24 July 2025
EMADOC-1700519818-1976152
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

TAKHZYRO

Lanadelumab

Procedure no: EMA/PAM/0000258207

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**
☐	Start of procedure	24 March 2025	24 March 2025
☐	CHMP Rapporteur AR	28 April 2025	24 April 2025
☐	CHMP comments	12 May 2025	n/a
☐	Updated CHMP Rapporteur AR	15 May 2025	n/a
☐	Request for supplementary information	22 May 2025	22 May 2025
☐	Submission of MAH responses	24 June 2025	23 June 2025
☐	Re-Start of procedure	25 June 2025	25 June 2025
☐	CHMP Rapporteur AR	9 July 2025	9 July 2025
☐	CHMP comments	14 July 2025	n/a
☐	Updated CHMP Rapporteur AR	17 July 2025	n/a
☒	CHMP outcome	24 July 2025	24 July 2025

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1. Introduction

On 7 March 2025, 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 TAK-743 (SHP643)-402, ENABLE ("A Three-year, Non-interventional, Prospective, Multicenter Study to Evaluate the Long-term Effectiveness of Lanadelumab in Real-world Clinical Practice") 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:

- ***Study TAK-743 (SHP643)-402:*** *ENABLE: A Three-year, Non-interventional, Prospective, Multicenter Study to Evaluate the Long-term Effectiveness of Lanadelumab in Real-world Clinical Practice*

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

ENABLE was a multicentre, noninterventional, prospective study involving patients with HAE who began treatment with lanadelumab in accordance with current product labelling in real-world clinical practice.

As this was a noninterventional study, it did not influence treatment decisions or interfere with standard medical care. Patients were followed for up to 24 months (if enrolled on or after 1 March 2021) or 36 months (if enrolled before 1 March 2021) after their enrollment date.

Methods

Study participants

Eligible subjects should have initiated lanadelumab in accordance with current product labelling and have initiated lanadelumab in accordance with current product labelling and have available HAE attack-

related data 3 months before enrolment. Exclusion criteria included concomitant medications that were contraindicated to treatment with lanadelumab according to current product labelling, pregnancy or breastfeeding.

Treatments

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

Objective

The primary objective for this study was to

- Evaluate the effectiveness of lanadelumab on the occurrence of hereditary angioedema (HAE) attacks in real-world clinical practice

The secondary objectives for this study were to evaluate

- Effectiveness of lanadelumab on additional clinical measures and on patient-reported outcomes (PROs) and patients' caregiver-reported outcomes
- Utilization patterns of lanadelumab
- Safety and tolerability of lanadelumab

The exploratory objectives for this study were to evaluate the effectiveness of lanadelumab on the

- Achievement of attack-free status
- Control of HAE

Outcomes/endpoints

The primary effectiveness outcome was the IRR of on-treatment patient-reported HAE attacks after lanadelumab initiation compared with the history of HAE attacks from the last 3 months before lanadelumab use

Sample size

Approximately 200 subjects were planned for inclusion.

Randomisation and blinding (masking)

N/A

Statistical Methods

Quantitative parameters were summarized by presenting the population, the mean, SD, median, Q1 (25%), Q3 (75%), and minimum and maximum values. Categorical variables were summarized as frequencies and percentages. All responses on PROs and caregiver-reported outcomes were scored per the developer's guidelines, including the approach to any missing item responses.

The primary effectiveness outcome was the IRR of on-treatment patient-reported HAE attacks after lanadelumab initiation compared with the history of HAE attacks from the last 3 months before lanadelumab use, which were analyzed using a negative binomial generalized linear model with an unstructured correlation matrix. Time-to-event outcomes were assessed using the Kaplan-Meier

method. Regarding the secondary outcomes, summary statistics were reported for the Angioedema Control Test (AECT), AE-QoL, FSS, HADS, TSQM-9, WPAI:GH, and AC-QoL per the defined observational periods. Finally, safety events were evaluated and presented descriptively as well.

Results

Participant flow

The total number of subjects enrolled in the study was 139.

A total of 8 paediatric patients were enrolled in the study and were included in the safety set and the full analysis set (FAS). Two paediatric patients discontinued the study due to withdrawal by patient and physician decision, respectively.

Recruitment

The first patient was enrolled on 11 December 2019, and the last patient was enrolled on 12 September 2022.

Patients were enrolled from 18 sites across Austria, Germany, Israel, Kuwait, Italy, Spain, and Switzerland.

Baseline data

Of the 8 paediatric patients, 5 were female, none were Hispanic or Latino, and all were White. The paediatric patients were all aged 12 to <18 years. The youngest subject enrolled was 14 years old.

Six paediatric patients had HAE-C1INH-Type1, 1 had HAE-C1INH-Type2, and 1 had HAE-nC1INH

Efficacy results

HAE Attack rate

The observed HAE attack rates in paediatric patients based on the patient diary attack records are summarized in Table 1

Table 1. Observed HAE Attack-Rate Comparison from Patient Diary Attack Records (Adolescents Only, FAS) (modified from Table 14.2.1c by Assessor)

	FAS (N=8)			
	Pre-Lanadelumab	During-Lanadelumab		
	(N=8)	Early [a] (N=8)	Steady-state [b] (N=8)	Cumulative (N=8)
All Lanadelumab users	N=8	N=8	N=8	N=8
Attack rate (Attacks/month) [d]				
n	8	8	8	8
Mean (SD)	5.61 (4.896)	1.27 (1.291)	0.68 (1.076)	0.76 (1.112)
Median	4.97	0.81	0.14	0.23
Q1, Q3	2.00, 7.00	0.41, 2.23	0.07, 1.11	0.09, 1.24
Min, Max	0.8, 16.1	0.0, 3.2	0.0, 2.8	0.0, 2.9
The ratio of attack rate between during-Lanadelumab period and pre-Lanadelumab period [e]				
n	Ref.	8	8	8
Mean (SD)	Ref.	0.39 (0.480)	0.13 (0.171)	0.18 (0.219)
Median	Ref.	0.20	0.08	0.09
Q1, Q3	Ref.	0.11, 0.51	0.02, 0.15	0.03, 0.32
Min, Max	Ref.	0.0, 1.5	0.0, 0.5	0.0, 0.6
(1 - Ratio) %	Ref.	60.99	87.19	82.10
Lanadelumab users, newly on prophylaxis [f]	N=6	N=6	N=6	N=6

Attack rate (Attacks/month) [d]				
n	6	6	6	6
Mean (SD)	6.54 (5.298)	1.56 (1.392)	0.87 (1.200)	0.97 (1.229)
Median	5.67	1.22	0.19	0.36
Q1, Q3	3.00, 8.00	0.41, 3.25	0.08, 1.98	0.11, 2.08
Min, Max	0.8, 16.1	0.0, 3.2	0.0, 2.8	0.0, 2.9
The ratio of attack rate between during-Lanadelumab period and pre-Lanadelumab period [e]				
n	Ref.	6	6	6
Mean (SD)	Ref.	0.44 (0.549)	0.15 (0.194)	0.21 (0.246)
Median	Ref.	0.20	0.08	0.09
Q1, Q3	Ref.	0.14, 0.61	0.03, 0.17	0.04, 0.49
Min, Max	Ref.	0.0, 1.5	0.0, 0.5	0.0, 0.6
(1 - Ratio) %	Ref.	56.22	85.39	78.96

Assessor's comment

The baseline attack rate in ENABLE, 6.54 attacks/months in lanadelumab naïve subjects, was higher than in some other studies, e.g., the pivotal study HELP for approval of adults and adolescents over the age of 12 years (3.7 attacks/month). A reduction in attack rate of approximately 80% was seen in ENABLE.

The results from the ENABLE study do not indicate any lack of efficiency in the paediatric study population.

HAE Attack details

The analysis of the HAE attacks is based on the patient diary attack records. One paediatric patient did not complete the diary.

During the pre-lanadelumab period, no attack details, including affected body part, HAE severity, and HAE treatment, were reported for any of the attacks.

During the early period of prophylactic treatment with lanadelumab in the paediatric population, for the 25 attacks for which detailed information was provided, the most frequently affected body part was the peripheral body (19 [76.0%] attacks), followed by the abdomen (12 [48.0%] attacks). Most attacks were Grade 3 (severe; 15 [60.0%] attacks) or Grade 2 (moderate; 7 [28.0%] attacks) in severity; no Grade 4 (life-threatening) attacks were reported. 22 [88.0%] attacks required on-demand treatment, with icatibant being the most common treatment (14 [63.6%] of treated attacks), followed by plasma-derived C1INH (13 [59.1%] of treated attacks).

During the steady-state period of prophylactic treatment with lanadelumab, for the 92 attacks for which detailed information was provided, the most frequently affected body part was the abdomen (65 [70.7%] attacks, followed by the peripheral body (25 [27.2%] attacks). Most attacks were Grade 2 (moderate; 53 [57.6%] attacks) or Grade 3 (severe; 34 [37.0%] attacks) in severity; no Grade 4 (life-threatening) attacks were reported. 90 [97.8%] attacks required on-demand treatment, with icatibant being the most common treatment (60 [66.7%] of treated attacks), followed by plasma-derived C1INH (43 [47.8%] of treated attacks).

Assessor's comment

This is noted.

Healthcare resource utilization (HCRU) outcomes

In the paediatric study population, 3 paediatric patients experienced a total of 10 healthcare encounters within 3 months before enrolment and 22 healthcare encounters after enrolment (from enrolment to first lanadelumab exposure [≤4 days] and the post-lanadelumab period [mean duration: 27.45 months; range: 7.1-39.6 months]). All healthcare encounters were emergency room visits.

Assessor's comment

This is noted.

HRQoL Outcomes

AECT

The AECT is a PRO instrument used to assess control of angioedema among patients with recurrent angioedema (including HAE). A total score of ≥10 indicates well controlled disease.

At baseline (n=6), the mean (SD) AECT total score was 5.3 (2.94). The mean (SD) AECT total score increased to 8.7 (4.93) at Month 1 (n=6) and to 13.2 (3.90) at Month 2 (n=5), suggesting well-controlled disease. The improved mean (SD) AECT total score was maintained throughout the study period: 13.6 (3.91) at Month 24 (n=5) and 13.3 (2.31) at Month 36 (n=3).

AE-QoL

A score of ≥39 in AE-QoL indicates moderate to large impairment in quality of life (QoL).

At baseline (n=7), the mean (SD) AE-QoL total score was 40.8 (25.14). At Month 1 (n=6), the mean AE-QoL total score decreased to 30.4 (27.94), suggesting improved HRQoL and lower impairment. The improved mean (SD) AE-QoL total score was maintained throughout the study period: 20.3 (24.97) at Month 24 (n=5) and 21.6 (12.25) at Month 36 (n=3). Similar trend was observed in the domain scores (functioning score, fatigue/mood score, fears/shame score, and food score).

Assessor's comment

For the patient related outcome (PRO) scales FSS and HADS, the MAH has only presented individual data for the paediatric population a. This is however not pursued as this is not expected to have any impact on the B/R in the approved paediatric population.

Safety results

None of the 8 paediatric patients experienced a TEAE that was considered related to lanadelumab.

Assessor's comment

The only information on safety in the paediatric population presented by the MAH is the statement that no paediatric patients experienced a TEAE that was considered related to lanadelumab.

This presentation is not considered adequate. The MAH is asked to present a short summary of TEAEs, excluding HAE attacks, in the paediatric population of the ENABLE study. It should be stated whether any Serious adverse event (SAE) was reported in the paediatric population and whether any adverse event led to discontinuation of lanadelumab in this population. Preferred terms (PT) reported for more than one subjects should be presented **(LoQ)**.

2.3.3. Discussion on clinical aspects

ENABLE was a multicentre, noninterventional, prospective study involving patients with HAE who began treatment with lanadelumab in accordance with current product labelling in real-world clinical practice. A total of 8 paediatric patients were enrolled in the study.

The results from the ENABLE study do not indicate any lack of efficiency in the paediatric study population.

The MAH has presented an extended summary of safety, as requested.

There were no fatal events during the study. No subject discontinued from the study or from lanadelumab treatment due to lanadelumab-related TEAE.

In total, 6/8 subject (75%) reported at least one TEAE. None of the TEAEs were assessed as related by the Investigator. Data sufficient for secondary assessment was not provided.

Three subjects reported in total five SAEs: migraine in one subject, abdominal pain and arthralgia in one subject and thoracic vertebral fracture and pneumothorax in one subject. No additional information is provided.

Only two Preferred Terms were reported for more than one subject: Toothache [2] and Hyperuricaemia [2]. The report of hyperuricaemia is somewhat notable, since this is not a common condition in the paediatric population. Notwithstanding, no conclusions could be drawn from two reports.

It is agreed with the MAH that no new safety signals for lanadelumab emerged from the paediatric population of ENABLE. No additional actions are considered warranted.

3. Rapporteur's overall conclusion and recommendation

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

No amendments to the Product information are proposed by the MAH. This is agreed.

The benefit/risk ratio for Takhzyro remains unchanged.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

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

1. The safety presentation for the paediatric subpopulation is not considered adequate. The MAH is asked to present a short summary of TEAEs, excluding HAE attacks, in the paediatric population of the ENABLE study. It should be stated whether any Serious adverse event (SAE) was reported in the paediatric population and whether any adverse event led to discontinuation of lanadelumab in this population. Preferred terms (PT) reported for more than one subjects should be presented

The timetable is a 30-day response timetable with clock stop.

MAH responses to Request for supplementary information

Question 1

The safety presentation for the paediatric subpopulation is not considered adequate. The MAH is asked to present a short summary of TEAEs, excluding HAE attacks, in the paediatric population of the ENABLE study. It should be stated whether any Serious adverse event (SAE) was reported in the

paediatric population and whether any adverse event led to discontinuation of lanadelumab in this population. Preferred terms (PT) reported for more than one subjects should be presented

Summary of MAH's response

The MAH has prepared summaries of non-HAE attack TEAEs, including a presentation by SOC and PT, for the paediatric subpopulation in the ENABLE study.

The ENABLE study included a paediatric subpopulation of 8 subjects, all adolescents aged 12 to <18 years. Non-HAE attack TEAEs in the paediatric subpopulation are summarized in Table 2.

Table 2. Summary of Treatment-Emergent Adverse Events (TEAE) (Excluding HAE Attack Reported Adverse Events) (Adolescents Only, Safety Set) (edited by Assessor)

	Safety Set (N=8)	
	Patients	Events
Any TEAE, n (%)	6 (75)	36 (100)
Severity, n (%)		
Mild	0	0
Moderate	2 (33.3)	15 (41.7)
Severe	4 (66.7)	14 (38.9)
Missing	0	7 (19.4)
Seriousness, n (%)		
Non-serious	3 (50.0)	31 (86.1)
Serious	3 (50.0)	5 (13.9)
Missing	0	0
Relationship to Lanadelumab treatment, n (%)		
Related	0	0
Not related	6 (100.0)	36 (100.0)
Missing	0	0

No subject discontinued from the study or from lanadelumab treatment due to Lanadelumab-related TEAE.

As shown in Table 3, these SAEs included simultaneous SAEs of thoracic vertebral fracture and pneumothorax in 1 subject, simultaneous SAEs of abdominal pain and arthralgia in 1 subject, and an SAE of migraine in 1 subject. The severity of all SAEs was severe.

Thoracic vertebral fracture was ongoing, and all other SAEs were resolved at the last assessment.

Table 3. SAEs in the Pediatric Population of ENABLE

Subject ID	SOC/PT	Start/Stop Dates	Severity	Treatment	Relationship	Action Taken	Outcome	Caused Discon-tinuation?
	Nervous system disorders/ migraine		Severe	Medication	Not related	Not applicable	Recovered/ resolved	No
	Gastrointestinal disorders/ abdominal pain		Severe	Medication	Not related	Not applicable	Recovered/ resolved	No
	Musculoskeletal and connective tissue disorders/ arthralgia		Severe	Medication	Not related	Not applicable	Recovered/ resolved	No
	Injury, poisoning, and procedural complications/ thoracic vertebral fracture		Severe	Medication	Not related	Not applicable	Recovering/ resolving	No
	Respiratory, thoracic and mediastinal disorders/ pneumothorax		Severe	Medication	Not related	Not applicable	Recovered/ resolved	No

Non-HAE attack TEAEs are summarized by MedDRA SOC and PT and relationships to lanadelumab in Table 4.

TEAEs were most commonly reported in the SOCs metabolism and nutrition disorders (5 events in 4 subjects), gastrointestinal disorders (8 events in 3 subjects), and infections and infestations (3 events in 3 subjects). The events reported in 2 subjects were toothache (6 events) and hyperuricemia (2 events). All other PTs were reported in 1 subject.

No new safety signals for lanadelumab emerged from the pediatric population of ENABLE.

Table 4. Treatment-emergent Adverse Events (Excluding HAE Attack Reported Adverse Events) by System Organ Class and Preferred Term (Adolescents Only, Safety Set) (edited and truncated by Assessor)

	Safety Set (N=8)	
System Organ Class (SOC) Preferred Term (PT)	Patients n (%)	Events n (%)
Any TEAE, n (%)	6 (75)	36 (100)
Blood and lymphatic system disorders	1 (12.5)	2 (5.6)
Haemorrhagic diathesis	1 (12.5)	1 (2.8)
Lymphadenopathy	1 (12.5)	1 (2.8)
Congenital, familial and genetic disorders	1 (12.5)	1 (2.8)
Ehlers-Danlos syndrome	1 (12.5)	1 (2.8)
Gastrointestinal disorders	3 (37.5)	8 (22.2)
Toothache	2 (25.0)	6 (16.7)
Abdominal pain	1 (12.5)	1 (2.8)
Nausea	1 (12.5)	1 (2.8)
Infections and infestations	3 (37.5)	3 (8.3)
COVID-19	1 (12.5)	1 (2.8)
Helicobacter gastritis	1 (12.5)	1 (2.8)
Pulpitis dental	1 (12.5)	1 (2.8)
Injury, poisoning and procedural complications	2 (25.0)	2 (5.6)
Limb injury	1 (12.5)	1 (2.8)
Thoracic vertebral fracture	1 (12.5)	1 (2.8)
Metabolism and nutrition disorders	4 (50.0)	5 (13.9)
Hyperuricaemia	2 (25.0)	2 (5.6)
Dairy intolerance	1 (12.5)	1 (2.8)
Iron deficiency	1 (12.5)	1 (2.8)
Type 2 diabetes mellitus	1 (12.5)	1 (2.8)

Musculoskeletal and connective tissue disorders	1 (12.5)	1 (2.8)
Arthralgia	1 (12.5)	1 (2.8)
Nervous system disorders	2 (25.0)	4 (11.1)
Hemiparesis	1 (12.5)	1 (2.8)
Hypoaesthesia	1 (12.5)	1 (2.8)
Migraine	1 (12.5)	1 (2.8)
Neuralgia	1 (12.5)	1 (2.8)
Product issues	1 (12.5)	1 (2.8)
Device expulsion	1 (12.5)	1 (2.8)
Reproductive system and breast disorders	1 (12.5)	1 (2.8)
Endometriosis	1 (12.5)	1 (2.8)
Respiratory, thoracic and mediastinal disorders	2 (25.0)	2 (5.6)
Oropharyngeal pain	1 (12.5)	1 (2.8)
Pneumothorax	1 (12.5)	1 (2.8)
Skin and subcutaneous tissue disorders	2 (25.0)	4 (11.1)
Alopecia	1 (12.5)	1 (2.8)
Cold urticaria	1 (12.5)	1 (2.8)
Drug eruption	1 (12.5)	1 (2.8)
Ingrowing nail	1 (12.5)	1 (2.8)
Vascular disorders	2 (25.0)	2 (5.6)
Hypertension	1 (12.5)	1 (2.8)
Phlebitis	1 (12.5)	1 (2.8)

Assessment of MAH's response

The MAH has presented an extended summary of safety, as requested.

There were no fatal events during the study. No subject discontinued from the study or from lanadelumab treatment due to lanadelumab-related TEAE.

In total, 6/8 subject (75%) reported at least one TEAE. None of the TEAEs were assessed as related by the Investigator. Data sufficient for secondary assessment was not provided.

Three subjects reported in total five SAEs: migraine in one subject, abdominal pain and arthralgia in one subject and thoracic vertebral fracture and pneumothorax in one subject. No additional information is provided.

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It is agreed with the MAH that no new safety signals for lanadelumab emerged from the paediatric population of ENABLE. No additional actions are considered warranted.

Conclusion

Issue **resolved**.