30 May 2024
EMA/285123/2024
Human Medicines Division

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

Firazyr

Icatibant

Procedure no: EMEA/H/C/000899/P46/036

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	01 Apr 2024	01 Apr 2024	☐
☐	CHMP Rapporteur Assessment Report	06 May 2024	22 Apr 2024	☐
☐	CHMP members comments	21 May 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	n/a	☐
☒	CHMP adoption of conclusions:	30 May 2024	30 May 2024	☐

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

HAE	hereditary angioedema
HRQoL	health-related quality of life
INH	inhibitor
MCR	medical chart review
SD	standard deviation

1. Introduction

On 12-MAR-24, the MAH submitted a completed paediatric study for Firazyr, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Study TAK-743-4009 was completed on 13 Jan 2023. Takeda acknowledges the submission of the final study results for TAK-743-4009 is not in line with the requirements of Article 46 of the Regulation (EC) 1901/2006. The delay in having this submission completed is due to insufficient oversight of regional and local clinical trials and narrowed training on Article 46 requirements. Corrective actions are in process. Preventative actions have been put in place to strengthen internal processes, to train relevant stakeholders in the organisation on paediatric requirements and to monitor studies in scope of Article 46. Takeda is committed to proactively monitoring upcoming studies including paediatric patients to support timely submission of the CSR per Article 46 timelines.

Assessor's comment

The MAH informs that the submission of the p46 was delayed due to insufficient global oversight of regional and local clinical trials and narrowed training on Article 46 requirements, and that corrective actions are in process.

This is acknowledged and no other actions are considered warranted.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *Study TAK-743-4009 (A Retrospective Observational Chart Review Study Evaluating the Burden of Illness and Treatment Patterns in Hereditary Angioedema Type I and II)* is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study was performed in a post-marketing setting using commercial Firazyr.

2.3. Clinical aspects

Firazyr (icatibant) is authorised since 2008 in European Union for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency. In 2017, the indication was extended to adolescents and children aged 2 years and older.

Icatibant is a selective competitive antagonism at the bradykinin type 2 (B2) receptor.

2.3.1. Introduction

The MAH submitted a final report for:

- ***TAK-743-4009:*** *A Retrospective Observational Chart Review Study Evaluating the Burden of Illness and Treatment Patterns in Hereditary Angioedema Type I and II*

The study is not part of any PIP of Firazyr.

Assessor's comment

Since this is a p46 procedure for a Phase 4 non-interventional study that is not part of the EU RMP, only the paediatric data are assessed.

2.3.2. Clinical study

Description

TAK-743-4009 was an observational, multi-country, historical cohort study conducted via medical chart review (MCR) of patients ≥12 years of age with inadequately controlled HAE type I or type II, including a 1-time cross-sectional health-related quality of life (HRQoL) data collection component. The study took place in 20 countries across Europe, Canada, and Israel.

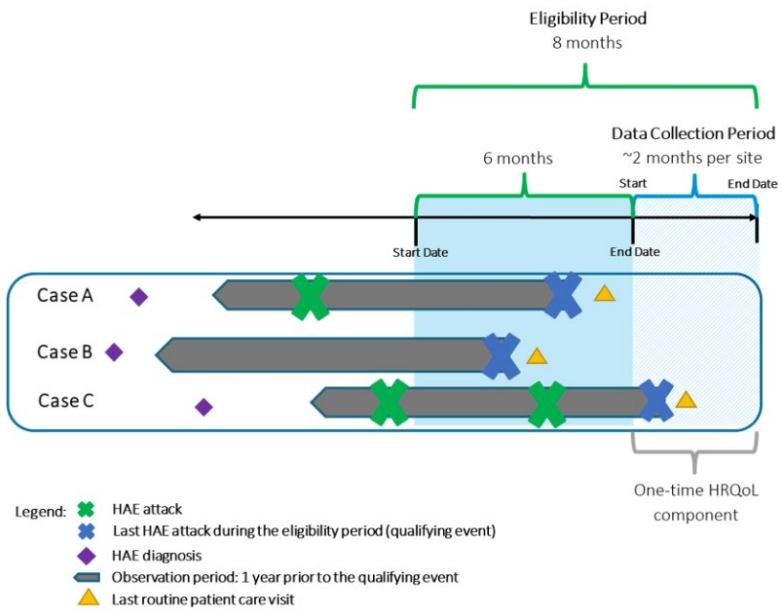
Information pertaining to patient care was already documented in patient medical records at the time of chart abstraction.

De-identified data on patient demographics, HAE medical history and information on diagnostics, treatments and disease course assessments that are routinely performed in accordance with current guidelines and/or local standard of care were collected from patient medical records and entered into an electronic data capture system.

Historic medical chart data collection was anchored to the patient's last documented HAE attack within the eligibility period (defined as the qualifying event) and spanned one year prior to the qualifying event (defined as the observation period). The eligibility period covered the previous six months from the start of data collection and, if applicable, the two-month data collection period (if the qualifying event was recorded within the data collection period, the patient was considered eligible, provided all the other selection criteria were met).

A schematic view of the study is given in Figure 1.

Figure 1: Study Design Schematic



Methods

Study participants

Inclusion Criteria: Patients were included in the study if they were 12 years or older at the time of the last documented HAE attack during the eligibility period, had a physician-confirmed diagnosis (or confirmation available in their medical records) of HAE type I or type II, had at least one documented HAE attack during the eligibility period, was not adequately or was sub- optimally controlled per their treating physician, and had provided consent or assent, as applicable (where required by local regulations).

Exclusion Criteria: Patients were excluded from the study if they were enrolled in a therapeutic investigational drug or device trial during the observation period or had initiated long-term prophylaxis with lanadelumab at any point after their diagnosis.

Treatments

This was a retrospective, observational study with no impact on dosing.

Objective(s)

Primary objectives were to characterise the clinical course, management, and treatment as follows:

1. Evaluate HAE attack characteristics in terms of frequency, location affected and severity
2. Describe the use of HAE prophylaxis and on-demand medications and their patterns of prescription

Secondary objectives were to:

3. Quantify healthcare resource utilisation (HRU), including the rates of visits to healthcare professionals (HCP) and visits to emergency rooms/emergency departments (ER/ED), and hospitalisations related to HAE
4. Obtain evidence from subgroups of patients having different disease activity patterns and associated burden
5. Describe the health-related quality of life (HRQoL) of patients

Sample size

Since the primary objective of this study was descriptive with no hypothesis testing, the sample size consideration was based on the precision of the primary objective (number of HAE attacks from at least once a week to less than once a month). Assuming enrolment of 210 patients as per protocol, a precision estimate of 17.8% to 29.1% on two-sided 95% confidence intervals (CIs) was expected assuming the event rate was 23% (HAE attacks at least once a week). The final study population included 214 patients.

Statistical Methods

Analyses were primarily descriptive.

Results

In total, 216 patients were enrolled and had their medical chart abstracted. Of these. Six subjects were < 18 years of age.

Only data for the paediatric subpopulation are presented.

Baseline data

The mean (standard deviation, SD) age of paediatric patients treated with Firazyr at the time of the qualifying event was 16.5 (2) years.

There were 3 male and 3 female patients.

The mean (SD) duration of disease was 10.38 (2.7) years.

All 6 patients had type I HAE and 4 (66.7%) patients had a family history of HAE and all 5 patients who had functional C1-INH testing had baseline levels below the normal range.

All 6 paediatric patients reported multiple reasons for inadequate control of HAE disease symptoms and disease control status. Reasons included frequency of HAE attacks (5 patients, 83.3%); impact on quality of life (5 patients, 83.3%); attacks impacted ability to attend school or work (4 patients, 66.7%); severity of HAE attacks (3 patients, 50.0%); disease control could be improved (3 patients, 50.0%); attacks that required additional visits to the clinic, emergency room, or hospitalization (2 patients, 33.3%); experienced unexpected triggers of attacks (2 patients, 33.3%); insufficient efficacy of current treatment (1 patient, 16.7%); high doses of current treatment required (1 patient, 16.7%); and side effects of long-term prophylaxis treatment (1 patient, 16.7%).

Efficacy results

This retrospective study had no efficacy objective and therefore efficacy data were not collected. A summary of the research objectives is presented below.

HAE Treatment History

Among the 6 paediatric patients treated with Firazyr, 1 patient reported using 1 or more long-term prophylactic therapies prior to the index event, including danazol, tranexamic acid, and Berinert. The mean (SD) duration of time on each therapy was 3.6 (2.3) months. All 6 patients used one or more on-demand treatment; 5 patients (83.3%) used on-demand treatment without long-term prophylaxis and 1 patient (16.7%) used on-demand treatment in addition to long-term prophylaxis. Of the 6 paediatric patients treated with Firazyr as on-demand therapy, 2 (33.3%) patients also used Berinert.

HAE Attack Characteristics

Among the 6 paediatric patients treated with Firazyr, 71 HAE attacks were reported during the observation period (12 months) with a mean (SD) of 11.8 (18) attacks. Four (66.7%) patients experienced 1 to 5 attacks, 1 (16.7%) patient experienced 6 to 10 attacks, and 1 (16.7%) patient experienced 41 to 50 attacks during the observation period; 5 (83.3%) patients had less than 1 attack per month and 1 (16.7%) patient had 3 or more attacks per month. No life-threatening attacks were reported, and most attacks were mild or moderate in severity; 4 (66.7%) patients had mild attacks, 5 (83.3%) patients had moderate attacks, and 3 (33.3%) patients reported severe HAE attacks during the observation period.

The mean (SD) duration of HAE attacks was 1.7 (1) days. All 6 paediatric patients reported multiple trigger factors with a mean (SD) of 4.2 (3) trigger factors. These factors included mental stress (6

patients, 100%), physical exertion (4 patients, 66.7%), mechanical trauma (4 patients, 66.7%), infection (3 patients, 50.0%), menstruation (3 patients, 50.0%), dental procedures (2 patients, 33.3%), fatigue/exhaustion (1 patient, 16.7%), medical procedures (1 patient, 16.7%), and oestrogen-containing oral contraceptive use (1 patient, 16.7%). All 6 paediatric patients had 2 or more HAE attacks that required on-demand treatment. The mean (SD) number of attacks that required on-demand treatment was 10.5 (17).

Hereditary angioedema attacks during the observation period affected several body parts including abdominal (6 patients, 100%); peripheral extremities (4 patients, 66.7%); laryngeal/pharyngeal (3 patients, 50.0%); facial (2 patients, 33.3%); genital (2 patients, 33.3%); cutaneous, head, or trunk (each reported in 1 patient, 16.7%); and 1 patient reported an unknown body part that was affected by an HAE attack.

During the observation period, 5 (83.3%) patients had at least 1 HAE attack with prodromal symptoms. The mean (SD) number of attacks with prodromal symptoms was 9.8 (19). Four (66.7%) patients had 2 or fewer attacks with prodromal symptoms and 2 (33.3%) patients had 5 or more attacks with prodromal symptoms. Prodromal symptoms included nausea (4 patients, 66.7%), fatigue (2 patients, 33.3%), malaise (2 patients, 33.3%), erythema marginatum (2 patients, 33.3%), muscle aches (1 patient, 16.7%), and symptom(s) of unknown type (1 patient, 16.7%).

Healthcare Resource Utilization

During the 1-year observation period, all 6 paediatric patients treated with Firazyr visited a primary care HAE specialist at least once. The mean (SD) number of visits during the observation period was 2.5 (2). All patients had a planned visit for routine HAE consultation/management and 2 (33.3%) patients also reported unplanned visits; 1 (16.7%) patient for emergency HAE consultation and 1 (16.7%) patient for an HAE-related phone consultation. During the observation period, 1 patient was referred to a gastroenterologist to manage abdominal pain symptoms.

There were no HAE attack-related hospitalizations during the observation period; 1 patient had 2 HAE attack-related emergency room visits for observation after using on-demand therapy for HAE attacks with upper-airway symptoms.

EQ-5D-5L and EQ-5D-Y

The patient-reported EQ-5D-5L questionnaire was completed by 3 of the paediatric patients treated with Firazyr. These 3 patients were over 18 years old at the time the questionnaire was completed but below 18 years old when treated with Firazyr. Of the 3 patients, 2 (66.7%) patients reported slight problems with pain/discomfort, 1 (33.3%) patient reported severe problems with pain/discomfort, 1 (33.3%) patient reported moderate problems with mobility, 1 (33.3%) patient reported slight problems with usual activities, 1 (33.3%) patient reported extreme problems with usual activities, and 1 (33.3%) patient reported each of slight, moderate, or severe problems with anxiety/depression. No patients reported any problems with self-care.

The patient-reported EQ-5D-Y questionnaire was completed by 2 paediatric patients who were treated with FIRAZYR. For individual questions, no patient reported major issues for any of the 5 categories.

Safety results

Not applicable. This retrospective study had no safety objective and therefore adverse events were not collected.

2.3.3. Discussion on clinical aspects

TAK-743-4009 was an observational, multi-country, historical cohort study conducted via medical chart review (MCR) of patients ≥12 years of age with inadequately controlled HAE type I or type II. Six subjects aged 12-<18 years were enrolled in the study.

Since this is a p46 procedure for a Phase 4 non-interventional study that is not part of the EU RMP, only the paediatric data are assessed.

This retrospective study had no efficacy objective and therefore efficacy data were not collected. A summary of the research objectives (Baseline demographic data, HAE Treatment History, HAE Attack Characteristics, Healthcare Resource Utilization, and health-related quality of life [HR-QoL]) was presented.

The study had no safety objective and therefore adverse events were not collected.

No new and unexpected data emerged from the very limited paediatric subpopulation of study TAK-743-4009. The MAH considers no additional actions warranted. This is fully agreed.

3. Rapporteur's overall conclusion and recommendation

No new and unexpected data emerged from the very limited paediatric subpopulation of study TAK-743-4009. The MAH considers no additional actions warranted. This is fully agreed.

The benefit/risk ratio for the Firazyr remains unchanged.

☒ **Fulfilled:**

No regulatory action required.