14 November 2024
EMA/550456/2024
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/P46/010

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

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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	16/09/2024	16/09/2024	☐
☐	CHMP Rapporteur Assessment Report	21/10/2024	15/10/2024	☐
☐	CHMP members comments	04/11/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07/11/2024	n/a	☐
☒	CHMP adoption of conclusions:	14/11/2024	14/11/2024	☐

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1. Introduction

On 30 Aug 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 *SERENITI: Effectiveness of lanadelumab in real-life practice in France/ a non-interventional, ambispective, multicenter study* (TAK-743-5006) 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-743-5006***: *SERENITI: Effectiveness of lanadelumab in real-life practice in France/ a non-interventional, ambispective, multicenter study*

2.3.2. Clinical study

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.

Description

SERENITI was a noninterventional, multicenter, ambispective cohort study, which enrolled patients diagnosed with HAE and who initiated treatment with lanadelumab anytime from October 2018 to May 2021. Study patients were recruited from a representative sample of study sites located in Metropolitan France.

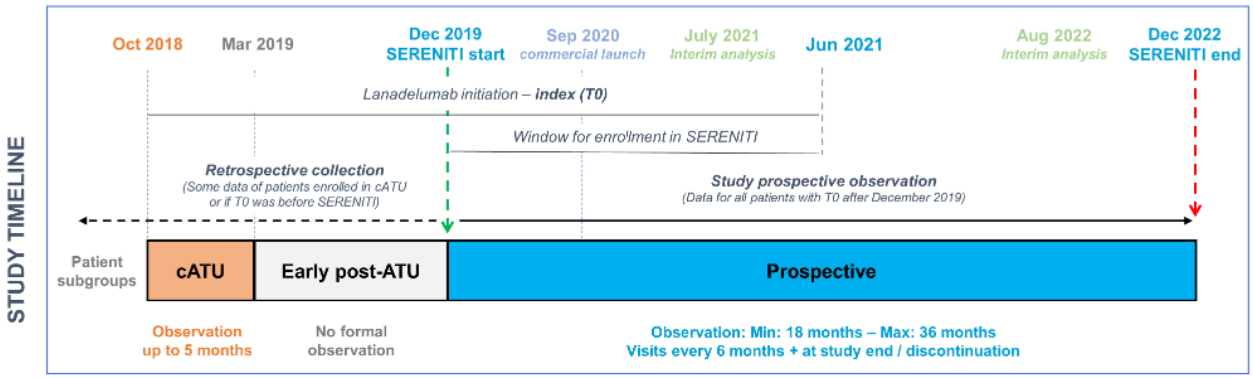
Given the implementation of early access programs which preceded the launch of SERENITI study (01 Dec 2019), 3 different subgroups of patients were defined with respect to the period when treatment with lanadelumab was initiated:

- cATU patients (01 Oct 2018 – 13 Mar 2019) initiated treatment with lanadelumab as part of the "authorization for temporary use in a cohort" program. Data was defined as retrospective up to the enrolment of patients in the SERENITI study, and prospective afterwards. Following the approval in the EEA on 22 Nov 2018 of the MA for lanadelumab through centralized procedure, cATU was officially terminated on 13 Mar 2019.
- Early post-ATU patients (14 Mar 2019 – 30 Nov 2019) initiated treatment with lanadelumab upon cATU termination and before the official start of SERENITI study. The post-ATU program was implemented to enable patients to qualify for lanadelumab treatment before the official

commercial launch of the medicine (24 Sep 2020). With respect to SERENITI study, post-ATU data was retrospective up to the official enrolment in the study, and prospective afterwards.

- Prospective patients (01 Dec 2019 – 30 Jun 2021) were enrolled following the investigator's decision to initiate treatment with lanadelumab after the official launch of SERENITI study (01 Dec 2019). With respect to the study, data collection was retrospective (ie, patient chart for historical data), and prospective afterwards. Of note, the patients assigned to this group were either prescribed lanadelumab in the context of the post-ATU program, or upon the commercial launch of lanadelumab.

Table 1: SERENITI Study Design



Methods

Study participants

Main criteria for inclusion:

- Age of 12 years or older,
- Patients diagnosed with HAE and eligible for treatment for routine prevention of recurrent attacks of HAE as per physician's opinion,
- Patients who received at least one dose of lanadelumab since October 2018, or for whom the physician has made the decision to prescribe lanadelumab,
- Patients able to understand complete the self-evaluation questionnaire,
- Patients (or at least one parent or legal representative) who have provided a written informed consent to participate in the non-interventional study.

Main criteria for exclusion:

Given the purpose and the design of this real-life, non-interventional study, no exclusion criteria were defined.

Treatments

Commercial Takhzyro was administered according to the approved posology (recommended starting dose is 300 mg lanadelumab every 2 weeks).

Objective(s)

Primary objective:

To evaluate the effectiveness of lanadelumab on the occurrence of hereditary angioedema (HAE) attacks in real-life clinical practice, as assessed by the monthly rate of physician-confirmed HAE attacks over the first 6 and 12 months since lanadelumab initiation, in the total cohort of patients treated since October 2018 in France and according to predefined subgroups of interest.

Secondary objectives:

The study's secondary objectives included the evaluation of the following items in the total cohort of patients and in subgroups of interest:

- The utilization patterns of lanadelumab:
    - Description of the population treated by lanadelumab,
    - Evaluation of factors associated with dose adjustments (modifications) in clinical practice.
- The effectiveness of lanadelumab, as assessed by time points or clinical measures other than the primary endpoint,
- Patient-reported outcomes (PROs),
- Safety and tolerability of lanadelumab,
- Healthcare resource utilization (HCRU).

Outcomes/endpoints

Primary endpoint:

The primary endpoint was the calculation of the monthly rate of physician-confirmed HAE attacks over the first 6 and 12 months since lanadelumab initiation (T0, index date).

Secondary endpoints:

- A characterization of lanadelumab utilization patterns, including the description of lanadelumab users (e.g., socio-demographics, medical history, comorbidities, anthropometry)
- A characterization of lanadelumab clinical effectiveness by using multiple clinical measures:
    - Monthly rate of physician-confirmed HAE attacks over 24, 36 and 48 months since T0 (if available),
    - Time to first physician-confirmed HAE events since T0,
    - The proportion of patients free from attacks (6M, 12M, 24M, 36M, 48M),
    - The monthly attack rate since T0 according to severity, anatomical location, attacks that required rescue medication, attacks that required hospitalization,
    - Time to first physician confirmed HAE event according to treatment status.
- HAE attack rates analysed using additional analytical methods (graphic-based analysis and pictorial representation, Kaplan-Meier survival analysis, multivariate approach),

- An analysis of patient-reported outcomes (PRO) related to quality of life in the context of HAE and lanadelumab use (AAS28 score, AE-QoL questionnaire, EQ-5D, injection satisfaction questionnaire),
- An analysis of safety and tolerability outcomes, characterizing the incidence and the type of adverse events (AE), serious adverse events (SAE), and adverse events of special interest (AESI), as well as an analysis of AEs leading to dose reduction and/or to temporary or permanent treatment discontinuation,
- An analysis of healthcare resource utilization related to HAE, characterizing the number of hospitalizations, the number of laboratory analyses related to HAE, the documentation of injection administration support for HAE, the number of sick leaves days.

Sample size

Not applicable

Randomisation and blinding (masking)

Not applicable

Statistical Methods

The analysis of the study's primary and secondary endpoints was conducted using general statistical methodology, which included the use of descriptive statistics methods (1), the application of statistical tests (2), and the implementation of time-to-event and multivariate analysis modelling (3)

Results

Recruitment

Eighteen study centres located across Metropolitan France took part to the SERENITI study for a total of 22 investigators, enrolling 163 hereditary angioedema patients, of which 162 were analysed.

Baseline data

Of the 162 patients included in the FAS, 10 patients were children (cATU program: 3 patients, early post-ATU phase: 2 patients, and prospective patients: 5 patients).

There were equal number of male and female paediatric patients (5 patients each). The mean (SD) age of the paediatric patients was at initiation of lanadelumab 15.4 (2.45) years. At inclusion in the SERENITI study, three of the paediatric subjects had reached > 18 years of age. The mean (SD) BMI was 21.3 (5.36) kg/m2. Arterial blood pressure measures were available for 5 paediatric patients, with a mean (SD) value of 110.4 (11.55) mmHg for systolic blood pressure, and 68.8 (2.68) mmHg for diastolic blood pressure. Regarding the socio-professional characteristics of patients, 1 (10.0%) patient was in full-time employment, 8 (80.0%) patients were students, and 1 (10.0%) patient was in part-time employment. Of the 5 female patients, none was pregnant nor breastfeeding.

All 10 paediatric patients were diagnosed with type I HAE, with a mean (SD) C1-INH protein level of 8.1 (4.0) mg/dL. Seven (87.5%) patients displayed ≤50.5% functional activity, and 9 (90%) patients reported family history of HAE. The first signs of HAE were reported at a mean (SD) age of 4.9 (4.6) years and the mean (SD) time between the first signs of HAE and lanadelumab initiation was 10.5 (4.15) years.

All 10 paediatric patients reported at least 1 attack, with a total of 107 reported attacks over the last 6 months prior T0. The mean (SD) monthly attack rate was 1.78 (1.01) attacks per month, ranging from 0.5 to 4 attacks per month.

Assessor's comment

Ten paediatric subjects were included in the study. The mean age at treatment start was 15.4 years. At the time of inclusion in the SERENETI study, 3 of these subjects had reached >18 years of age.

The baseline HAE attack rate was 1.78 attacks per month, ranging from 0.5 to 4 attacks per month.

Efficacy results

The mean (SD) monthly attack rate was 0.00 (0.00) from T0 to 6M, 0.09 (0.15) from T0 to 12M, 0.08 (0.16) from T0 to 24M, 0.03 (0.04) from T0 to 36M, and 0.05 (0.02) from T0 to 48M.

Despite the limited sample size in paediatric patients, similar changes were observed upon lanadelumab initiation in both adult and paediatric patients. The analysis of change from baseline in monthly attack rate showed significant reduction in occurrence of HAE attacks ($p<0.02$), suggesting that age did not affect the performance of lanadelumab with respect to HAE attack rate.

Assessor's comment

In the paediatric population, HAE attack rate decreased from 1.78 attacks/month to 0.05 attacks/month during the 48 months of treatment. This is largely in line with the previous experience of lanadelumab.

Safety results

Exposure

Lanadelumab was initiated on average after 10.5 ± 4.15 years after onset of first signs of HAE (range: 2.3-16.7 years).

Among the 10 paediatric patients, 9 reported a total of 33 modifications in administration frequency of lanadelumab, of which 11 instances reported increase in administration intervals and 4 instances reported reduction in administration interval. One case of temporary discontinuation of lanadelumab was also reported, as well as 2 cases of permanent discontinuation which were not due to AEs.

Assessor's comment

The MAH informs that there were two cases of permanent discontinuation and one case of temporary discontinuation of lanadelumab in the paediatric population. The MAH states that this was not due to AEs.

Key Safety Findings

Overall, of the total 10 paediatric patients enrolled, 6 paediatric patients had a total of 15 AEs.
The most commonly reported System Organ Classes (occurring in ≥3 patients) were skin and subcutaneous tissue disorders and general disorders and administration site conditions (4 patients each), and gastrointestinal disorders (3 patients). Of the 15 AEs, 3 were considered definitely related to lanadelumab by the investigator, 2 were considered possibly related, and 1 was considered probably related. Eight AEs were considered not related to lanadelumab and the relationship was missing for 1 AE.

There were no deaths or SAEs reported. None of the AEs led to dose reduction or temporary/permanent discontinuation of lanadelumab treatment.

Four patients had 6 AESIs; 1 patient had 1 event of disordered coagulation and 3 patients had 5 events of injection site reactions; all were nonserious. Of the 6 AESIs, 3 were considered definitely related to lanadelumab by the investigator and 3 were considered not related to lanadelumab. The outcome was resolved for 2 AESIs and ongoing/continuing treatment for 4 AESIs.

There were no events related to immunogenicity or liver toxicity.

Assessor's comment

There were no deaths or SAEs reported. Six AESI were reported of which five were related to Injection site reactions and the sixth to Disordered coagulation (epistaxis).

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

SERENITI was a noninterventional, multicenter, ambispective cohort study, which enrolled patients diagnosed with HAE and who initiated treatment with lanadelumab anytime from October 2018 to May 2021. Study patients were recruited from a representative sample of study sites located in Metropolitan France. Study subjects could start lanadelumab treatment in e.g., early access programmes prior to the approval of Takhzyro.

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.

Ten paediatric subjects with a mean age of 15.4 years at lanadelumab initiation were enrolled in the study. Three subjects reached 18 years of age during the study. Two paediatric patients discontinued the treatment with lanadelumab permanently and one subject discontinued treatment temporarily. This was not due to AEs.

The mean HAE attack rate during the 6-month pre-index observation period in the paediatric population was 1.8 HAE attacks per month. The mean HAE attack rate during the 48-month observation period in the paediatric population was 0.05 attacks/month. This is largely in line with the previous experience of lanadelumab.

There were no deaths or SAEs reported in the paediatric population. The safety results in the paediatric population seem to be in line with the known safety profile of lanadelumab.

3. Rapporteur's overall conclusion and recommendation

The effectiveness of lanadelumab in the paediatric subpopulation of the SERENITI study is largely in line with the previous experience of lanadelumab. No new or unexpected safety issues were identified.

No amendments to the Product information are proposed.

The benefit/risk ratio for Takhzyro remains unchanged.

☒ Fulfilled:

No regulatory action required.