



EUROPEAN MEDICINES AGENCY
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

TAKHZYRO

Lanadelumab

Procedure no: EMEA/H/C/004806/P46/009

Note

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



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	24/06/2024	24/06/2024	☐
☐	CHMP Rapporteur Assessment Report	29/07/2024	23/07/2024	☐
☐	CHMP members comments	12/08/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16/08/2024	n/a	☐
☒	CHMP adoption of conclusions:	22/08/2024	22/08/2024	☐

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1. Introduction

On 28 May 2024, the MAH submitted a completed paediatric study for Takhzyro, 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 **SHP643-304**: "A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects with Hereditary Angioedema" is a stand-alone study.

Based on the study results, no updates to the Product Information are required. 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:

- **SHP643-304**: "A Multi-center, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Lanadelumab (SHP643) in Chinese Subjects with Hereditary Angioedema".

In China, lanadelumab (authorised on 02 Dec 2020 under the name Takhzyro) is indicated for prophylaxis to prevent attacks of HAE in subjects 12 years and older. As part of the approval requirements and postapproval commitment in China, the China Health authority requested further efficacy and safety data to be collected from Chinese subjects with Type I or Type II HAE. To meet this request, Takeda conducted Study SHP643-304.

2.3.2. Clinical study

As this is a p46 procedure that is not part of the EU RMP, only the paediatric data are assessed.

Description

Methods

Study SHP643-304 comprised a screening period up to 4 weeks, a washout period of 2 weeks, a run-in period of 4 to 8 weeks, a treatment period of 26 weeks, and a follow-up period of 4 weeks.

Following informed consent, subjects underwent screening assessments. Screened adult subjects who were on long term prophylaxis (LTP) (eg, androgens) for hereditary angioedema (HAE) were required to undergo a minimum 2-week washout period prior to the run-in period. Screened subjects who were not on LTP therapy for HAE or who had completed the required washout period were enrolled and entered a run-in period of 4 to 8 weeks to determine their baseline attack rate. Only subjects meeting a minimum baseline attack rate of at least 1 investigator-confirmed attack per 4 weeks were eligible

for treatment. After completion of the 26-week treatment period, subjects were followed for an additional 4 weeks and attended the follow-up visit on Day 210 (± 3 days).

Study participants

The main eligibility criteria were adults and adolescents aged ≥ 12 years of age with Chinese descent, defined as born in China and having Chinese parents and Chinese maternal and paternal grandparent, documented diagnosis of HAE Type I or Type II, and at least 1 investigator-confirmed HAE attack per 4 weeks during the run-in period.

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 objective of the study was:

- To evaluate the safety of repeated subcutaneous (SC) administrations of lanadelumab in Chinese subjects with hereditary angioedema (HAE).

The secondary objectives of the study were:

- To evaluate the pharmacokinetics (PK) of repeated SC administrations of lanadelumab in Chinese subjects with HAE
- To evaluate the pharmacodynamics (PD) of repeated SC administrations of lanadelumab in Chinese subjects with HAE
- To evaluate the efficacy of repeated SC administrations of lanadelumab in Chinese subjects with HAE
- To evaluate the immunogenicity of repeated SC administration of lanadelumab and the effect on lanadelumab PK, PD, efficacy, and safety

Outcomes/endpoints

Primary endpoints were Safety assessments, e.g., treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and adverse events of special interest (AESIs), Clinical laboratory testing, and vital signs.

Secondary endpoints included for example PK parameters, Number of investigator-confirmed HAE attacks during the efficacy evaluation periods, Number of investigator-confirmed moderate or severe HAE attacks during the efficacy evaluation periods, and Immunogenicity.

Sample size

Approximately 20 subjects were planned for this study.

Randomisation and blinding (masking)

This was an open label, single arm study.

Statistical Methods

No statistical hypothesis testing was performed.

Results

Participant flow

All 20 enrolled subjects were included in the full analysis set (FAS) while 19 subjects were included in the Per-Protocol Analysis Set (PPAS). One subject was excluded from the PPAS due to not completing the requested 4-week run-in period.

One adolescent subject was enrolled in the study.

Recruitment

The Study was conducted at 4 sites in China.

Baseline data

The adolescent subject (12 to 18 years) was a Chinese patient diagnosed with unspecified HAE, with onset 2 years earlier.

At study entry (screening visit), this subject's BMI was 21.5 kg/m². The primary attack location was combination, with a history of laryngeal attack. During the last 3 months prior to screening, this subject experienced 8 HAE attacks, including 5 mild attacks, 2 moderate attacks, and 1 severe attack. The average attack duration was >48 hours.

Efficacy results

This subject experienced 3 HAE attacks (including 1 mild HAE attack and 2 moderate attacks) during the run-in period. She fulfilled the criteria for "subjects who experienced 3 or more investigator-confirmed attacks before the end of the 4 weeks exited the run-in period early and proceeded to the treatment period" in the protocol. The HAE attack rate during run-in was 5.3 attacks per 4-weeks with no LTP use.

The subject experienced 1 moderate HAE attack during the 182-days-long lanadelumab treatment period (Day 180 to Day 181), and 1 HAE attack during the follow-up period (Day 210 to Day 211). Icatibant was given as supportive treatment for each attack.

Safety results

Overall, the adolescent subject experienced 6 AEs during the study, including 3 events of hereditary angioedema prior to Day 0; 1 event of hereditary angioedema and 1 event of COVID-19 during the treatment period (Day 0 to Day 182); and 1 event of hereditary angioedema during the follow-up period. None of these AEs were reported as related to the study drug, and no action was taken with the study drug due to these AEs.

For this subject, all immunogenicity results remained ADA negative during the study.

2.3.3. Discussion on clinical aspects

This procedure present final data from Study SHP643-304.

Study SHP643-304 was an open-label, single arm, descriptive study designed to assess the safety and effectiveness of lanadelumab in adults and adolescents aged 12 years and older with Chinese descent and a diagnosis of HAE 1 or 2.

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

One adolescent subject was included in the study. During the run-in period, her HAE attack rate was 5.3 attacks/ 4 weeks. During the 182-days-long treatment period she experienced one HAE attack, corresponding to approximately 0.15 attacks/ 4 weeks. A second attack was reported during the four-week-long follow up period, rendering a total HAE rate of 0.27 attacks/ 4weeks under lanadelumab treatment. This is largely in line with the previous experience of lanadelumab.

Six TEAEs were reported by this subject, of which 5 reports represented the HAE attacks during run-in, treatment period, and follow-up. The last AE was an episode of COVID-19. It is agreed with the MAH that none of the AEs are likely to be secondary to treatment.

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. Rapporteur's overall conclusion and recommendation

The effectivity of lanadelumab in one adolescent Chinese subject in study SHP643-304 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.