21 March 2024
EMA/153700/2024
Human Medicines Division

Assessment report

TAKHZYRO

International non-proprietary name: Lanadelumab

Procedure No. EMEA/H/C/004806/P46/008

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	22 Jan 2024	22 Jan 2024	☐
☐	CHMP Rapporteur Assessment Report	26 Feb 2024	22 Feb 2024	☐
☐	CHMP members comments	11 Mar 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	14 Mar 2024	n/a	☐
☒	CHMP adoption of conclusions:	21 Mar 2024	21 Mar 2024	☐

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1. Introduction

On 13 December 2023, the MAH submitted a completed study for Takhzyro, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study was not a paediatric study per se but included paediatric patients ≥12 years old.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that ***TAK-743-4008****: Post Authorization Study to Monitor Efficacy, Effectiveness, and Safety of Lanadelumab (Takhzyro®) in patients aged 12 years and older with hereditary angioedema (HAE) in Argentina* 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 Takhzyro.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- ***TAK-743-4008****: Post Authorization Study to Monitor Efficacy, Effectiveness, and Safety of Lanadelumab (Takhzyro®) in patients aged 12 years and older with hereditary angioedema (HAE) in Argentina.*

The study is not part of any PIP of Takhzyro

2.3.2. Clinical study

CHMP'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.

Description

Study TAK-743-4008 was a noninterventional real-world study designed to investigate the safety and effectiveness of lanadelumab in patients aged 12 years and older with a diagnosis of HAE according to currently approved indications in routine clinical practice settings in Argentina.

This study included all patients who received at least 1 dose of lanadelumab for treatment of HAE according to currently approved indications in Argentina. Patients were treated, followed, and monitored by their physicians according to local clinical practice.

Methods

Study participants

The eligibility criteria for each patient in this study were:

- Patients (≥12 years) with investigator confirmed diagnosis of HAE.
- Have received at least one dose of lanadelumab according to approved indications.
- Signed the mandatory consent that has been agreed with national regulatory authorities (ANMAT) as applicable.
- Patients with hypersensitivity to the active substance or any of the excipients have been excluded.

Treatments

Commercial Takhzyro was administered according to the approved posology. All patients were treated with a dose of 300 mg q2wks subcutaneously.

Objective(s)

The primary study objective was to assess the safety profile of lanadelumab in patients 12 years and older with a diagnosis of HAE in the real-world setting of routine clinical practice in Argentina. The secondary aim was to study the efficacy and effectiveness of lanadelumab in the real-world setting of routine clinical practice in Argentina.

Outcomes/endpoints

The primary endpoint variables were:

- Incidence of adverse events of special interest such as hypersensitivity, immunogenicity, liver toxicity; and Embryo-fetal toxicity (assessed through follow-up of all pregnancies).
- Incidence of all other adverse events (AEs; serious and non-serious).

The secondary endpoint variables were:

- The monthly mean rate of investigator-confirmed HAE attacks during the treatment period with assessments at 12 and 24 weeks. HAE attack is defined as a discrete episode during which the patient progressed from no angioedema to symptoms of angioedema based on the investigator's judgment. In general, the event must have symptoms or signs consistent with an attack in $\geq$ 1 of the typical locations (peripheral angioedema; abdominal angioedema; laryngeal/tongue angioedema).
- The monthly mean rate of investigator confirmed moderate or severe HAE attacks during the treatment period with assessments at 12 and 24 weeks. The overall severity of the attack was determined by the investigator using the following definitions: mild (transient or mild discomfort), moderate (mild to moderate limitation in activity), and severe (marked limitation in activity).
- The monthly mean rate of investigator-confirmed HAE attacks requiring acute treatment during the treatment period with assessments at 12 and 24 weeks.
- The proportion of patients who were attack-free during the treatment period with assessments at 12 and 24 weeks.

Sample size

This study aimed to include all patients with a confirmed diagnosis of HAE who received treatment with lanadelumab in the approved indication after marketing authorization in Argentina.

Statistical Methods

Descriptive statistics was used in the analysis.

Results

Participant flow

All paediatric subjects attended 12 Week assessment and 24 Week assessment.

Recruitment

A total of 33 specialized physicians were informed of this study and invited to participate. Overall, 31 physicians agreed to participate, and 29 enrolled at least 1 patient in this study.

Baseline data

The overall study population (N=48) included 41 (85.4%) adult patients and 7 (14.6%) adolescent patients.

Demographics and baseline characteristics are summarized in Table 1.

Table 1: Baseline Patient Characteristics in the Safety Population

	Adults (N=41)	Adolescents (N=7)	Overall (N=48)
Age (years)			
At start of treatment; Mean (SD)	41 (12.4)	15.6 (1.6)	37.3 (14.6)
At symptom onset; Mean (SD)	14.1 (11.0)	6 (2.6)	12.9 (10.6)
Gender, n (%)			
Female	32 (78.0)	2 (28.6)	34 (70.8)
Male	9 (22.0)	5 (71.4)	14 (29.2)
Hereditary angioedema type; n (%)			
Type I	39 (95.1)	7 (100)	46 (95.8)
Type II	1 (2.4)	0 (0)	1 (2.1)
Not available	1 (2.4)	0 (0)	1 (2.1)
History of laryngeal attacks			
Number of patients (%)	29 (70.7)	2 (28.6)	31 (64)
Number of attacks in 24 weeks before treatment			
Median number of attacks in 24 weeks (IQR)	45 (24.0-60.0)	18 (13.0-20.5)	33 (20.0-57.2)
Mean normalized monthly rate (95% CI)[a]	8.21 (7.3-9.1)	3.6 (2.4-5.2)	7.5 (6.8-8.3)
Normalized monthly rate category in the 24 weeks before treatment; n (%)			
<2	4 (9.8)	1 (14.3)	5 (10.4)
2 <3	2 (4.9)	2 (28.6)	4 (8.3)
≥3	35 (85.4)	4 (57.1)	39 (81.2)
Use of long-term prophylaxis in last 12 weeks			
No prophylaxis	26 (63.4)	6 (85.7)	32 (66.7)
Received prophylaxis[b]	15 (36.6)	1 (14.3)	16 (33.3)
Plasma-derived C1-inhibitor	6 (14.6)	1 (14.3)	7 (14.6)
Oral therapy	6 (14.6)	0 (0)	6 (12.5)
Combined therapy (C1-inhibitor and oral)	3 (7.3)	0 (0)	3 (6.3)

CI=confidence interval; CSR=clinical study report; IQR=interquartile range; n=number of patients in category indicated; SD=standard deviation
a Normalized number of attacks rate per month, and 95% CI was calculated for a Poisson distribution.
b Prophylaxis: Number of patients receiving plasma-derived C1-inhibitor and/or oral therapy (androgens or antifibrinolytics)

CHMP's comment

Seven paediatric subjects were included in the study. The mean age at treatment start was 15.6 years (min 12.2, max 16.9).

The mean attack HAE rate during the 24 weeks prior to treatment in the paediatric population was 3.6 attacks/month.

Efficacy results

No primary efficacy endpoints were evaluated within the present study.

Among the 7 adolescent patients in the study population, the overall effectiveness assessment showed that their mean normalized monthly attack rate was reduced from 3.6 (95% CI: 2.4, 5.2) at baseline

to 0.2 (95% CI: 0.0, 0.7) at 12 weeks and to 0 (95% CI: 0.0, 0.5) at 24 weeks. These correspond to attack rate changes of -3.3 (95% CI: - 2.1, -4.9) and -3.6 (95% CI: -2.4, -5.2) per month for the first 12 weeks and for the period between 12 to 24 weeks after lanadelumab initiation, respectively ($p<0.01$ for both periods).

Similar reductions in the mean normalized monthly attack rate, in the number of attacks requiring treatment, and in the number of moderate or severe attacks were observed in both the adult and adolescent subgroups in both treatment periods.

CHMP's comment

In the paediatric population, the mean attack rate was reduced from 3.6 attacks/month prior to treatment to 0.2 attacks/month after 12 weeks of treatment and 0.0 attacks after 24 months of treatment. This is largely in line with the previous experience of lanadelumab.

Safety results

Overall, 18 (37.5%) patients in the study population (14 [34%] adults and 4 [57%] adolescents) experienced at least 1 TEAE. A total of 24 TEAEs (20 in adults and 4 in adolescents) were reported.

The four TEAEs reported by adolescent patients (N=7) were injection site pain (2 [28.5%] patients) and injection site reaction and headache (1 [14.2%] patient each). All of the reported TEAEs were mild or moderate in severity. All TEAEs were assessed as related to study medication.

CHMP's comment

Four TEAEs were reported by the seven paediatric patients. Three of the four TEAEs were injections site reactions. No paediatric patient reported a serious AE, an AE of special interest, or discontinued the study due to an AE.

The safety results in the paediatric population seem to be in line with the known safety profile of lanadelumab.

2.3.3. Discussion on clinical aspects

This procedure present final data from Study TAK-743-4008.

Study TAK-743-4008 was a noninterventional real-world study designed to investigate the safety and effectiveness of lanadelumab in patients aged 12 years and older with a diagnosis of HAE according to currently approved indications in routine clinical practice settings in Argentina.

Since this is a p46 procedure and the study was not part of the EU RMP, only the paediatric data are assessed.

Seven paediatric subjects (12.2-16.9 years) were included in the study. In the paediatric population, the mean attack rate was reduced from 3.6 attacks/month during the 24 weeks prior to treatment to 0.2 attacks/month after 12 weeks of treatment and 0.0 attacks after 24 months of treatment. This is largely in line with the previous experience of lanadelumab.

Four TEAEs were reported by the seven paediatric patients. Three of the four TEAEs were injections site reactions. No paediatric patient reported a serious AE, an AE of special interest, or discontinued the study due to an AE.

The safety results in the paediatric population seem to be in line with the known safety profile of lanadelumab.

The MAH proposes no amendments to the Product information, which is agreed.

3. CHMP's overall conclusion and recommendation

The effectiveness of lanadelumab in the paediatric subpopulation of study TAK-743-4008 is largely in line with the previous experience of lanadelumab. The safety seems to be in line with the known safety profile of lanadelumab. No amendments to the Product information are proposed.

The benefit/risk ratio for Takhzyro remains unchanged.

☒ **Fulfilled:**

No regulatory action required.