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Human Medicines Division

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

Vimpat

lacosamide

Procedure no: EMEA/H/C/000863/P46/047

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	11 Sep 2023	11 Sep 2023	☐
☐	CHMP Rapporteur Assessment Report	16 Oct 2023	16 Oct 2023	☐
☐	CHMP members comments	30 Oct 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Nov 2023	n/a	☐
☒	CHMP adoption of conclusions:	09 Nov 2023	09 Nov 2023	☐

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1. Introduction

On Aug 28, 2023, the MAH submitted a completed paediatric study for Vimpat (lacosamide), 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 EP0012 is a long-term extension study, which part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Oral solution, tablets

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- EP0012: A Phase 3 study to assess the long-term safety, tolerability, and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTCS in study participants ≥4 years of age with IGE.

In this P46 assessment report, only the results of the paediatric subjects included in study EP0012 are presented.

2.3.2. Clinical study

EP0012: A Phase 3 study to assess the long-term safety, tolerability, and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTCS in study participants ≥4 years of age with IGE.

Description

Study participants were eligible to enter EP0012 if they completed SP0982, were Baseline failures from SP0982, or had transitioned from SP0982 for Safety Follow-up only.

Methods

Study participants

Adults and children from 4 years of age with idiopathic generalized epilepsy (IGE).

Treatments

Up-titration from starting dose if treatment-naïve for lacosamide, and maintenance dose if treated during the main study (SP0982).

Objective(s)

The primary objective was to assess the safety and tolerability of LCM as an adjunctive therapy for primary generalized tonic-clonic seizures (PGTCS) in study participants with IGE during long term exposure.

Pediatric study participants continued in the study for up to 5 years of participation or until the approval of the extension of indication to cover the target age group was granted. Adult and pediatric study participants were completers if they continued in the study for the maximum duration in their respective region.

The secondary objectives were to assess the efficacy of adjunctive LCM therapy during long term exposure for the treatment of study participants with IGE experiencing PGTCS and to allow study participants who have completed SP0982 and eligible Baseline failures from SP0982 to receive LCM.

Outcomes/endpoints

No primary efficacy variables were defined for this study.

Secondary efficacy variable: The percent change from Combined Baseline in PGTCS frequency per 28 days by Completer Cohort

Sample size

Randomisation and blinding (masking)

Statistical Methods

Results

Participant flow

Table: Summary of study participant disposition and discontinuation reasons (SS)

Disposition	Development in EP0012 Pediatrics (≥4 to <18 years) N=44 n (%)
Started study [a]	44 (100)
Completed the study <94 weeks of treatment	2 (4.5)
Treated ≥94 weeks of treatment	35 (79.5)
Discontinued within 94 weeks of treatment	7 (15.9)
Primary reason for discontinuation	
Adverse event	3 (6.8)

Table: Summary of study participant disposition and discontinuation reasons (SS)

Disposition	Development in EP0012 Pediatrics (≥4 to <18 years) N=44 n (%)
Lack of efficacy	2 (4.5)
Protocol violation	0
Lost to follow up	0
Consent withdrawn	2 (4.5)
Other	0
Completed study	32 (72.7)
Discontinued	12 (27.3)
Primary reason for discontinuation	
Adverse event	4 (9.1)
Lack of efficacy	2 (4.5)
Protocol violation	0
Lost to follow up	1 (2.3)
Consent withdrawn	5 (11.4)
Other	0

CSR=clinical study report; SS=Safety Set
Note: Completed <94 weeks of treatment were those study participants who completed the study prior to Visit 11.
Treated ≥94 weeks were those study participants who completed Visit 11 (or Termination Visit instead).
Discontinued within 94 weeks of treatment were those study participants who discontinued prior to Visit 11.
Note: Completed study were those study participants who the Investigator indicated had completed the study.
Note: Discontinuation were those study participants who discontinued the study.
[a] Started study meant that study participant received the first dose of treatment in EP0012.
Data source: EP0012 final CSR Table 1.2.1

32 of 44 (72.7%) paediatric patients completed the study, 12 (27.3%) discontinued, with the main reasons being AE (4), lack of efficacy (2), consent withdrawn (5).

The majority of study participants were at sites in Western/Central Europe (19 study participants [43.2%]) and Asia/Pacific/Other (15 study participants [34.1%]). A total of 7 study participants (15.9%) were at sites in Eastern Europe, 3 study participants (6.8%) were at sites in Latin and North America.

Baseline data

Table : Study participant demographics (SS)

Variable Statistic	Development in EP0012 Pediatrics (≥4 to <18 years) N=44
Age (years), n (%)	
Mean (SD)	12.8 (3.8)
Min, max	4, 17
Age (years) [a], n (%)	
≥4 to <12	16 (36.4)
12 to <18	28 (63.6)
Age (years) [b], n (%)	
≤18	44 (100)
Gender, n (%)	
Male	16 (36.4)
Female	28 (63.6)

BMI=body mass index; CSR=clinical study report; EudraCT=European Union Drug Regulating Authorities Clinical Trials; max=maximum; min=minimum; SD=standard deviation; SS=Safety Set

[a] EudraCT age categories.

[b] clinicaltrials.gov age categories.

Data source: EP0012 final CSR Table 3.1

The age span in the paediatric study population was 4-17 years with the mean age at entry 12.8 years.

The mean time since first epilepsy diagnosis was 4.51 years (range: 0.5 to 16.0 years) and the mean age at epilepsy diagnosis was 8.59 years (range: 0.4 to 15.9 years).

All patients (44) had generalised idiopathic epilepsy, of which 3 each had childhood and juvenile absence epilepsy, respectively, and 7 had juvenile myoclonic epilepsy.

The mean Combined Baseline PGTCS frequency per 28 days was 1.74 (range: 0.5 to 19.4). The majority of study participants (40 study participants [90.9%]) had ≤2 seizures per 28 days.

In the ≥4 to <18 years category, the majority of study participants (43 study participants [97.7%]) used concomitant AEDs and/or benzodiazepines during the Treatment Period. The most common AEDs and/or benzodiazepines by PT were valproate (29 study participants [65.9%]), levetiracetam (17 study participants [38.6%]), lamotrigine (15 study participants [34.1%]), clobazam (6 study participants [13.6%]), and clonazepam (5 study participants [11.4%]).

Number analysed

Forty-four study participants (100%) were exposed to LCM for a total of 129.96 study participant-years. Thirty-eight study participants (86.4%) completed ≥12 months of LCM treatment (127.99 study participant-years of exposure), and 35 study participants (79.5%) completed ≥24 months of LCM treatment (123.25 study participant-years of exposure). During Years 3, 4, and 5, 63.6%, 38.6%, and 13.6% study participants, respectively, were exposed to LCM.

Efficacy results

Table : Percent change from Combined Baseline in PGTCS frequency per 28 days by Completer Cohort (FAS)

Completer Cohort	Time period Statistic	Development in EP0012 Pediatrics (≥4 to <18 years) N=44
	Combined Baseline, n	34
	Mean (SD)	1.58 (3.16)
	Median (min, max)	1.00 (0.8, 19.4)
22 Weeks	0 to 22 weeks, n	34
	Mean (SD)	-75.12 (59.79)
	Median (min, max)	-100.00 (-100.0, 228.1)
46 Weeks	0 to 46 weeks, n	33
	Mean (SD)	-74.16 (63.12)
	Median (min, max)	-100.00 (-100.0, 247.8)
94 Weeks	0 to 94 weeks, n	30
	Mean (SD)	-73.66 (79.79)
	Median (min, max)	-100.00 (-100.0, 336.9)
142 Weeks	0 to 142 weeks, n	24
	Mean (SD)	-67.94 (92.12)
	Median (min, max)	-94.41 (-100.0, 356.2)
190 Weeks	0 to 190 weeks, n	15
	Mean (SD)	-56.20 (114.75)
	Median (min, max)	-95.84 (-100.0, 352.1)
238 Weeks	0 to 238 weeks, n	6
	Mean (SD)	-89.04 (16.27)
	Median (min, max)	-98.31 (-100.0, -62.2)

CSR=clinical study report; FAS=Full Analysis Set; max=maximum; min=minimum; PGTC=primary generalized tonic-clonic; PGTCS=primary generalized tonic-clonic seizure; SD=standard deviation
Note: Results were based upon average seizure frequency over 28 days.
Note: Combined Baseline was the combined 12-week Historical and 4-week Prospective Baseline from SP0982.
Note: A minimum -100% change from Combined Baseline means that the study participant had 0 PGTC seizures during the Treatment Period (time period under study) as compared with the Combined Baseline.
Data source: EP0012 final CSR Table 8.1.1

In the ≥4 to <18 years category, a median percent change of 96.14 (range: 100.0 to 344.7) from Combined Baseline in PGTCS frequency per 28 days was observed during the Treatment Period.

During the Treatment Period, in the ≥4 to <18 years category, the percentages of study participants that were PGTCS ≥50% and ≥75% responders was 84.1% and 72.7%, respectively.

Primary generalized tonic-clonic seizure ≥50% seizure worsening during time period was low for all time periods. For the 0 to 22 weeks, 0 to 46 weeks (>22 weeks), 0 to 94 weeks (>46 weeks), 0 to 142 weeks (>94 weeks), 0 to 190 weeks (>142 weeks), and 0 to 238 weeks (>190 weeks) time periods, 4.5%, 5.1%, 5.4%, 2.9%, 3.6%, and 5.6% of study participants, respectively, experienced ≥50% seizure worsening.

For study participants completing 22 weeks, 46 weeks, 94 weeks, 142 weeks, 190 weeks, and 238 weeks, seizure free status was achieved in 61.8%, 54.5%, 53.3%, 37.5%, 40.0%, and 50.0% of study participants, respectively.

Myoclonic seizures

In the ≥4 to <18 years category, a total of 11 study participants (25.0%) had a history of or reported myoclonic seizures during the Combined Baseline and Treatment Period. The median number of days with myoclonic seizures per 28 days at Prospective Baseline was 0 (range: 0 to 17). The median observed results in days with myoclonic seizures during the Treatment Period was 0 (range: 0 to 5).

During the Treatment Period, in the ≥4 to <18 years category, the percentages of study participants that were myoclonic seizures ≥50% and ≥75% responders in days was 33.3% and 16.7%, respectively.

At least 50% myoclonic seizure worsening in days was reported for 1 study participant (8.3%) during the 0 to 22 weeks time period. Taking into account seizure reporting during the entire Treatment Period, no study participants experienced ≥50% myoclonic seizures worsening.

Absence seizures

In the ≥4 to <18 years category, a total of 25 study participants (56.8%) had a history of or reported absence seizures during the Combined Baseline and/or the Treatment Period.The median number of days with absence seizures per 28 days at Prospective Baseline was 0 (range: 0 to 6). The median observed results in days with absence seizures for the Treatment Period was 0 (range: 0 to 22).

During the Treatment Period, in the ≥4 to <18 years category, the percentages of study participants that were absence seizures ≥50% and ≥75% responders in days was 24.0% and 12.0%, respectively.

Table : Percent change from Combined Baseline in PGTCS frequency per 28 days by Completer Cohort (FAS)

Completer Cohort	Time period Statistic	Development in EP0012 Pediatrics (≥4 to <18 years) N=44

No study participants in the ≥4 to <18 years category experienced ≥50% absence seizures worsening during the Treatment Period.

Safety results

Table : Incidence of TEAEs considered related to LCM per Investigator by PT (SS)

MedDRA v16.1 SOC PT	Development in EP0012 Pediatrics (≥4 to <18 years) N=44 n (%) [#]
Any related TEAE	16 (36.4) [41]
Cardiac disorders	**1 (2.3) [1]**
Atrioventricular block first degree	1 (2.3) [1]
Ear and labyrinth disorders	**2 (4.5) [4]**
Vertigo	2 (4.5) [4]
Eye disorders	**2 (4.5) [2]**
Diplopia	1 (2.3) [1]
Hypoaesthesia eye	1 (2.3) [1]
Gastrointestinal disorders	**4 (9.1) [5]**
Nausea	3 (6.8) [3]
Faecal incontinence	1 (2.3) [1]
Vomiting	1 (2.3) [1]
General disorders and administration site conditions	**4 (9.1) [4]**
Gait disturbance	2 (4.5) [2]
Fatigue	1 (2.3) [1]
Irritability	1 (2.3) [1]
Investigations	**1 (2.3) [1]**
Blood alkaline phosphatase increased	1 (2.3) [1]
Metabolism and nutrition disorders	**2 (4.5) [2]**
Hyperuricaemia	1 (2.3) [1]
Overweight	1 (2.3) [1]

Table : Incidence of TEAEs considered related to LCM per Investigator by PT (SS)

MedDRA v16.1 SOC PT	Development in EP0012 Pediatrics (≥4 to <18 years) N=44 n (%) [#]
Nervous system disorders	**8 (18.2) [16]**
Dizziness	5 (11.4) [7]
Somnolence	4 (9.1) [5]
Ataxia	1 (2.3) [1]
Dizziness postural	1 (2.3) [1]
Myoclonic epilepsy	1 (2.3) [1]
Status epilepticus	1 (2.3) [1]
Psychiatric disorders	**2 (4.5) [5]**
Learning disorder	2 (4.5) [4]
Aggression	1 (2.3) [1]
Renal and urinary disorders	**1 (2.3) [1]**
Proteinuria	1 (2.3) [1]

AE=adverse event; CSR=clinical study report; LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participants who reported at least 1 TEAE within SOC/PT.
Note: [#] was the number of individual occurrences of the TEAE.
Note: Each study participant was counted once within each SOC and PT according to the relationship for all TEAEs within that SOC or PT. An AE with missing LCM relationship was treated as related.
Data source: EP0012 final CSR Table 10.4

Potential DILI

In the ≥4 to <18 years category, the incidence of TEAEs associated with potential drug-induced liver injury (PDILI) was low; 2 study participants (4.5%) reported 2 TEAEs related to PDILI (by PT of alanine aminotransferase increased), both of which were mild or moderate in intensity and were considered not related to LCM by the Investigator.

No study participants reported TEAEs meeting the criteria for Hy's Law.

Deaths

A fatal TEAE was reported for 1 study participant (2.3%) in the ≥4 to <18 years category, which was considered not related to LCM by the Investigator.

A brief description of the event:

- A participant experienced a fatal AE by accident 1 day after the last LCM dose. The event was serious, severe in intensity, and was considered not related to LCM by the Investigator. The study participant was exposed to LCM for a total of 1403 days and was on LCM 600mg/day for 1106 days.

Concomitant AEDs used by the study participant during the study included valproate, diazepam, and perampanel.

Vital signs

There were no meaningful trends in the vital signs values.

2.3.3. Discussion on clinical aspects

The objective of this study was to assess the safety and tolerability of LCM as an adjunctive therapy for primary generalized tonic-clonic seizures (PGTCS) in study participants with IGE during long term exposure. 44 paediatric patients were enrolled into the study, 36/44 were rollover patients from main study SP0982, 8 were direct enrollers. 38 completed at least 12 months treatment, 35 completed at least 24 months of treatment. During Years 3, 4, and 5, 63.6%, 38.6%, and 13.6% study participants, respectively, were exposed to LCM.

Efficacy: Following adjunctive treatment with LCM, consistent reductions in percent change in PGTCS per 28 days from Combined Baseline were observed across time periods for paediatric study participants, which was generally consistent with observations for all study participants, including adults. Low incidences of new or worsening of known myoclonic or absence seizures were reported, and consistently low rates of PGTCS ≥50% seizure worsening over time.

Safety: Lacosamide was generally well tolerated as adjunctive therapy for PGTCS in study participants ≥4 years of age with IGE, and no new safety concerns were identified. The safety findings were consistent with the known safety profile of LCM in adults and paediatrics; therefore, the benefit risk ratio remains favourable.

The MAH does not propose any changes to SmPC for VIMPAT based on the present results. This is concurred by the rapporteur. Even though it is noted that for some other newer antiepileptic medicines including Fycompa (perampanel) and Briviact (brivaracetam), short summaries of open-label long-term study results have been presented in the SmPC section 5.1, the data included was for the whole extension study population and not just the paediatric participants.

3. CHMP overall conclusion and recommendation

In this open-label long-term extension study in paediatric patients from 4 years of age, the long-term efficacy of adjunctive lacosamide for PGTCS was maintained. Lacosamide was generally well tolerated and no new safety concerns were identified. The long-term safety and efficacy in paediatric patients were consistent with previous data. The MAH does not propose any changes to SmPC for Vimpat (lacosamide) based on the present results. This is concurred by the CHMP.

☒ **Fulfilled:**

No regulatory action required.