treatment center. Change from Ig20Gly to HyQvia in 7 patients (including 2 patients who were initially on HyQvia and transitioned back) was due to a reduction of infusions per month.

The median number of infusions was 1 infusion/month (range: 1.0 – 1.5) with the median infusion volume per site of 124.8 ml (range: 34.7 –300.0). The most common injection site was abdomen in 25 (89.3%) patients with a median injection volume of 139.7 ml (range: 34.7 – 300.0). All infusions were performed using a pump (n = 28), and most infusions were performed with a 9 mm needle (57.1%, n = 16). Treatment ramp-up phases were performed in 18 (64.3%) patients. The median initial dose of HyQvia was 0.2 g/kg b.w. (range: 0.1 – 0.4); the median final dose was 0.4 g/kg b.w. (range 0.2 – 0.7). The median infusion volume increased from 100 ml (range: 25.0 – 150.0) to a median volume of 150 ml (range: 75.0 – 300.0). The median infusion rate increased from an initial median value of 10 ml/h (range: 5.0 – 30.0) to a final median rate of 120 ml/h (range: 60.0 - 300.0).

Clinical characteristics of paediatric patients with PID

The most common PID diagnosis in the FAS was agammaglobulinaemia (32.1%, n = 9), common variable immunodeficiency (CVID) (32.1%, n = 9) and hypogammaglobulinaemia (25%, n = 7). The median age at diagnosis was 4.0 years old (range: 0.0 – 14.0) with the median disease duration until study enrolment of 6.0 years (range: 2.0 – 14.0). Prior to HyQvia, 24 (85.7%) participants received IG treatment. PID diagnosis was reported in first-degree relatives in 5 (17.9%) participants.

The full details of patient characteristics are provided in the PID-4001 study report, Section 7.2.

No new information related to treatment effectiveness is provided in this document.

Safety results

A summary of the safety analysis of HyQvia in study PID-4001 is presented here. A summary of bacterial infections reported during the study is provided in Table 1. No serious bacterial infections (SBIs) occurred. 13 patients experienced 83 non-serious infection episodes (1.88 per patient year). The mean duration of antibiotic therapy due to bacterial infections was 12.8 days (SD: 17.1). No hospitalisations were reported.

Table 1: Bacterial and serious bacterial infections after initial treatment – Full analysis set

Parameter	Overall, N=28	Age 12 or less, N=21	Age above 12, N=7
Number of patients	0		
patient-years of therapy [1]	0		
Non-serious infections			
Number of patients	13	11	2
Number of BI	83	70	13
patient-years of therapy [1]	1.88	2.13	1
Parameter	**Overall, N=16**	**Age 12 or less, N=13**	**Age above 12, N=3**
Time of antibiotic therapy [days]			
Number of patients	11	9	2
patient-years of therapy [2]	12.8 (17.1)	9.6 (10.6)	27.5 (38.9)
Hospitalization time [days]			
Number of patients	0	0	0
mean (SD)	-	-	-

Note:

[1] patient-years calculated for the total sum of HyQvia treatment duration

[2] patient-years calculated for the sum of HyQvia treatment duration among patients longer than 365 days on therapy

Table presents data only for patients who were on treatment longer than 365 days.

Source: PID-4001 study report, Table 38

Only one adverse event (AE), a general disorder and administration site condition, was reported during the study among patients treated with HyQvia and was classified as non-serious ADR. The patient did not recover until the end of the study. No serious adverse events (SAE) were reported. No SBIs and 83 non-SBIs (bacterial infections, BI) were reported. An incidence of non-SBIs was 1.88 infections/patient year (PY) with a mean duration of antibiotic therapy of 12.8 days. There was one AE reported: non-serious and related to study medication.

Administration of HyQvia was consistent with the local label, safe, and well tolerated in Polish paediatric patients with PID. The incidence rate of bacterial infections was consistent with the existing safety profile of HyQvia. Only one ADR was reported. In summary, this study supports the feasibility of administering HyQvia to children and adolescents with PIDs every 3–4 weeks using a single infusion site and indicates flexibility in modifying infusion parameters.

2.3.3. Discussion on clinical aspects

The aim of study PID-4001 (study acronym: IG-TATRY) was to document the management of both Cuvitru (SCIG 20%) and HyQvia (fSCIG) use in 28 paediatric patients with primary immunodeficiencies (PID). This was a retrospective, observational study, and results are based on real-world data. The primary objectives were to determine treatment patterns and clinical characteristics of the study population. Secondary objectives included the determination of IgG trough levels depending on dose intervals and of treatment pattern of IgG replacement therapy. Exploratory objectives were the determination of the number of SBI and overall infections as well as possible hospitalisations or ER visits due to infections. HyQvia was administered according to the summary of product characteristics. IgG concentration values differed based on diagnosis, serum IgG levels across PID diagnoses in the study population were available for the time interval of 22–28 days after HyQvia administration. The median IgG concentration ranged between 7.0 and 9.1 g/l and was thus above the minimum recommended trough level. Most of the enrolled patients received HyQvia during the study and completed it. The clinical characteristics of the study population are considered representative, and treatment patterns were in line with HyQvia labelling. It is concurred that the study results support the use of HyQvia in the paediatric population according to the labelling. Change of the infusion site was

not indicated as the treatment was well tolerated. During the observation period, no SBIs and no hospitalisations or emergency room visit were reported. The overall annualised rate of infection was lower compared to the pivotal study 160603 and is generally below or around reported averages in this population, thus within the expected range. The incidence of adverse events was very low as only one AE was reported.

3. CHMP overall conclusion and recommendation

It is concurred that the treatment with HyQvia in the investigated paediatric study population with PID every 3 to 4 weeks was consistent with the label and well tolerated.

☒ **Fulfilled**

No regulatory action required.