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SCIENCE MEDICINES HEALTH

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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/P46/035

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 12 December 2022, 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.

2. Scientific discussion

2.1. Information on the development program

TAK-667-3001*: A Multicenter, Open-Label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema* is a standalone study in EU but part of the paediatric clinical development programme in Japan.

2.2. Information on the pharmaceutical formulation used in the study

Icatibant in a syringe (10 mg/mL) was administered as subcutaneous injection.

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 final report for:

- **TAK-667-3001**: A Multicenter, Open-Label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

The submitted study was conducted in Japan to support the use in paediatric patients aged 2 years and older with HAE. This paediatric indication was authorised on 24 August 2022.

The study was completed on 26 July 2021

2.3.2. Clinical study

Description

This was a multicenter, open-label, phase 3 study to evaluate the safety, efficacy and PK of SC administration of icatibant in Japanese children and adolescents from 2 to less than 18 years of age with acute attacks of HAE.

Subjects eligible at pre-treatment physical examination and assessment received treatment with single-dose SC administration of icatibant per attack according to the subject's body weight within 12 hours after the onset of symptom.

During the study, subjects were closely monitored in the hospital/study center for at least 8 hours after administration of icatibant and received physical examinations and assessments to evaluate safety, efficacy and PK. After discharge, follow-up to assess the subject's condition at >24-48 hours after final administration (Day 2) was conducted via a telephone call by investigators and follow-up of safety assessments were conducted 7 days after initial administration of icatibant (Day 8) at the study site.

After having received initial treatment with icatibant, subjects who subsequently experienced an acute attack continued to receive treatment with icatibant for up to a total of 3 eligible icatibant-treated attacks.
The study ended when at least 3 subjects were enrolled and/or when the planned enrolment period was completed.

Methods

Study participants

Japanese children and adolescents (2 to 17 years of age, inclusive, at the time of informed consent) with acute attacks of hereditary angioedema type I or type II.

Treatments

Up to 30 mg Icatibant in a syringe (10 mg/mL) was administered as subcutaneous injection using a five-weight-band dosing.

The dosing is the same as the approved dosage and administration in the EU.

Objective(s)

To evaluate the safety, efficacy and PK of icatibant for the treatment of acute attacks in Japanese children and adolescents with type I or type II HAE

Outcomes/endpoints

Primary Endpoint

Frequency and severity of treatment-emergent adverse events (TEAEs), including injection site reactions

Secondary Endpoints

Secondary safety endpoints included electrocardiogram parameters, vital signs, Clinical laboratory parameters and immunogenicity (presence of anti-icatibant antibodies).

Secondary efficacy endpoints included time to onset of symptom relief and time to minimal symptom (several parameters studied), scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score, subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R) (4-17 years), investigator assessment of HAE-related pain using the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale (2-<4 years), incidence of rescue medication use and the proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC icatibant using investigator-rated symptom scores.

Secondary pharmacokinetic endpoints included plasma concentrations of icatibant and its major metabolites at 0.5, 1.0, 2.0, and 4.0 hours after the first SC injection for an initial attack.

Sample size

The planned sample size chosen of 3 subjects was based on the feasibility and was not statistically determined.

Although there had been no accurate reports regarding the number of paediatric HAE patients in Japan, it was estimated approximately 30 to 50 patients based on the population estimate and the percentage of children among Japanese HAE patients confirmed in the latest Japanese HAE survey. However, comprehensive feasibility assessment for medical institutions across Japan found much less candidate subjects and only few clinical sites were able to conduct the study due to some hurdles in implementation. In addition, considering a difficulty to obtain informed consent in a paediatric study, the number of patients to be enrolled was assumed to be 3.

Randomisation and blinding (masking)

N/A

Statistical Methods

Due to the small sample size, no statistical inferences (statistical test nor confidence interval) were performed

Results

Participant flow

Screened: 6 subjects

Enrolled: 2 subjects

Treated with at least one dose of icatibant: 2 subjects

HAE attacks treated during study: 4 (1 and 3 attacks, respectively, for the two participants)

Baseline data

Both subjects were 1-2 years of age at first HAE symptom. Time since last attack at first treatment was 2 and 3 months respectively for the two subjects.

Efficacy results

Both subjects experienced symptom relief and achieved minimum symptoms:

Time to onset of symptom relief by an investigator-rated symptom score was 0.9 hour for Subject #001 and 1.0 hour for Subject #002 (all three attacks).

Time to onset of symptom relief by Faces Pain Scale-Revised (FPS-R) was 0.9 hour for Subject #001 and 1.0 hour for Subject #002 (all three attacks).

Time to minimal symptoms by an investigator-rated symptom score was 0.9 hours for Subject #001 and 1.0 hour for Subject #002 (all three attacks).

Time to minimal symptom as assessed by the FPS-R was 0.9 hour for Subject #001 and 1.0 hour for Subject #002 (all three attacks).

Neither subject used rescue medication during the study period.

Safety results

There were no TEAEs except for injection site reactions in this study. Subject #001 and #002 developed mild to moderate injection site reactions and they had resolved by the time of the assessment at discharge.

There were no deaths, no treatment-emergent SAEs, and no discontinuations due to a TEAE in this study.

Pharmacokinetic results

Subject #001 was administered icatibant at a dose of 25 mg. Plasma concentrations of icatibant at 0.5, 1.0, 2.0, and 4.0 hour post-first dose were 962, 856, 401 and 68.9 ug/L, respectively. Plasma concentrations of metabolite M-I were 106, 187, 220 and 137 ug/L and plasma concentrations of metabolite M-II were 103, 184, 227 and 151 ug/L, respectively.

Subject #002 was administered icatibant at a dose of 15 mg. Plasma concentrations of icatibant at 0.5, 1.0, 2.0, and 4.0 hour post-first dose were 978, 882, 410 and 38.8 ug/L, respectively. Plasma concentrations of metabolite M-I were 103, 223, 247 and 124 ug/L, and plasma concentrations of metabolite M-II were 116, 216, 276 and 147 ug/L, respectively.

2.3.3. Discussion on clinical aspects

Firazyr 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.

The MAH has submitted the final study report from study TAK-667-3001. The study enrolled Japanese children and adolescents (2 to 17 years) with acute attacks of hereditary angioedema (HAE) type I or type II and was part of the paediatric clinical development programme in Japan. The primary objective was safety.

Due to feasibility issues, the study had a planned study size of at last 3 screened subjects. During the study, 2 subjects were treated for in total 4 HAE attacks (1 and 3 attacks, respectively).

Both subjects responded to treatment with Firazyr within 0.9 and 1 h, respectively, and no rescue medication was used. Both subjects reported transient injection site reactions. Except from this, there were no deaths, no treatment-emergent SAEs, no additional TEAE and no discontinuations due to a TEAE in this study. Observed concentrations were within previously reported exposure ranges, where safety and efficacy have been established.

3. CHMP overall conclusion and recommendation

No indication of lack of efficacy and no new and unexpected safety issues emerged from the extremely limited Study TAK-667-3001 in Japanese children from the age of two years and adolescents with Hereditary angioedema.

The benefit/risk ratio for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase-inhibitor deficiency remains unchanged.

☒ **Fulfilled:**

No regulatory action required

4. Request for supplementary information

Not applicable