15 September 2022
EMA/CHMP/804964/2022
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/P46/004

Note

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

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1. Introduction

On 25 March 2022, 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.

After circulation of the preliminary AR, EMA was notified by the MAH that an error had been discovered in the CSR of study SHP643-301 related to the calculation of patient-years for the dosing frequency columns in the data tables for the overall study period and overall treatment period. Thus, an updated preliminary AR was circulated, in which an amended CSR for review was requested.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study SHP643-301 is part of the hereditary angioedema Paediatric Investigation Plan (001864-PIP01-15), with latest EMA Decision number P/0022/2022.

The CSR is provided as a P46 legally binding measure (LEG), as no changes to the PI are proposed with this submission.

2.2. Information on the pharmaceutical formulation used in the study

The investigational product was a sterile, preservative-free, ready-to-use solution with a lanadelumab concentration of 150 mg/mL provided in a single-use 2-mL glass vial (150 mg/1 mL) identical to the commercially available product. For use in paediatric subjects enrolled in this study (2 to <12 years) less than 12 years of age, the full 1 mL (150 mg dose) was to be withdrawn from the vial and administered to the subject.

CHMP comment

The commercial product was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

Lanadelumab is approved in EU for routine prophylaxis to prevent attacks of Hereditary angioedema (HAE) in patients 12 years and older since 2018. The recommended starting dose for lanadelumab is 300 mg every 2 weeks (q2wks) administered as a subcutaneous (SC) injection. In patients who are stably attack-free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks (q4wks) may be considered.

The MAH submitted a final report for:

- ***Study SHP643-301***: *An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 years of Age (SPRING STUDY)*

2.3.2. Clinical study SHP643-301 (*SPRING*)

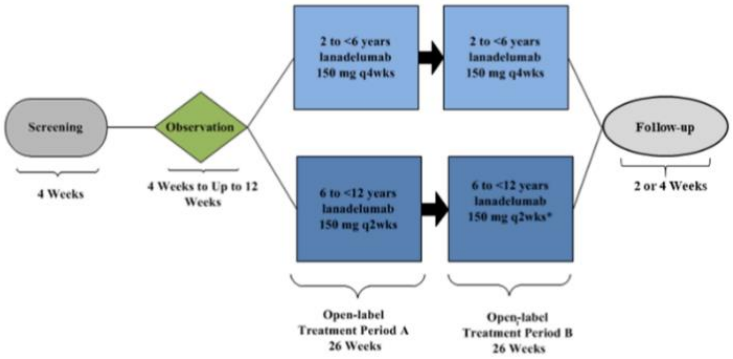
CHMP comment

The MAH has informed their intention to submit an indication extension to paediatric patients 2 years and older based on the results from Study SHP643-301. No update of the SmPC is proposed in the current procedure. Therefore, only a brief assessment of key findings in Study SHP643-301 will be performed in this report. A thorough assessment of Study SHP643-301 will be undertaken in the upcoming variation, together with any additional paediatric data submitted at that time point.

Description

Study SHP643-301 was an open-label study in paediatric subjects 2 to <12 years of age (Figure 1: SHP643-301 Study Design)

Figure 1: SHP643-301 Study Design



q2wks=every 2 weeks; q4wks=every 4 weeks

Subjects 6 to <12 years of age were to receive lanadelumab 150 mg q2wks in Treatment Period A and could have remained on the same dose regimen in Treatment B or, if the subjects had been well controlled (eg, attack-free) for 26 weeks, the subjects could switch to a dose of 150 mg q4wks at the discretion of the investigator and following approval by the sponsor's medical monitor.

Subjects 2 to <6 years of age were to receive lanadelumab 150 mg q4wks in both Treatment Period A and Treatment Period B.

CHMP comment

The MAH claims that the open label, uncontrol design of the study was driven by feasibility. The MAH argues that this could be compensated by efficacy and safety of lanadelumab versus placebo having been shown in e.g., the pivotal adult study DX-2930-03 (*HELP*). Furthermore, the MAH notes that a cross-over design with placebo could have alleviated the issue of small cohorts, such a design is not feasible given the very long half-life of lanadelumab

This may need further discussion in a future application for an extended indication. The MAH could consider providing prevalence data from the literature for HAE in different age cohorts with such an application to support the claim that a controlled study would not be feasible.

Methods

Study participants

Subjects aged 2 to <12 years of age at screening with a documented diagnosis of HAE (Type I or II) were enrolled. The diagnosis of HAE was based upon a clinical history consistent with HAE and diagnostic testing results obtained during screening from a sponsor-approved central laboratory. Moreover, a historical baseline HAE attack rate of at least 1 attack per 3 months was required for eligibility.

CHMP comment

The eligibility criteria in Study SHP643-301 were very similar to the eligibility criteria in Study DX-2930-03 (*HELP*) (the pivotal study at the original marketing authorisation for Takhzyro), including restriction of eligibility to subjects with HAE Type I or II.

Treatments

The lanadelumab dose regimens were:

- 150 mg q2wks for subjects 6 to <12 years old (with an option to switch to 150 mg q4wks after 26 weeks of treatment)
- 150 mg q4wks for subjects 2 to <6 years old

The proposed fixed-dose regimens of lanadelumab 150 mg q2wks in subjects 6 to <12 years of age and lanadelumab 150 mg q4wks in subjects 2 to <6 years of age were expected to provide similar exposure to lanadelumab 300 mg q2wks, the recommended dose regimen in the lanadelumab prescribing information for adults and adolescents with HAE. The proposed dose regimens were based on the population PK modelling and simulation.

CHMP comment

The dose regimens will be assessed in a future application for a paediatric indication.

Objective(s)

The primary objective of this study was to evaluate the safety and PK of lanadelumab in paediatric subjects (2 to <12 years of age) with HAE.

Outcomes/endpoints

Assessment of safety was a primary endpoint for Study SHP643-301.

Clinical outcome measures were secondary endpoints for Study SHP643-301. These outcomes were based on 5 efficacy evaluation periods: the overall treatment period (Day 0 through Day 364), Treatment Period A (Day 0 through Day 182), Treatment Period B (Day 183 through Day 364), an overall presumed steady-state period (Day 70 through Day 364), and the presumed steady-state period for Treatment Period A (Day 70 through Day 182).

The primary clinical outcome endpoint was the normalized number of investigator-confirmed HAE attacks for the overall treatment period. Key clinical outcome endpoints included normalized number of investigator-confirmed HAE attacks for each efficacy evaluation period other than the overall treatment period and achievement of attack-free status for each efficacy evaluation period.

Sample size

The sample size for this paediatric study was driven by feasibility considerations as enrolment of paediatric subjects 2 to <12 years old was expected to be difficult. The primary emphasis was to assess the safety and PK of lanadelumab in this age group but also to generate data on clinical outcomes if subjects had sufficient baseline attack frequency for evaluation. At least 20 subjects were to be enrolled to ensure that a minimum of 15 subjects complete 1 year (52 weeks) of treatment on the study

Randomisation and blinding (masking)

N/A

Statistical Methods

CHMP comment
The statistical methods will be assessed in a future application for a paediatric indication. Very briefly, statistical analyses were descriptive in nature.

Results

Participant flow

A total of 24 subjects were screened. Of these 24 subjects, three subjects were screen failures. The remaining 21 subjects received at least one dose of lanadelumab and were therefore included in the safety, PK, and PD sets. Overall, 20 (95.2%) subjects completed Treatment Period A, Treatment Period B, and the study.
One (4.8%) subject in the 2 to <6 years-cohort discontinued the study prematurely due to withdrawal by the parent/guardian.

CHMP comment
The MAH aimed at including at least 20 subjects in the study. This was fulfilled, as 21 subjects entered the study. Of these, 20 subjects completed the study. The planned number of subjects with one-year-data was thereby reached.

Recruitment

The study was conducted in 17 centres across five countries (US, Canada, Spain, Hungary, and Germany)

CHMP comment
In total, 29% of the subjects were from Europe.

Baseline data

There were approximately equal numbers of female (12 [57%]) and male (9 [43%]) subjects and most subjects where White (20 [95%]).

The overall mean (SD) age of subjects was 7.9 (2.1) years, and the median (range) age of subjects was 8.7 (3.5-10.9) years. The majority of subjects (17 [81%]) were in the 6 to <12 years age group.

The overall mean (SD) age at onset of angioedema symptoms was 3.2 (2.7) years.

The mean (SD) number of attacks in the last year overall was 15.5 (14.66), the majority (16 [76.2%]) were of moderate severity and lasted a mean (SD) of 2.7 (3.85) days.

The primary attack location for most subjects prior to entering the study (13 [62%]) was in the abdominal region. Approximately a third of subjects (7 [33%] subjects) experienced attacks in the peripheral region and 1 (4.8%) subject reported laryngeal as the primary attack location.

Subjects reported a mean (SD) baseline HAE attack rate of 1.8 (1.5) attacks per month.

CHMP comment

Only four subjects were recruited to the 2 to <6 years-cohort, receiving the 150 mg q4wks-dosing. Furthermore, one of these subjects discontinued the study before reaching three months.

This will be further discussed in a future application for a paediatric indication.

Pharmacokinetics results

Pharmacokinetic analyses were performed on all subjects in the safety set that had at least 1 evaluable postdose PK concentration value (N=21). Mean concentration-time profiles of lanadelumab were assessed by age and the original treatment assignment at the start of the study (ie, subjects aged 2 to <6 years, 150 mg q4wks; subjects aged 6 to <12 years, 150 mg q2wks). The observed mean concentrations in plasma suggest that PK steady-state was achieved for subjects aged 6 to <12 years (originally assigned q2wk dosing) by Visit 8 (Day 56). For subjects aged 2 to <6 years (originally assigned q4wks dosing), predose mean concentrations in plasma suggest that PK steady-state was observed by Visit 12 (Day 84).

When compared to adult and adolescent HAE subjects receiving the marketed dose of lanadelumab (300 mg q2wks), children aged 6 to <12 years (originally assigned lanadelumab 150 mg q2wks) exhibited similar steady-state exposure while children aged 2 to <6 years (originally assigned lanadelumab 150 mg q4wks) exhibited similar steady-state total and maximum exposure but lower exposure at the end of the dosing interval.

CHMP comment

The pharmacokinetic results in the paediatric population, and comparison to adult data will be further assessed in a future application for a paediatric indication. The model-based analyses have not been assessed at this time.

Efficacy results

For the efficacy analyses, subjects were analysed on the actual treatment received: subjects received treatment based on age in Treatment Period A (q4wks for subjects aged 2 to <6 years; q2wks for subjects aged 6 to <12 years) and in Treatment Period B, dose modification from q2wks to q4wks was allowed for subjects aged 6 to <12 years who were well-controlled (e.g., attack-free).

Normalized Number of Investigator-confirmed HAE Attacks

Table 1: Summary of Normalized Number of Investigator-confirmed HAE Attacks by Treatment Group During Overall Treatment Period and Overall Presumed Steady-state Period (Safety Set)

	Lanadelumab 150 mg q4wks[a] (N=11)			Lanadelumab 150 mg q2wks[a] (N=18)			Total (N=21)		
Parameter Period Statistic	Actual Value	Change From Baseline	Percent Change From Baseline	Actual Value	Change From Baseline	Percent Change From Baseline	Actual Value	Change From Baseline	Percent Change From Baseline
HAE Attack Rate (attacks/month)[b]									
Baseline Observation Period									
n	11			18			21		
Mean (SD)	1.45 (0.790)			1.91 (1.631)			1.84 (1.525)		
Median	1.12			1.28			1.44		
Min, max	0.6, 3.3			0.6, 6.7			0.6, 6.7		
Overall Treatment Period									
n	11	11	11	18	18	18	21	21	21
Mean (SD)	0.07 (0.219)	-1.38 (0.640)	-97.98 (6.715)	0.08 (0.157)	-1.83 (1.607)	-94.43 (15.531)	0.08 (0.170)	-1.76 (1.489)	-94.78 (14.606)
Median	0.00	-1.12	-100.00	0.00	-1.20	-100.00	0.00	-1.28	-100.00
Min, max	0.0, 0.7	-2.5, -0.6	-100.0, -77.7	0.0, 0.5	-6.5, -0.3	-100.0, -34.8	0.0, 0.5	-6.5, -0.3	-100.0, -34.8
Overall Presumed Steady-state Period									
n	10	10	10	18	18	18	20	20	20
Mean (SD)	0.09 (0.288)	-1.43 (0.605)	-97.21 (8.838)	0.07 (0.143)	-1.84 (1.628)	-94.83 (13.914)	0.08 (0.165)	-1.81 (1.528)	-94.86 (13.449)
Median	0.00	-1.41	-100.00	0.00	-1.18	-100.00	0.00	-1.47	-100.00
Min, max	0.0, 0.9	-2.3, -0.6	-100.0, -72.1	0.0, 0.5	-6.6, -0.3	-100.0, -42.4	0.0, 0.5	-6.6, -0.3	-100.0, -42.4

HAE=hereditary angioedema; max=maximum; min=minimum; q2wks=every 2 weeks; q4wks=every 4 weeks; SD=standard deviation.
a The actual treatment received during the given study period.
b The investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the given study period divided by the number of days the subject contributed to the period multiplied by 28 days. The investigator-confirmed HAE attack rate during the baseline observation period was the baseline HAE attack rate.
Notes: A month was defined as 28 days. Overall presumed steady-state period was from Day 70 through Day 364.

Achievement of Attack-free Status

During the overall treatment period, 16 (76.2%) subjects achieved attack-free status, the mean (SD) percentage of attack-free days during this period was 99.53 (0.99) %. Similar results were observed during Treatment Period A (17 [81.0%] subjects) and Treatment Period B (15 [75.0%] subjects).

CHMP comment

The key efficacy endpoints will be further assessed in a future application for a paediatric indication.

In the total population, HAE attack rate/month (mean [SD]) was reduced from 1.84 [1.5] to 0.08 [0.2] at the end of the Overall treatment period (D0 to D364) across both treatments. Similar results were observed for the additional efficacy evaluation periods Treatment Period A and Treatment Period B.

Overall, 76% of the subjects achieved of investigator-confirmed HAE attack-free status with 99% attack-free days.

The "presumed steady state"-data are considered of less interest.

Safety results

Assessment of safety was a primary endpoint for Study SHP643-301. The following safety results are based on the safety set. Due to dose modifications in Treatment Period B, a subject may have been treated with both q4wk and q2wk dosing regimens. Safety events were counted based on the actual treatment the subject received at the time of the event. As such, an individual subject may have been counted in both the q4wk and q2wk treatment groups, but the safety event was only counted once.

There were no deaths, serious adverse events (SAEs), discontinuations due to treatment-emergent adverse events (TEAEs), or investigator-confirmed AESIs reported in this study.

Overall, 17 (81.0%) of 21 subjects had 210 non-HAE attack TEAEs: 6 (54.5%) of 11 subjects (43 events) in the q4wks group and 15 (83.3%) of 18 subjects (167 events) in the q2wks group. The most commonly reported non-HAE attack TEAE was injection site pain (6 [28.6%] of 21 subjects, 88 events). The majority of TEAEs were mild or moderate in severity. One subject reported 20 severe non-HAE attack TEAEs of injection site erythema that were considered related to lanadelumab. Most of these severe events recovered within 1 hour and no treatment interruption was reported.

Five (23.8%) of 21 subjects had 23 HAE attack TEAEs: 1 (9.1%) of 11 subjects (5 events) in the q4wks group and 5 (27.8%) of 18 subjects (18 events) in the q2wks group. All HAE attack TEAEs were HAE events.

There were no clinically meaningful changes in laboratory or vital sign values during the treatment period identified in subjects originally assigned to q4wks or q2wks treatment.

At baseline, no subjects were ADA positive in either treatment group. For the overall treatment period, 3 (15.0%) subjects were ADA positive; all of which were in the q2wks group (3 [15%] subjects in Treatment Period A and 1 [5.3%] subject in Treatment Period B). Of these, 1 (33.3%) subject had neutralizing antibodies. The 3 subjects who were ADA positive were attack-free during the study, had similar lanadelumab concentrations and cHMWK levels than subjects who were ADA negative, and had no differences in hypersensitivity related events or TEAEs

CHMP comments

There were no deaths, serious adverse events (SAEs), discontinuations due to treatment-emergent adverse events (TEAEs), or investigator-confirmed AESIs reported in this study.

Of the reported 209 adverse events (AE), 127 were reported in the SOC General disorders and administration site conditions, mainly injection site reactions. Most AE were reported by one single subject.

Three subjects developed anti-drug antibodies (ADA) of which one was reported with neutralising antibodies. The three subjects were ADA positive were attack-free during the study and reported no differences in hypersensitivity related events or TEAEs.

Taken together, no new and unexpected safety findings were reported, affecting the approved population or in any way considered in need of additional actions at this time point.

2.3.3. Discussion on clinical aspects

Lanadelumab is approved in EU for routine prophylaxis to prevent attacks of Hereditary angioedema (HAE) in patients 12 years and older. In the current procedure, the MAH submitted a final report for Study SHP643-301, an open-label study in paediatric subjects 2 to <12 years of age in accordance with Article 46.

The MAH has informed their intention to submit an indication extension to paediatric patients 2 years and older based on the results from Study SHP643-301. No update of the SmPC is proposed in the current procedure. Therefore, only a brief assessment of key findings in Study SHP643-301 is considered within the scope of the current procedure. A thorough assessment of Study SHP643-301 will be undertaken in the upcoming variation, together with any additional paediatric data submitted at that time point.

The chosen dose regimens (150 mg q2wks for subjects 6 to <12 years old; 150 mg q4wks for subjects 2 to <6 years old) will be assessed in a future application for a paediatric indication.

The study enrolled 21 subjects. Only four subjects were recruited to the 2 to <6 years-cohort. Furthermore, one of these subjects discontinued the study before reaching three months. The remaining 20 subjects completed the study and the study drug.

In the total population, HAE attack rate/month (mean [SD]) was reduced from 1.84 [1.5] to 0.08 [0.2] at the end of the Overall treatment period (D0 to D364) across both treatments. Overall, 76% of the subjects achieved of investigator-confirmed HAE attack-free status with 99% attack-free days.

There were no deaths, serious adverse events (SAEs), discontinuations due to treatment-emergent adverse events (TEAEs), or investigator-confirmed AESIs reported in this study. No new and unexpected safety findings were reported, affecting the approved population or in any way considered in need of additional actions at this time point.

3. Rapporteur's updated overall conclusion and recommendation

Study SHP643-301 on the treatment of Hereditary Angioedema (HAE) in paediatric subjects 2 to <12 years of age was submitted in accordance with Article 46 of Regulation (EC) No1901/2006.

During the course of the current procedure, EMA was notified that an error was discovered in the CSR of study SHP643-301 related to the calculation of patient-years for the dosing frequency columns in the data tables for the overall study period and overall treatment period. An updated CSR was provided. The exposure was erroneously overestimated in the initial CSR compared to the corrected data and, as a consequence, the rate of events is higher than originally presented. However, the number of events of all kinds (TEAE, SAE, fatal events etc) were correct.
This is not considered to affect the conclusion that no new and unexpected safety findings were reported affecting the approved population or in any other way considered in need of additional actions at this time point.

Data from Study SHP643-301 will be assessed in detail in the upcoming variation.

The current procedure is considered approvable.

The benefit/risk ratio for the approved indication remains unchanged-

☒ **Fulfilled:**

No further action required; however, further data are expected in the context of an extension prior to any conclusion on product information amendments is made.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The Assessors have been notified that an error was discovered in the CSR of study SHP643-301 related to the calculation of patient-years for the dosing frequency columns in the data tables for the overall study period and overall treatment period. Thus, an amended CSR for review is requested.

MAH responses to Request for supplementary information

Question 1:

The Assessors have been notified that an error was discovered in the CSR of study SHP643-301 related to the calculation of patient-years for the dosing frequency columns in the data tables for the overall study period and overall treatment period. Thus, an amended CSR for review is requested.

Summary of the MAH's response

The Applicant is providing the amended CSR with this response submission. The CSR Amendment 1 body, synopsis and signature page with the amended data tables can be located in Module 5, section 5.3.5.2.

Assessment of the MAH's response

During the course of the current application, the MAH notified EMA that there was an error in the CSR of study SHP643-301presented in this procedure 25 April 2022. The error pertained to calculation of patient-years (PTY) for the dosing frequency columns in the data tables for the overall study period and overall treatment period. The MAH has provided an updated CSR as requested.

The exposure was erroneously overestimated in the initial CSR compared to the corrected data (10.0 PTY versus 5.6 PTY, respectively, in the q4w arm and 17.9 PTY versus 14.5 PTY in the q2w arm). However, the number of events of all kinds (TEAE, SAE, fatal events etc) were correct. As a consequence, the rate of events is higher than originally presented, and, since the error was not proportionate between the treatment arms, the difference between the treatment arms is smaller. As an example, the rate of "Any TEAE in ≥2 subjects" during the Overall treatment period was originally given to 4.2 events per PTY in the q4w arm and 9.3 events per PTY in the q2w, but corrected to 7.6 and 11.5 events per PTY, respectively for the q4w and q2w arms.

This is not considered to affect the conclusion that no new and unexpected safety findings were reported affecting the approved population or in any other way considered in need of additional actions at this time point. Data from Study SHP643-301 will be assessed in detail in the upcoming variation.

Conclusion

Issue **resolved**.