14 December 2023
EMA/8343/2024
Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

TAKHZYRO

Lanadelumab

Procedure No. EMEA/H/C/004806/P46/006

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	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 2023	17 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 2023	n/a	☐
☒	CHMP adoption of conclusions:	14 Dec 2023	14 Dec 2023	☐

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1. Introduction

On 02 October 2023, 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

Study SHP643-403 (EMPOWER) is a stand-alone study.

SHP643-403 (EMPOWER) is Phase 4 non-interventional study (observational) of lanadelumab (SHP643) that includes paediatric subjects under 18 years of age. The study is not part of the EU RMP.

2.2. Information on the pharmaceutical formulation used in the study

Commercial Takhzyro was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- ***SHP643-403*** *(EMPOWER Study)*

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. Data from the paediatric subpopulation is from Interim Analysis 3, which was based on a data cut-off date of 01 March 2022 and includes all available data up to that point.

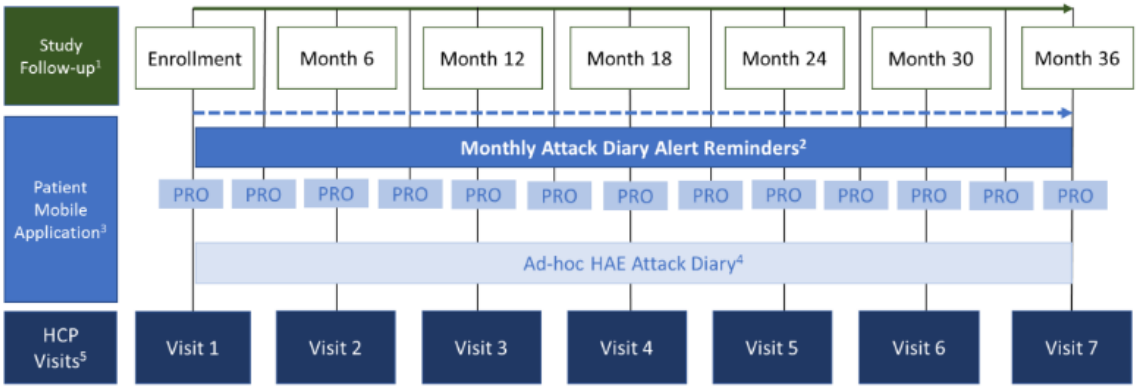
Clinical study number and title

SHP643-403*: An observational, non-interventional, study of patients with Hereditary Angioedema in the United States and Canada (EMPOWER Study)*

Description

This was a self-controlled prospective, observational cohort study of patients with a diagnosis of hereditary angioedema (HAE) Type I or II. The overall study design is presented in Figure 1.

Figure 1: Study Design Schematic



Abbreviations: eCOA = electronic clinical outcome assessment; HAE = Hereditary Angioedema; HCP = healthcare provider; PRO = patient reported outcome.
[1] Overall patient follow-up from date of enrollment until death, lost to follow-up, withdrawal, or 24 months for patients enrolled on or after 01 September 2020 and 36 months for patients enrolled earlier
[2] Monthly alerts would prompt the patient to enter any attack information for past month if they had not already
[3] eCOA would request the patient to complete PROs by using a mobile application at 3-month intervals (± 1 week)
[4] Patient would enter attack diary information ad hoc at the time of the HAE attack
[5] Patient encounters with their HCP, anticipated to occur every 6 months (± 2 months).

The follow-up period was 36 months for patients who enrolled in the study prior to 01 September 2020 and 24 months and follow-up period for patients who enrolled in the study on or after 01 September 2020. Data collection had to be ceased at the end of follow-up period, or at the time of withdrawal, loss to follow -up, or death.

Methods

Study participants

Patients were eligible to participate in the study if they were diagnosed with HAE Type I or Type II, and had voluntarily provided written, signed, and dated (personally or via a legally authorized representative) informed consent/and assent as applicable, and were able to use a mobile device for data collection. Patients were excluded if they were participating in any interventional clinical trial at the time of enrolment, were unable to provide written, signed, and dated informed consent/assent, or if the investigator believed that the patient was not a suitable candidate for the study.

All the patients who were enrolled in this prospective observational study have been categorized into one of two groups: the prevalent lanadelumab users and the new lanadelumab users. The prevalent lanadelumab users are defined as those patients who a) had received at least 4 lanadelumab doses prior to enrolment and b) were receiving lanadelumab at enrolment or received the last dose <70 days prior to enrolment. The new lanadelumab users had not started lanadelumab at the time of enrolment or already started lanadelumab prior to enrolment and had received <4 lanadelumab doses prior to enrolment date.

Treatments

Commercial Takhzyro was administered according to the approved posology.

Objective(s)

The objectives for the study are summarised in Table 1.

Table 1: Description of Outcome Measures According to Study Objective

Study Objectives	**Outcome Measures and Corresponding Data Collection According to Study Objective**
Primary Objective	**Primary Outcome**
Evaluate the real-world effectiveness of lanadelumab as measured by HAE attack-rate before and after lanadelumab initiation	Number of HAE attacks
Secondary Objectives	**Secondary Outcomes**
Describe the real-world utilization of lanadelumab in regular clinical care by examining treatment patterns of lanadelumab	• Duration of lanadelumab treatment • Administration dose (in mg) • Frequency of administration • Primary person administering the injections (self, caregiver, HCP, other) • Time from diagnosis to lanadelumab initiation • Number of injections before discontinuation of lanadelumab • Reason(s) for discontinuation • Reason(s) for modification

Describe HCRU for HAE attacks before and after lanadelumab initiation, including hospitalizations and ER visits, physician visits, and rescue medication use	• Number of visits to healthcare encounter
	• Type of healthcare encounter
	• Length of stay in healthcare encounters
	• Rescue medications taken at time of attack(s)
	  ○ Name of medication(s) used
	  ○ Who administered the drug(s) for the attack?

Compare PROs before and after lanadelumab initiation as measured by: AE-QoL, WPAI:GH, and TSQM-9	• See Section 9.4.2 for details on outcome measures from these instruments

Compare HAE control before and after lanadelumab initiation, as measured by the AECT	• Frequency of answers to the following questions from AECT
	  ○ In the last 3 months, how often have you had angioedema? (Response options: very often, often, sometimes, seldom, not at all)
	  ○ In the last 3 months, how much had your QoL been affected by angioedema? (Response options: very much, much, somewhat, a little, not at all)
	  ○ In the last 3 months, how much had the unpredictability of your angioedema bothered you? (Response options: very much, much, sometimes, seldom, not at all)
	  ○ In the last 3 months, how well had your angioedema been controlled by your therapy? (Response options: very well, well, somewhat, a little, not at all)

Describe the time to the first HAE attack over the study period	• Time to first HAE attack (days) will be analyzed before and after lanadelumab initiation for new and prevalent lanadelumab users • Kaplan-Meier (KM) estimates of the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CI

Exploratory Objectives	Exploratory Outcomes
Describe other attack-related measures of lanadelumab effectiveness during exposure to lanadelumab (e.g., attack-free periods [in days], severity and location of attacks)	Other attack-related measures during exposure to lanadelumab: • Duration of attack-free periods (in days): • For each attack, the following measures were collected: ○ Duration of attack ○ Severity of attack: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-threatening), Unknown ○ Location affected by attack (peripheral [e.g., skin], upper airway [e.g., larynx], abdomen, other organs) ○ HAE treatment received for the attack ○ Identified or suspected trigger for the attack (e.g., contact with chemicals, drug[s], food[s])
Describe treatment patterns for other HAE medications (e.g., C1-INH) among the study population	• Use of other HAE medications (e.g., C1-inhibitors, plasma kallikrein inhibitors, bradykinin receptor antagonists). For each medication used, the following information were collected ○ Start date and end date (or date of administration for on-demand treatments) ○ Dose ○ Administration of injections (self, caregiver, HCP, other) ○ Frequency of injections, if applicable ○ Time from diagnosis to initiation ○ Discontinuation date, if applicable ○ Number of injections before discontinuation ○ Reason(s) for discontinuation Outcomes that were reported for this objective were as follows: ○ Most common treatments during baseline period ○ Most common medication switches before/after lanadelumab initiation ○ Number of unique HAE treatments during follow-up

Results

Participant flow

A total of 168 patients were enrolled in the study; 116 patients were included in the safety set and 113 patients were included in the full analysis set.

A total of 11 (6.5%) patients completed the study prior to study termination by the sponsor, and 114 (67.9%) patients completed the study at study termination by the sponsor. Sixteen (9.5%) patients discontinued the study due to other reasons, 15 (8.9%) patients withdrew from the study, 6 (3.6%) patients were lost to follow-up, 3 (1.8%) patients discontinued due to physician decision, and 2 (1.2%) patients were discontinued due to death (COVID and traumatic brain injury, respectively, deemed not related to lanadelumab treatment).

Twelve patients under the age of 18 years were enrolled in the study.

Recruitment

The study encompassed 30 sites: 25 sites in the United States and 5 sites in Canada.

Baseline data

Demographics and other baseline characteristics based on an interim analysis 3 of paediatric patients (data cutoff date of 01 Mar 2022) are summarized in Table 2.

Table 2: Demographics and Other Baseline Characteristics for Paediatric Patients – Full Analysis Set (truncated by Assessor)

Characteristics	New Users (N=5)	Prevalent Users (N=7)
Age at enrollment (years)[a]		
n	5	7
Mean (SD)	14.0(2.74)	15.7(1.38)
Min, Max	12, 17	14, 17
Sex, n (%)		
n	5	7
Male	3 (60.0)	2 (28.6)
Female	2 (40.0)	5 (71.4)
Race, n (%)		
n	5	7
American Indian or Alaska Native	0	0
Asian	0	0
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	0
White	5 (100.0)	7 (100.0)
Other	0	0
Body mass index (kg/m^2)		
n	3	7
Mean (SD)	25.2(8.34)	29.4(10.67)
Min, Max	18, 34	18, 43
Type of HAE, n(%)		
n	5	7
Type I	4 (80.0)	6 (85.7)
Type II	1 (20.0)	1 (14.3)
Type I or Type II undifferentiated	0	0
Missing	0	0

CHMP's comment

The twelve paediatric subjects in study were 12-17 years of age. Five of the subjects were new users, seven prevalent users.

Efficacy results

Primary Effectiveness Objective

The primary effectiveness outcome measure was HAE attack incidence rates (per person-month) before and after lanadelumab initiation. A comparison of the HAE attack incidence rates (per person-month) and incidence rate ratios (IRRs) six months before and after lanadelumab initiation was provided.

Data from the paediatric population is summarised in Table 3.

Table 3: Observed Attack-Rate in Paediatric Patients – Full Analysis Set

	Pre-lanadelumab	Post-lanadelumab			Overall study period
		Early [a]	Steady [b]	Cumulative	
New lanadelumab users					
Number of HAE attacks					
n	5	5	5	5	-
Mean (SD)	7.0(12.96)	0.6(0.89)	1.2(1.79)	1.8(2.49)	-
Min, max	0, 30	0, 2	0, 4	0, 5	-
Patient duration in time period (days)					
n	5	5	5	5	-
Mean (SD)	182.6(0.00)	69.0(0.00)	517.0(38.81)	586.0(38.81)	-
Min, max	183, 183	69, 69	495, 586	564, 655	-
Model-estimated attack rate (attacks/months)					
Mean rate (SE)	1.19(0.76)	0.26(0.60)	0.07(0.61)	0.09(0.56)	-
95% CI [c]	(0.27, 5.24)	(0.08, 0.84)	(0.02, 0.23)	(0.03, 0.27)	-
IRR (vs Pre-enrollment)					
IRR	Ref.	0.22	0.06	0.08	-
95% CI		(0.03, 1.88)	(0.01, 0.54)	(0.01, 0.66)	-
% attack reduction		78.01	94.18	92.40	-
Prevalent lanadelumab users					
Number of HAE attacks					
n	5	-	-	-	-
Mean (SD)	1.4(1.14)	-	-	-	-
Min, max	0, 3	-	-	-	-
Patient duration in time period (days)					
n	7	-	-	-	-
Mean (SD)	182.6(0.00)	-	-	-	-
Min, max	183, 183	-	-	-	-
Attack rate (as treated)					
n	-	-	-	-	7
Mean (SD)	-	-	-	-	0.0(0.05)
Min, max	-	-	-	-	0, 0

CI=confidence interval; HAE=hereditary angioedema; IRR=incidence rate ratio, estimated using pre-lanadelumab as the reference class; Max=maximum; Min=minimum; n=number of patients with available data; Ref=reference class; SD=standard deviation; SE=standard error; -=data not applicable to this subgroup analysis

a Early state defined as the first 69 days after lanadelumab initiation.

b Steady state defined as the period of lanadelumab exposure starting at Day 70 after lanadelumab initiation. Not all patients could continue treatment until achievement of steady state at Day 69.

c Attack rate and its associated 95% CI were estimated using a generalized estimation equation where a negative binomial distribution and log link were used with an offset of the time to exposure.

The presented analysis is based on Interim Analysis 3 of paediatric patients. All patients were enrolled in Study SHP643-403 as of December 2022; Interim Analysis 3 was based on a data cutoff date of 01 Mar 2022 and includes all available data up to that point.

Disease severity category is based on monthly attack rates from recorded history of attacks prior to enrolment.

Source: Appendix 1,

CHMP's comment

For the paediatric subpopulation, only the primary endpoint has been presented separately.

The eligibility criteria did not include any minimum required HAE attack rate at baseline. The mean HAE attack rate/ month at baseline was therefore lower than in the clinical studies also in new lanadelumab users (1.19 vs 1.84 in the pivotal paediatric study for children 2-<12 years of age [study SHP643-301] and 3.66 in the pivotal study in adults and adolescents from the age of 12 years [Study DX-2930-03]). The number of subjects is small (n=12) which hampers detailed analysis. A decrease in mean HAE attack rate/month on treatment from 1.19 to 0.09 was observed in new paediatric lanadelumab users (n=5). In prevalent paediatric lanadelumab users (n=7), the mean HAE attack rate/month during the observation period was 0.

This is largely in line with the previous experience of lanadelumab.

Safety results

In paediatric patients, 2 (40.0%) new lanadelumab users experienced a total of 6 lanadelumab TEAEs. All events reported by paediatric new lanadelumab users were nonserious, considered not related to lanadelumab treatment, and either moderate (4 [66.7%] TEAEs) or mild (2 [33.3%] TEAEs) in severity.

Five (71.4%) paediatric prevalent lanadelumab users experienced a total of 6 lanadelumab TEAEs. All events reported by paediatric prevalent lanadelumab users were nonserious, considered not related to lanadelumab treatment, and either moderate (1 [16.7%] TEAEs) or mild (5 [83.3%] TEAEs) in severity. No lanadelumab-related TEAEs resulted in study discontinuation in the paediatric subpopulation.

CHMP's comment

In total 12 treatment emerging adverse event (TEAE) were reported in the paediatric subpopulation. No SAE was reported. There were no fatal event or discontinuation due to TEAE reported in the paediatric subpopulation.

The MAH has not provided any summary of the reported TEAE per SOC and PT for the paediatric subpopulation, which would have been expected. Nonetheless, since no adverse events were deemed serious and all events were mild or moderate, this is not further pursued.

2.3.3. Discussion on clinical aspects

This procedure presents the final data from Study SHP643-403.

SHP643-403 (EMPOWER) is Phase 4 non-interventional observational study of lanadelumab that includes paediatric subjects under 18 years of age. Since this is a P46 procedure and the study was not part of the EU RMP, only the paediatric data are assessed. The paediatric data was presented in Interim Analysis 3 of the study (cut-off date 01 Mar 2022).

Twelve patients under the age of 18 years (12-17 years) were enrolled in the study. Five of the subjects were new users, seven prevalent users.

For the paediatric subpopulation, only the primary endpoint has been presented separately. The eligibility criteria did not include any minimum required HAE attack rate at baseline. The mean HAE attack rate/ month at baseline was therefore lower than in the pivotal clinical studies. A decrease in mean HAE attack rate/month on treatment from 1.19 to 0.09 was observed in new paediatric

lanadelumab users (n=5). In prevalent paediatric lanadelumab users (n=7), the mean HAE attack rate/month during the observation period was 0. This is largely in line with the previous experience of lanadelumab.

In total, 12 treatment emerging adverse event (TEAE) were reported in the paediatric subpopulation. No SAE was reported. There were no fatal event or discontinuation due to TEAE reported in the paediatric subpopulation. The MAH has not provided any summary of the reported TEAE per SOC and PT for the paediatric subpopulation, which would have been expected. Nonetheless, since no adverse events were deemed serious and all events were mild or moderate, this is not further pursued.

3. CHMP's overall conclusion and recommendation

The effectiveness of lanadelumab in the paediatric subpopulation of study SHP643-403 is largely in line with the previous experience of lanadelumab. The safety seems to be in line with the known safety profile of lanadelumab.

The benefit/risk ratio for Takhzyro remains unchanged.

☒ **Fulfilled:**

No regulatory action required.