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

RAYVOW

lasmiditan

Procedure no: EMA/PAM/0000347948

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
☐	Start date	25 May 2026	25 May 2026
☐	CHMP Rapporteur AR	29 June 2026	29 June 2026
☐	CHMP comments	13 July 2026	no comments
☐	Updated CHMP Rapporteur AR	16 July 2026	pAR=uAR
☐	CHMP Request for Supplementary Information	23 July 2026	23 July 2026
☐	Submission deadline	18 Aug 2026	17 Aug 2026
☐	Re-start date	19 Aug 2026	19 Aug 2026
☐	CHMP Rapporteur AR	02 Sep 2026	20 Aug 2026
☐	CHMP comments	07 Sep 2026	No comments
☐	Updated CHMP Rapporteur AR	10 Sep 2026	pAR=uAR
☒	CHMP outcome	17 Sep 2026	17 Sep 2026

¹ Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

² Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On 4 May 2026, the MAH submitted the clinical study synopsis for two completed paediatric studies for RAYVOW (lasmiditan), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended:

- H8H-MC-LAHV (LAHV): Pediatric Options for Migraine Relief: A Randomized, Double-Blind, Placebo-Controlled Study of Lasmiditan for Acute Treatment of Migraine (PIONEER-PEDS1);
- H8H-MC-LAHW (LAHW): A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine (PIONEER-PEDS2).

Both studies form part of the agreed Paediatric Investigation Plan (PIP) EMEA-002166-PIP01-17-M08 for lasmiditan and were conducted in paediatric patients aged 6 to less than 18 years with migraine. Study LAHV was designed to evaluate the efficacy, safety and tolerability of lasmiditan for the acute treatment of a single migraine attack, whereas Study LAHW was designed to evaluate the long-term safety, tolerability and efficacy of intermittent lasmiditan treatment over a period of up to 12 months.

According to the MAH, both studies were terminated prematurely following a business decision to permanently discontinue development and marketing of lasmiditan. The MAH stated that this decision was not related to product quality or safety concerns. No changes to the Summary of Product Characteristics are proposed by the MAH.

A short critical expert overview was also provided.

2. Scientific discussion

2.1. Information on the development program

Studies H8H-MC-LAHV (PIONEER-PEDS1) and H8H-MC-LAHW (PIONEER-PEDS2) are part of the paediatric clinical development programme for lasmiditan in the acute treatment of migraine with or without aura in paediatric patients aged 6 to less than 18 years. The studies were conducted in the context of the agreed Paediatric Investigation Plan (PIP) EMEA-002166-PIP01-17-M08.

The paediatric development programme comprised a Phase 1 pharmacokinetic study (H8H-MC-LAHX), a pivotal efficacy and safety study (H8H-MC-LAHV), and a long-term safety study (H8H-MC-LAHW). Study LAHX was used to support the weight-based dosing regimen subsequently implemented in Studies LAHV and LAHW.

- Study LAHV was a Phase 3, randomised, double-blind, placebo-controlled study designed to evaluate the efficacy, safety and tolerability of lasmiditan for the acute treatment of a single migraine attack in paediatric patients.
- Study LAHW was a Phase 3, 12-month, open-label study designed to evaluate the long-term safety and tolerability of intermittent lasmiditan treatment and to collect supportive efficacy data in paediatric patients with migraine.

Studies LAHV and LAHW were terminated prematurely following a business decision to permanently discontinue development and marketing of lasmiditan. According to the MAH, this decision was not related to product quality or safety concerns. No variation application and no updates to the product information are proposed by the MAH.

2.2. Information on the pharmaceutical formulation used in the studies

In study LAHV, lasmiditan film-coated tablets and matching placebo film-coated tablets were used.

Weight-based dosing regimens were implemented to achieve exposures comparable to the adult lasmiditan doses of 50 mg, 100 mg and 200 mg. Participants with body weight ≤ 40 kg received reduced tablet strengths corresponding to the intended adult-equivalent exposures.

In study LAHW, lasmiditan film-coated tablets containing 25 mg, 50 mg, 100 mg and 200 mg of active substance were used. Participants were randomised to weight-based dose regimens corresponding to adult exposures of 100 mg or 200 mg, with dose reduction permitted for tolerability reasons.

The dose selection in both studies was based on pharmacokinetic data generated in the paediatric Phase 1 study H8H-MC-LAHX.

No extemporaneous formulations were used in either study.

2.3. Clinical aspects

Introduction

The MAH submitted clinical study synopses for the two paediatric studies LAHV and LAHW.

Both studies formed part of the agreed paediatric development programme for lasmiditan in the acute treatment of migraine with or without aura in paediatric patients.

Clinical studies

Clinical study H8H-MC-LAHV (PIONEER-PEDS1)

Description

Study title: Pediatric Options for Migraine Relief: A Randomized, Double-Blind, Placebo-Controlled Study of Lasmiditan for Acute Treatment of Migraine (PIONEER-PEDS1).

Study Number: H8H-MC-LAHV.

EudraCT: 2019-004378-24.

EU trial number: 2023-506253-38-00.

Study LAHV was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study evaluating the efficacy, safety and tolerability of lasmiditan for the acute treatment of a single migraine attack in paediatric patients aged 6 to less than 18 years with migraine.

This study consisted of 3 periods:

- 30-day screening period
- 12-week treatment period, and
- an EOS visit conducted within 28 days of treating a single migraine attack or after completion of the treatment period without dosing.

The study was conducted at 152 centres in 14 countries.

The first participant was enrolled on 15 June 2020 and the study was terminated early on 12 November 2025 following a business decision to discontinue lasmiditan development.

Methods

Study participants

Eligible participants were aged 6 to less than 18 years with a diagnosis of migraine with or without aura according to ICHD-3 criteria. Participants were required to have a history of migraine for more than 6 months and to report between 2 and 8 moderate-to-severe migraine attacks per month during the 2 months preceding screening. Participants were required to weigh at least 15 kg.

Key exclusion criteria included congenital heart disease, clinically relevant cardiovascular abnormalities, clinically significant hepatic abnormalities, pregnancy, unstable medical conditions, and active suicidality or significant suicide risk.

Treatments

Lasmiditan and matching placebo film-coated tablets were administered orally. Dosing was weight-based and intended to achieve exposures comparable to adult doses of 50 mg, 100 mg and 200 mg.

In Stage 1, participants received placebo or lasmiditan corresponding to 100 mg adult exposure.

Table 1 Treatment Regimens by weight - Stage 1

Weight Category	LTN 100 mg Exposure	Placebo
Body weight $\leq$ 40 kg	LTN 50 mg	PBO
Body weight >40 kg	LTN 100 mg	PBO

In Stage 2, placebo non-responders were randomised to placebo or lasmiditan corresponding to adult-equivalent exposures of 50 mg, 100 mg or 200 mg.

Table 2 Treatment Regimens by Weight – Stage 2

Weight Category	LTN 50 mg Exposure	LTN 100 mg Exposure	LTN 200 mg Exposure	Placebo
Body weight $\leq$ 40 kg	LTN 25 mg	LTN 50 mg	LTN 100 mg	PBO
Body weight >40 kg	LTN 50 mg	LTN 100 mg	LTN 200 mg	PBO

Objective(s)

The primary objective was to demonstrate superiority of lasmiditan 200 mg over placebo with respect to pain freedom at 2 hours after dosing in paediatric patients with migraine.

Key secondary objectives were to demonstrate superiority of lasmiditan 100 mg and lasmiditan 50 mg over placebo with respect to pain freedom at 2 hours after dosing. Additional secondary objectives evaluated pain relief, most bothersome symptom (MBS) freedom, associated migraine symptoms, sustained pain freedom, use of rescue medication and other patient-reported outcomes.

Outcomes/endpoints

The primary endpoint was the proportion of participants who achieved pain freedom at 2 hours after dosing in the lasmiditan 200 mg group compared with placebo.

The key secondary endpoints were the proportions of participants achieving pain freedom at 2 hours after dosing in the lasmiditan 100 mg and 50 mg groups compared with placebo. Additional efficacy endpoints included pain relief, MBS freedom, sustained pain freedom and absence of associated migraine symptoms. Safety endpoints included adverse events, serious adverse events, laboratory assessments, vital signs, growth and development assessments, and suicidality evaluations.

Sample size

Approximately 1,633 participants were planned to be enrolled to obtain an efficacy analysis population of approximately 800 participants.

Following early termination of the study, 847 participants were randomised and 521 placebo non-responders were included in the efficacy analysis population in Stage 2.

Randomisation and blinding (masking)

The study consisted of a two-stage design.

In Stage 1, participants were randomised in a 1:40 ratio to lasmiditan or placebo. Participants who were placebo non-responders at 15 minutes after dosing were eligible for Stage 2 and were randomised in a 2:1:1:1 ratio to placebo, lasmiditan 50 mg, lasmiditan 100 mg or lasmiditan 200 mg.

The study was conducted in a double-blind manner using matching placebo tablets.

Statistical Methods

The primary efficacy analysis compared lasmiditan 200 mg with placebo for pain freedom at 2 hours post-dose using a repeated-measures model incorporating treatment, time, age group, treatment-by-time interaction and preventive treatment use. Multiplicity control was applied to the primary and key secondary endpoints. No multiplicity adjustment was applied for other secondary endpoints.

Results

Participant flow

A total of 1004 participants were screened, of whom 847 were randomly assigned in Stage 1 to receive PBO (n=827) or LTN 100 mg (n=20). Overall, 626 participants (73.9%) received study treatment, while 221 participants (26.1%) were randomly assigned but not treated.

Among randomly assigned participants, 610 participants (73.8%) in the PBO group and 16 participants (80.0%) in the LTN 100 mg group were treated. Of treated participants, 71 participants (11.3%) were classified as responders and 531 participants (84.8%) as nonresponders; 24 participants (3.8%) had missing 15-minute assessments. Most treated participants completed the EOS, including 70 responders (98.6%), 523 nonresponders (98.5%), and 21 participants with missing assessments (87.5%).

Among participants who were randomly assigned but not treated, 177 participants (80.1%) completed the end of study, and 44 participants (19.9%) discontinued. The most common reason for discontinuation was lost to follow-up (19 participants; 43.2%), followed by withdrawal by participant (10 participants; 22.7%).

In Stage 2 of Study H8H-MC-LAHV, all randomly assigned participants classified as nonresponders entered the treatment period.

All 10 LTN nonresponders from Stage 1 received PBO in Stage 2, and all completed the EOS.

Of the 521 PBO nonresponders,

- 209 participants received PBO, of whom 206 (98.6%) completed EOS
- 104 participants received LTN 50 mg, of whom 103 (99.0%) completed EOS
- 105 participants received LTN 100 mg, of whom 102 (97.1%) completed EOS, and
- 103 participants received LTN 200 mg, of whom 102 (99.0%) completed EOS.

Recruitment

Participants were recruited between June 2020 and November 2025 at 152 centres across Belgium, Canada, France, Germany, India, Italy, Japan, Mexico, the Netherlands, Romania, Russia, Spain, the United Kingdom and the United States.

Baseline data

Baseline demographic and disease characteristics were generally balanced between treatment groups. The mean age was approximately 13.5 years, approximately two-thirds of participants were female and the majority were aged 12 to less than 18 years. The mean duration of migraine history was approximately 4 years and participants experienced approximately 4.5 to 5 migraine attacks per month. Approximately one-third of participants reported migraine with aura.

Number analysed

The efficacy analysis population comprised 209 placebo-treated participants, 104 participants treated with lasmiditan 50 mg, 105 participants treated with lasmiditan 100 mg and 103 participants treated with lasmiditan 200 mg.

Efficacy results

The primary endpoint was met. The proportion of participants who were pain free at 2 hours after dosing was statistically significantly higher in the lasmiditan 200 mg group than in the placebo group (44/102 [43.1%] versus 59/204 [28.9%]; OR 1.815, 95% CI 1.094–3.010; $p=0.021$).

Table 3 Estimated Proportion of Participants > 6 to < 18 Years of Age with Pain Freedom at 2 Hours After Dosing (Stage 2 LTN 200 mg Vs Stage 2 PBO)

Treatment	Stage 2 PBO	Stage 2 LTN 200 mg
N	204	102
n (Raw Rate)	59 (28.922)	44 (43.137)
Model Estimated Rate (SE)	26.215 (4.135)	39.200 (6.012)
95% CI of Estimated Rate	(18.927, 35.095)	(28.203, 51.414)
Vs. PBO		
Odds Ratio	-	1.815
95% CI for Odds Ratio	-	(1.094, 3.010)
p-value	-	0.021

The key secondary endpoints were not met. Pain freedom at 2 hours after dosing was not statistically significantly different from placebo for lasmiditan 50 mg (OR 1.031; $p=0.911$) or lasmiditan 100 mg (OR 0.903; $p=0.708$).

Secondary analyses indicated statistically significant improvements for selected endpoints in the lasmiditan 200 mg group, including MBS freedom and pain relief at certain time points; however, these analyses were not controlled for multiplicity.

Safety results

No deaths occurred during the study. Serious adverse events were reported in two participants receiving lasmiditan; neither event was considered related to study treatment. No treatment-emergent serious adverse events were reported and no participant discontinued the study because of an adverse event.

Treatment-emergent adverse events occurred more frequently in the lasmiditan groups than in the placebo group (27.4% versus 11.4%), with a dose-related increase observed across lasmiditan dose groups. The most frequently reported treatment-emergent adverse events were dizziness, somnolence and nausea.

Table 4 Summary of TEAEs (≥5%) by SOC and Most Frequent PTs Within Each SOC

System Organ Class Preferred Term	Stage ½ PBO N = 298 n (%)	All Stage ½ LTN N = 328 n (%)
Participants with ≥1 TEAE	34 (11.4)	90 (27.4)
Nervous system disorders	11 (3.7)	57 (17.4)
Dizziness	6 (2.0)	38 (11.6)
Somnolence	4 (1.3)	19 (5.8)
Headache	3 (1.0)	4 (1.2)
Paraesthesia	0 (0.0)	4 (1.2)
General disorders and administration site conditions	8 (2.7)	35 (10.7)
Malaise	0 (0.0)	8 (2.4)
Asthenia	0 (0.0)	8 (2.4)
Fatigue	5 (1.7)	8 (2.4)
Gastrointestinal disorders	13 (4.4)	30 (9.1)
Nausea	8 (2.7)	17 (5.2)
Vomiting	4 (1.3)	6 (1.8)
Abdominal discomfort	1 (0.3)	5 (1.5)

Most adverse events were mild in severity and consistent with the known safety profile of lasmiditan in adults.

No clinically meaningful findings were identified with respect to growth, development, laboratory parameters or vital signs.

Clinical study H8H-MC-LAHW (PIONEER-PEDS2)

Description

Study title: A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine (PIONEER-PEDS2).

Study Number: H8H-MC-LAHW.

EudraCT: 2019-004379-38.

EU trial number: 2023-506724-85-00.

Study LAHW was a Phase 3, multicentre, randomised, open-label study designed to evaluate the long-term safety and tolerability of intermittent lasmiditan treatment in paediatric patients with migraine. Secondary objectives included the evaluation of efficacy over repeated migraine attacks during a treatment period of up to 12 months.

The study was conducted at 126 centres in 14 countries.

The first participant was enrolled on 30 June 2020 and the study was terminated early on 4 December 2025 following a business decision to discontinue lasmiditan development.

Methods

Study participants

Eligible participants were children and adolescents aged 6 to less than 18 years with migraine who had previously completed Study H8H-MC-LAHX or Study H8H-MC-LAHV. Participants were required to weigh at least 15 kg. For participants receiving preventive migraine medication, treatment had to be stable for at least 3 months prior to enrolment.

Key exclusion criteria included pregnancy, breastfeeding, acute, serious or unstable medical conditions, and active suicidality or significant suicide risk in the opinion of the investigator.

Treatments

Participants received oral lasmiditan film-coated tablets.

Randomisation was performed in a 1:1 ratio to weight-based dose regimens corresponding to adult-equivalent exposures of 100 mg or 200 mg.

Table 5 Treatment Regimens by Weight

Weight Category	LTN 50 mg Exposure^a	LTN 100 mg Exposure	LTN 200 mg Exposure
Body weight ≤40 kg	LTN 25 mg	LTN 50 mg	LTN 100 mg
Body weight >40 kg	LTN 50 mg	LTN 100 mg	LTN 200 mg

Participants were permitted to treat up to 8 migraine attacks per month.

One dose reduction for tolerability reasons was allowed after treatment of at least three migraine attacks at the assigned dose.

Objective(s)

The primary objective was to evaluate the safety and tolerability of long-term intermittent use of lasmiditan for the acute treatment of migraine in paediatric patients.

The secondary objective was to evaluate the efficacy of intermittently administered lasmiditan in the treatment of multiple migraine attacks over time.

Outcomes/endpoints

The primary endpoints were the nature, frequency and severity of treatment-emergent adverse events (TEAEs) and the proportion of participants discontinuing treatment due to adverse events.

Secondary efficacy endpoints included the proportion of treated migraine attacks with pain freedom at 2 hours after dosing, pain relief at 2 hours after dosing and resolution of the most bothersome symptom (MBS) at 2 hours after dosing, assessed during successive 3-month intervals throughout the study.

Sample size

The study was not powered on the basis of formal statistical considerations. As an open-label extension study, enrolment depended on participation in and completion of Studies LAHX and LAHV. The study aimed to include at least 200 participants who treated on average at least one migraine attack per month for 6 months and at least 75 participants who treated on average at least one migraine attack per month for 12 months.

Due to early termination of the development programme, these targets were not fully achieved. A total of 558 participants were randomised.

Randomisation and blinding (masking)

Participants were randomised in a 1:1 ratio to treatment regimens corresponding to adult-equivalent exposures of 100 mg or 200 mg.

The study was conducted in an open-label manner and no blinding was applied.

Statistical Methods

The study was primarily descriptive in nature.

Safety analyses were based on the incidence and characteristics of adverse events.

Efficacy analyses summarised the proportions of treated migraine attacks associated with pain freedom, pain relief and MBS freedom at 2 hours after dosing during predefined 3-month intervals.

No formal hypothesis testing for efficacy was specified.

Results

Participant flow

A total of 583 participants were screened and 558 participants were randomised, with 279 assigned to each treatment group.

Overall, 508 participants (91.0%) received study treatment and 50 participants (9.0%) were not treated. Among treated participants, 329 (64.8%) completed the study and 179 (35.2%) discontinued prematurely.

The most common reason for discontinuation was withdrawal by the participant.

Recruitment

Participants were recruited between June 2020 and December 2025 at 126 centres in Belgium, Canada, France, Germany, India, Italy, Japan, Mexico, the Netherlands, Romania, Russia, Spain, the United Kingdom and the United States.

Baseline data

Baseline demographic and disease characteristics were generally balanced between treatment groups.

The mean age was 13.6 years and approximately 64% of participants were female. Approximately 75% of participants were aged 12 years or older.

The mean duration of migraine history was approximately 4.2 years and participants reported approximately 4.8 migraine attacks per month during the preceding two months.

Migraine with aura was reported in approximately one-third of participants.

Number analysed

The safety and efficacy analyses included 508 treated participants, comprising 259 participants in the randomised lasmiditan 100 mg group and 249 participants in the randomised lasmiditan 200 mg group.

Efficacy results

No primary efficacy endpoint was included in the study.

Across the 12-month treatment period, the proportion of treated migraine attacks associated with pain freedom at 2 hours after dosing was 45.5%, the proportion associated with pain relief at 2 hours after dosing was 66.6%, and the proportion associated with MBS freedom at 2 hours after dosing was 44.1%. These proportions were generally maintained across the successive 3-month intervals evaluated during the study.

Safety results

No deaths were reported during the study. Serious adverse events were reported in 13 participants (2.6%). Two serious adverse events (drug hypersensitivity and subclavian vein thrombosis) were considered related to study treatment by the investigator.

Overall, 242 participants (47.6%) experienced at least one TEAE. TEAEs were reported more frequently in the lasmiditan 200 mg group (53.4%) than in the lasmiditan 100 mg group (42.1%).

Most TEAEs were mild to moderate in severity.

Twenty-four participants (4.7%) discontinued the study because of adverse events and 28 participants (5.5%) discontinued study treatment because of adverse events.

Table 6 Overview of Adverse Events

	Randomized LTN 100 mg (N=259)	Randomized LTN 200 mg (N=249)	All LTN (N=508)
Number of participants* ^a	n (%)	n (%)	n (%)
AE leading to death* ^b	0	0	0
Serious AE	6 (2.3)	7 (2.8)	13 (2.6)
Discontinuations from study due to an AE	11 (4.2)	13 (5.2)	24 (4.7)
Discontinuations from study treatment due to an AE	13 (5.0)	15 (6.0)	28 (5.5)
Treatment-emergent adverse events	109 (42.1)	133 (53.4)	242 (47.6)
Treatment-emergent adverse events related to study treatment* ^c	79 (30.5)	105 (42.2)	184 (36.2)

The most frequently reported TEAEs were dizziness, somnolence and nausea.

Table 7 Summary of TEAEs (≥5%) by SOC and Most Frequent PTs Within Each SOC

System Organ Class Preferred Term	Randomized LTN 100 mg (N=259) n (%)	Randomized LTN 200 mg (N=249) n (%)	All LTN (N=508) n (%)
Participants with ≥1 TEAE	109 (42.1)	133 (53.4)	242 (47.6)
Nervous system disorders	65 (25.1)	92 (36.9)	157 (30.9)
Dizziness	42 (16.2)	62 (24.9)	104 (20.5)
Somnolence	21 (8.1)	26 (10.4)	47 (9.3)
Paraesthesia	4 (1.5)	8 (3.2)	12 (2.4)
General disorders and administration site conditions	36 (13.9)	31 (12.4)	67 (13.2)
Fatigue	9 (3.5)	14 (5.6)	23 (4.5)
Asthenia	10 (3.9)	10 (4.0)	20 (3.9)
Feeling abnormal	4 (1.5)	4 (1.6)	8 (1.6)
Malaise	4 (1.5)	4 (1.6)	8 (1.6)
Gastrointestinal disorders	33 (12.7)	31 (12.4)	64 (12.6)
Nausea	21 (8.1)	21 (8.4)	42 (8.3)
Vomiting	10 (3.9)	4 (1.6)	14 (2.8)
Abdominal pain upper	3 (1.2)	4 (1.6)	7 (1.4)
Infections and infestations	16 (6.2)	13 (5.2)	29 (5.7)
Nasopharyngitis	4 (1.5)	5 (2.0)	9 (1.8)
COVID-19	4 (1.5)	0 (0.0)	4 (0.8)
Influenza	1 (0.4)	2 (0.8)	3 (0.6)
Musculoskeletal and connective tissue disorders	12 (4.6)	16 (6.4)	28 (5.5)
Pain in extremity	2 (0.8)	5 (2.0)	7 (1.4)
Muscular weakness	6 (2.3)	3 (1.2)	9 (1.8)
Myalgia	1 (0.4)	3 (1.2)	4 (0.8)

No clinically meaningful effects on growth, development, laboratory parameters or vital signs were identified during the study.

Discussion on clinical aspects

The submitted paediatric data package comprises one randomised, double-blind, placebo-controlled efficacy and safety study (LAHV) and one 12-month open-label extension study primarily designed to assess long-term intermittent safety (LAHW). Overall, the studies provide paediatric data on lasmiditan in patients aged 6 to less than 18 years with migraine; however, the interpretability of the efficacy and safety findings is limited by early termination of the programme and by the reduced sample size compared with the planned study population.

Study LAHV did not reach the planned sample size. Approximately 1,633 participants were planned to be enrolled in order to obtain an efficacy analysis population of approximately 800 participants, whereas 521 placebo non-responders were included in the Stage 2 efficacy analysis population. This reduction in sample size limits the precision of treatment effect estimates and reduces the robustness of subgroup and secondary endpoint analyses. The limitation is particularly relevant for the younger paediatric subgroup, where the number of participants was small and formal model-based analyses could not be performed because the statistical model did not converge.

The two-stage design of Study LAHV should also be taken into account. Participants first entered a double-blind placebo-challenge period and only placebo non-responders were subsequently randomised into the main efficacy analysis period. This design was intended to mitigate the known high placebo response in paediatric migraine trials. However, it also means that the primary efficacy analysis was conducted in an enriched population of early placebo non-responders rather than in an unselected

paediatric migraine population. The external validity of the observed treatment effect is therefore limited, and the magnitude of benefit may not fully reflect expected effectiveness in routine clinical use.

Efficacy was demonstrated only for the highest lasmiditan dose evaluated. Lasmiditan 200 mg was statistically superior to placebo for pain freedom at 2 hours after dosing, whereas the 50 mg and 100 mg doses did not demonstrate superiority over placebo for the key secondary endpoints. The absence of a consistent dose-response pattern across the prespecified efficacy hierarchy limits the overall robustness of the efficacy conclusion. The finding supports an effect at the highest exposure level but does not establish efficacy across the paediatric dose range.

The evidence in younger children aged 6 to less than 12 years is particularly limited. In this subgroup, the model-based analysis did not converge and only descriptive response rates were available. Observed pain freedom at 2 hours was numerically high in the placebo group and did not show a consistent advantage for lasmiditan across dose groups. Consequently, no reliable conclusion on efficacy in children aged 6 to less than 12 years can be drawn from the submitted data.

Secondary efficacy analyses in Study LAHV showed favourable results for some endpoints, including MBS freedom and pain relief for lasmiditan 200 mg. However, these analyses were not controlled for multiplicity, except for the predefined primary and key secondary endpoints. Therefore, these findings should be considered supportive and exploratory. They may provide internal consistency with the primary endpoint for the 200 mg dose but cannot independently substantiate efficacy.

Study LAHW provides supportive information on repeated intermittent use of lasmiditan over time, but its open-label design, absence of a placebo or active comparator control, and descriptive statistical approach preclude firm conclusions on efficacy. The observed proportions of attacks with pain freedom, pain relief and MBS freedom at 2 hours after dosing should be interpreted as descriptive only and are subject to expectation bias, attrition bias and selection effects inherent to an open-label rollover study.

The safety findings from both studies are broadly consistent with the known safety profile of lasmiditan, with dizziness, somnolence and nausea among the most frequently reported treatment-emergent adverse events. A dose-related increase in TEAEs was observed, particularly in Study LAHV and in the 200 mg group of Study LAHW. No deaths were reported. However, the early termination of the programme, incomplete long-term exposure, and discontinuation of a substantial proportion of participants in Study LAHW limit the ability to detect less common or longer-term paediatric safety risks.

Overall, the submitted data suggest that lasmiditan at the highest evaluated exposure level can provide acute efficacy in adolescents and older paediatric patients with migraine, as reflected by the positive primary endpoint in Study LAHV. However, the evidence is limited by the reduced sample size, the enriched placebo non-responder design, the lack of demonstrated efficacy at lower doses, limited robustness in children aged 6 to less than 12 years, and the exploratory nature of most secondary endpoints. Study LAHW provides supportive safety data for intermittent use but does not provide confirmatory efficacy evidence. The premature termination of the paediatric development programme further limits the completeness of the evidence base and should be reflected in the overall regulatory conclusion.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted final study synopses for Studies H8H-MC-LAHV (PIONEER-PEDS1) and H8H-MC-LAHW (PIONEER-PEDS2), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

Study LAHV was a randomised, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of lasmiditan for the acute treatment of migraine in paediatric patients aged 6 to less than 18 years. The study met its primary endpoint, demonstrating superiority of lasmiditan corresponding to the adult 200 mg dose over placebo for pain freedom at 2 hours after dosing. However, the key secondary endpoints for the lower dose groups were not met. The robustness of the efficacy findings is limited by failure to achieve the planned sample size, the two-stage placebo non-responder design, and the limited evaluability of the younger age subgroup (6 to <12 years).

Study LAHW was a 12-month open-label study primarily designed to evaluate long-term safety and tolerability. The safety findings were generally consistent with the known safety profile of lasmiditan. The efficacy results from LAHW are considered supportive only due to the uncontrolled open-label design.

Overall, the submitted studies provide clinically relevant information regarding the efficacy and safety of lasmiditan in paediatric patients. Although the MAH has indicated that it does not intend to pursue a paediatric indication and does not propose amendments to the product information, the Rapporteur considers that the submitted data may have implications for the information currently included in sections 4.8 and 5.1 of the SmPC.

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarifications as part of this procedure (see section "Request for supplementary information").

4. Request for supplementary information

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

1. Studies H8H-MC-LAHV and H8H-MC-LAHW form part of the agreed paediatric development programme for lasmiditan and provide efficacy and safety data in paediatric patients aged 6 to less than 18 years with migraine.

The MAH has stated that it does not propose amendments to the product information. The submitted studies constitute completed paediatric studies submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 and provide new efficacy and safety information in paediatric patients.

The MAH is requested to provide either:

a) proposed wording for sections 4.8 and 5.1 of the SmPC reflecting a concise, balanced and scientifically accurate summary of the results from Studies H8H-MC-LAHV and H8H-MC-LAHW, including the principal limitations of the available evidence;

or

b) a detailed justification explaining why inclusion of these data in the product information is not considered warranted in light of the submitted data and the stated intention to withdraw the marketing authorisation.

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

MAH responses to Request for supplementary information

The MAH did not provide proposed amendments to Sections 4.8 and 5.1 of the SmPC and maintained its position that inclusion of the results from Studies LAHV and LAHW in the product information is not warranted.

Regarding efficacy, the MAH considered the results of Study LAHV to be of limited interpretability because the study was terminated prematurely and enrolled 521 of the planned 800 participants in the efficacy analysis population. According to the MAH, the reduced sample size limits the precision and clinical interpretability of the estimated treatment effects and does not provide a sufficiently robust basis for an efficacy statement in Section 5.1 of the SmPC. The MAH further noted that Study LAHW was an open-label study primarily designed to assess long-term safety and tolerability and therefore does not provide confirmatory efficacy evidence.

Regarding safety, the MAH stated that no new or unexpected adverse events were identified in the paediatric population and that the observed adverse event profile was generally consistent with the established safety profile of lasmiditan in adults. On this basis, the MAH considered that the results do not warrant an update of Section 4.8.

The MAH further considered that the current statement in Section 4.2 that the safety and efficacy of lasmiditan in children and adolescents aged 6 to <18 years have not been established remains appropriate.

CHMP comment:

The Rapporteur does not fully agree with the MAH's conclusion that the results of Studies LAHV and LAHW are insufficiently relevant to warrant reflection in the product information. While Study LAHV did not achieve the originally planned sample size and the resulting limitations in precision and subgroup interpretability are acknowledged, the study nevertheless generated controlled efficacy and safety data in paediatric patients and met its prespecified primary efficacy endpoint for the highest lasmiditan dose. The limitations of the study affect the strength and scope of the conclusions that can be drawn but do not, per se, render the generated data uninformative.

In particular, the Rapporteur does not consider the MAH's argument that the reduced sample size precludes any meaningful information in Section 5.1 to be sufficiently substantiated. A concise description of the study results could appropriately communicate both the positive primary efficacy finding and the important limitations of the evidence, including the premature termination of the study, the failure to demonstrate superiority for the lower doses and the limited evidence in children aged 6 to <12 years.

Similarly, while no new safety signal was identified, Studies LAHV and LAHW provide paediatric safety information that was not previously available. Therefore, the absence of a new safety signal does not in itself establish that the paediatric findings are irrelevant to the product information.

Furthermore, following completion of these studies, the current statement in Section 4.2 that "No data are available" in children and adolescents aged 6 to <18 years is no longer factually accurate. However, the available evidence remains insufficient to establish the safety and efficacy of lasmiditan in the overall paediatric population or to support a paediatric indication.

Therefore, although the MAH's scientific justification for not reflecting the paediatric data in the SmPC is not fully endorsed, no further regulatory action regarding the product information is considered necessary in the specific circumstances of this procedure.

The issue is considered resolved.

☒ **Fulfilled**

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

None

Clinical studies

Product Name: RAYVOW Active substance: Lasmiditan

Study title	Study number	Date of completion	Date of submission of final study report
Pediatric Options for Migraine Relief: A Randomized, Double-Blind, Placebo-Controlled Study of Lasmiditan for Acute Treatment of Migraine (PIONEER-PEDS1)	H8H-MC-LAHV (LAHV)	Date of early termination: 12 November 2025	Date of submission of clinical study synopsis: 4 May 2026
A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine (PIONEER-PEDS2)	H8H-MC-LAHW (LAHW)	Date of early termination: 4 December 2025	Date of submission of clinical study synopsis: 4 May 2026