21 March 2024
EMA/153698/2024
Human Medicines Division

Assessment report

TAKHZYRO

International non-proprietary name: Lanadelumab

Procedure No. EMEA/H/C/004806/P46/007

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	21 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 15 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.

Of note, the MAH comments that the submission of the final study results for TAK-743-4006 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 global 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.

CHMP'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-743-4006****: "Retrospective, Observational Chart-Review Study Evaluating Clinical Effectiveness and Disease/Treatment Management Among Patients who Initiated Long-term Prophylaxis with Takhzyro in a Real-world Setting (INTEGRATED)"* is a stand-alone study.

The study is not part of any PIP of Takhzyro.

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-743-4006****: "Retrospective, Observational Chart-Review Study Evaluating Clinical Effectiveness and Disease/Treatment Management Among Patients who Initiated Long-term Prophylaxis with Takhzyro in a Real-world Setting (INTEGRATED)"*

2.3.2. Clinical study

CHMP's comment
As 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.

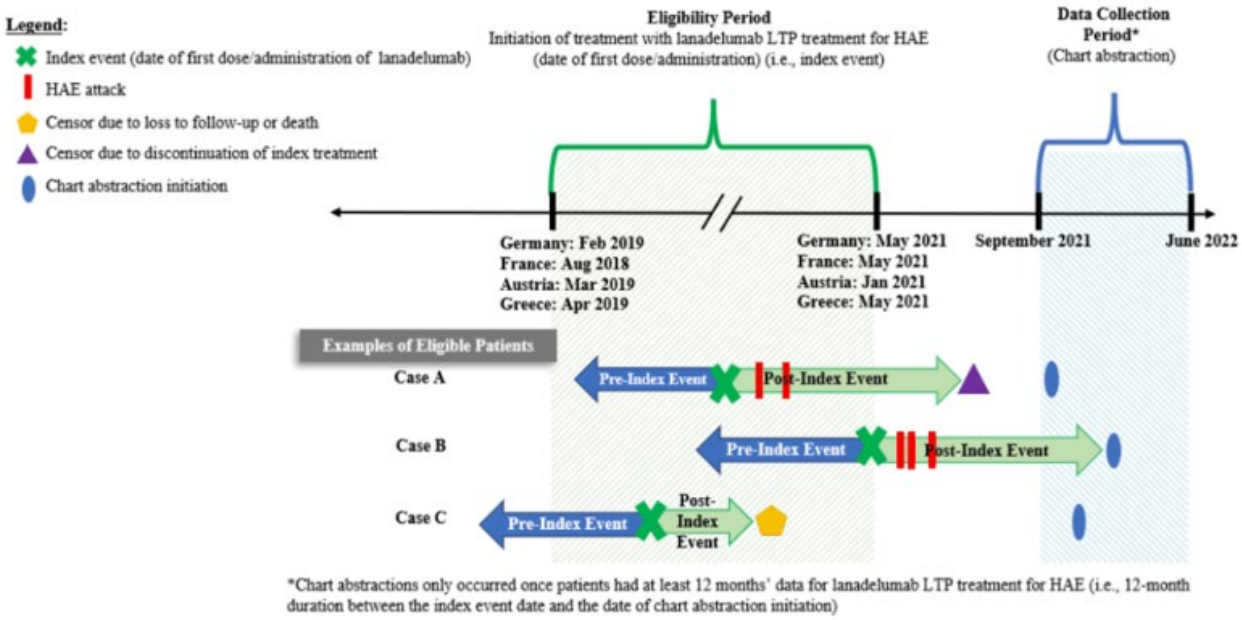
Description

Methods

Study TAK-743-4006 was an observational, multi-country, historical cohort study conducted via retrospective review of the medical charts of who initiated long-term prophylaxis (LTP) treatment with lanadelumab within a routine clinical setting in selected European countries (Germany, France, Austria, and Greece).

A schematic of the overall study design is provided in Figure 1.

Figure 1: Study Design Schematic



Data collection spanned 2 main periods anchored to the index event date:

• Pre-index event period: began on the date of diagnosis of HAE and ended 1 day before the day of index during the eligibility period.

• Post-index event period: began on the index date during the eligibility period and ended at the earliest of index treatment discontinuation, death, loss to follow-up, or date of chart abstraction initiation (where informed consent/assent was required per local regulations, this was the date of subject consent/assent).

Study participants

Adult or adolescent patients (aged ≥12 years) with HAE Type I or II who had initiated LTP with lanadelumab during the eligibility period.

Only subjects who were involved in a therapeutic investigational drug or device trial during the observation period or who did not have documented HAE attacks in the pre-index period and/or an available patient diary or systematic documentation of HAE attacks in the medical records during the post index period were excluded.

Treatments

Commercial Takhzyro was administered according to the approved posology.

Objective(s)

The primary objectives of the study were to assess the effectiveness of lanadelumab on attack-free rate in a real-world setting and also, the effectiveness of lanadelumab every 2 weeks (Q2W) and every 4 weeks (Q4W) adjustment on attack-free rate.

The secondary objectives were to evaluate the effectiveness of lanadelumab Q2W and Q4W adjustment on occurrence of specific attacks effectiveness of lanadelumab relative to prior treatment on attack-free rate, by treatment type; and to determine the characteristics of patients with Q4W adjustment and the primary reasons for down titration. Additional objectives were to evaluate the impact of disease management on attack-free rate and healthcare resource use (HRU) in the overall population, as well as subgroups of patients administered lanadelumab Q2W or Q4W adjustment.

Outcomes/endpoints

The primary outcomes were to assess the attack-free rate among patients treated with lanadelumab, including those with adjustments in interval of administration.

Statistical Methods

Analyses for primary and secondary outcomes were primarily descriptive.

Results

Participant flow

Overall, 207 patients were screened for the study; 9 patients were considered screen failures. Therefore, 198 patients were found eligible for the study and included in the analysis.

No patient withdrew consent or was withdrawn from the study.

Baseline data

The majority (98.0%; n=194) of patients were adults (≥18 years).

Four (2.0%) paediatric patients were included in the analysis. The mean (SD) age at index date was 14.0 (1.4) years (age span 13-16 years). Three (75.0%) patients were male, and 1 (25.0%) patient was female.

Of the 4 paediatric patients, 3 had Type I HAE and 1 had Type II HAE.

<u>Medical history</u>

One paediatric patient had comorbidities documented pre-index in the medical charts.

Overall, 3 patients had no history of life-threatening HAE attacks before starting index treatment; 1 patient had unknown history.

Pre-index use of LTP was documented in all 4 paediatric patients (CINRYZE: 3 patients and BERINERT: 1 patient) in the 12 months before index date. All patients used on-demand treatment pre-index (CINRYZE: 3 patients and FIRAZYR: 1 patient)

Pre-index HAE attack characteristics for the paediatric population are summarised in Table 1.

Table 1: HAE attack characteristics of INTEGRATED enrolled patients in the entire 12 months prior to index date as well as for pre-index month 12 (truncated by Assessor)

In the entire 12 month pre-index period	
Total number of HAE attacks	
N	4
Mean (SD)	27.5 (28.2)
Median	19
Q1, Q3	9.0, 46.0
Min, Max	4, 68
Proportion of patients with ≥ 1 HAE attacks, N(%)	
N	4
Yes	4 (100.0)
No	0
Number of severe HAE attacks	
N	4
Mean (SD)	3.3 (3.3)
Median	2
Q1, Q3	1.0, 5.5
Min, Max	1, 8
Number of life-threatening HAE attacks	
N	4
Mean (SD)	0.0 (0.0)
Median	0
Q1, Q3	0.0, 0.0
Min, Max	0, 0
Proportion of patients with ≥ 1 life-threatening HAE attacks, N(%)	
N	4
Yes	0
No	4 (100.0)
Number of HAE attacks requiring on-demand treatment	
N	4
Mean (SD)	27.5 (28.2)
Median	19
Q1, Q3	9.0, 46.0
Min, Max	4, 68
Number of hospitalisations related to HAE attacks	
N	4
Mean (SD)	0.0 (0.0)
Median	0
Q1, Q3	0.0, 0.0
Min, Max	0, 0
For pre-index month 12[2]	
Total number of HAE attacks	
N	4
Mean (SD)	2.5 (2.1)
Median	2.5
Q1, Q3	1.0, 4.0
Min, Max	0, 5

Lanadelumab treatment pattern

The mean (SD) time between HAE diagnosis and index date was 9.5 (3.74) years for paediatric patients.

Three (75.0%) patients had initial lanadelumab dosing Q2W and 1 (25.0%) patient initiated lanadelumab at Q4W. Three (75%) patients were initiated on self-administered lanadelumab.

The duration of lanadelumab treatment varied between 7.54 and 36.32 months (median: 30.1 months, IQR: 16.9, 35.1). The primary reasons for initiating lanadelumab were lack of/incomplete response to prior HAE prophylactic therapy in 1 patient and anticipated superior safety and efficacy in 3 patients. One patient discontinued the treatment with lanadelumab due to Patient's decision unrelated to AEs. One patient had ≥1 increase in interval of administration; the reason for increasing interval of administration was stably attack-free. The first increase in interval of administration occurred 6 months after index, in which an average of 13 lanadelumab administrations occurred.

CHMP's comment

Four paediatric subjects, aged 14-16 years, were enrolled in the study.

The mean number of HAE attacks during the 12-month pre-index observation period in the paediatric population was 27.5, equalling a mean HAE attack rate of approximately 2.3 HAE attacks per month.

Efficacy results

Overall, 2 paediatric patients experienced at least 1 HAE attack after starting lanadelumab.

In the first 12 months post-index, the mean (SD) number of attacks was 2.3 (2.6), and the range was 0 to 5 attacks. The mean (SD) time on Takhzyro in the study was 26.0 (13.0) months. On average for the entire follow-up, the mean (SD) number of attacks was 8.0 (13.5), and the range was 0 to 28 attacks.

In the 2 patients with post-index HAE attacks, the first HAE attack occurred within 2 to 3 weeks (median: 2.4 weeks, IQR: 2.0, 2.9) after starting lanadelumab treatment.

Two paediatric patients used on-demand treatment post-index; the mean (SD) number of attacks requiring on-demand treatment was 2.3 (2.6). The documented on-demand treatments used to treat attacks were BERINERT (1 patient) and CINRYZE (2 patients).

Severe HAE attacks post-index were documented in 2 paediatric patients; there were no life-threatening attacks. Attacks affected the extremities (1 patient), abdominal (2 patients), and other parts (1 patient).

CHMP's comment

The mean number of HAE attacks during the first 12-months of the post-index observation period in the paediatric population was 2.3, equalling a mean HAE attack rate of approximately 0.2 HAE attacks per month. This is largely in line with the previous experience of lanadelumab.

Over the entire post-index observation period, the mean number of HAE attack was 8.0. Of note, two of the subjects had no HAE attack during the observational period whereas one subject reported 28 attacks. The median number of attacks during the entire observational period was 2. The increase in mean attacks after the first 12 post-index months is therefore not considered to indicate a general loss of effect with time but rather reflect a large interindividual difference in HAE attack rate in a small population.

Safety results

This retrospective study had no safety objective and therefore, safety data (AEs) were not collected. No patient discontinued the treatment with lanadelumab for safety reasons.

One paediatric patient discontinued the treatment with lanadelumab due to patient's decision unrelated to AEs.

2.3.3. Discussion on clinical aspects

Study TAK-743-4006 was an observational, multi-country, historical cohort study conducted via retrospective review of the medical charts of adult or adolescent patients (aged ≥12 years) with HAE Type I or II who had initiated LTP with lanadelumab during the eligibility period within a routine clinical setting in selected European countries.

As 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.

Four paediatric subjects, aged 14-16 years, were enrolled in the study. One paediatric patient discontinued the treatment with lanadelumab due to patient's decision unrelated to AEs.

The mean number of HAE attacks during the 12-month pre-index observation period in the paediatric population was 27.5, equalling a mean HAE attack rate of approximately 2.3 HAE attacks per month. The mean number of HAE attacks during the first 12-months of the post-index observation period in the paediatric population was 2.3, equalling a mean HAE attack rate of approximately 0.2 HAE attacks per month. This is largely in line with the previous experience of lanadelumab.

There was an increase in mean number of attacks after the first 12 post-index months compared to the initial 12 months post-index. This is not considered to indicate a general loss of effect with time but rather reflect a large interindividual difference in HAE attack rate in a small population.

This retrospective study had no safety objective and therefore, safety data (AEs) were not collected. No patient discontinued the treatment with lanadelumab for safety reasons.

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-743-4006 is largely in line with the previous experience of lanadelumab. The study had no safety objective and therefore, safety data (AEs) were not collected. No patient discontinued the treatment with lanadelumab for safety reasons. No amendments to the Product information are proposed.

The benefit/risk ratio for Takhzyro remains unchanged.

☒ **Fulfilled:**

No regulatory action required.