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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/P46/041

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 10 November 2021, the MAH submitted a completed paediatric study for 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 SP848 was an open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children with epilepsy.

2.2. Information on the pharmaceutical formulation used in the study

Lacosamide is available as oral film-coated tablets (50mg, 100mg, 150mg, and 200mg), oral solution/syrup (10mg/mL), 10% dry syrup, and solution for infusion (10mg/mL). The specific indication statement, approved formulation(s), and posology for LCM differ based on the country; thus, local labels should be consulted for further information. Lacosamide has been approved worldwide in over 70 countries. The use of LCM in children aged ≥4 years was approved in the EU on 14 Sep 2017, in the US (tablets and oral solution [syrup] on 03 Nov 2017 and solution for intravenous [iv] on 16 Nov 2020), and in Japan (together with dry syrup and solution for iv pharmaceutical forms) on 08 Jan 2019. The use of LCM for oral and iv monotherapy and adjunctive therapy in children aged ≥1 month to <4 years of age was approved in the US on 15 Oct 2021 (tablets, oral solution, and solution for iv).

Study participants who completed SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or study participants from another applicable LCM pediatric clinical study in epilepsy (ie, SP0966 and EP0060) began with a LCM dose equivalent to the one they last received in the primary study and were able to continue on LCM oral solution (syrup) or switch to LCM tablets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study SP848 which was an open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children with epilepsy.

2.3.2. Clinical study

Clinical study number and title

Study SP848 is an open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children with epilepsy.

Description

The MAH stated that study SP848 was originally designed as an open-label extension study for pediatric study participants in SP847. SP847 was a multicenter, open-label study to investigate the

safety, tolerability, and pharmacokinetics (PK) of LCM oral solution (syrup) as adjunctive therapy in children with POS. SP848 was then amended to be open to study participants who participated in other LCM pediatric clinical studies, including POS and other epilepsy syndromes (ie, SP0966, a multicenter, open-label, exploratory study to investigate the safety and efficacy of LCM as adjunctive therapy in subjects ≥1 month to <18 years with epilepsy syndromes associated with generalized seizures; and EP0060, a multicenter, open-label study to investigate the safety and tolerability of iv LCM in children [≥1 month to <17 years of age] with epilepsy). In addition, beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric study participants ≥4 to ≤17 years of age with POS (deemed appropriate for treatment with adjunctive LCM) who had not previously participated in a LCM clinical study were permitted to enroll directly into SP848. For sites in Japan and China, additional eligible pediatric study participants ≥4 to ≤17 years of age with POS who had not previously received LCM were also allowed to enroll directly into SP848. The purpose of enrolling these study participants directly into SP848 was to obtain additional long-term safety exposures in the age range of ≥4 to ≤17 years of age.

The maximum duration of LCM administration for an individual study participant was to be approximately 2 years or until approval of the marketing application (for Japan only).

Methods

Study participants

Study SP848 included study participants ≥1 month to ≤18 years of age.

Of note, there was only 1 study participant who at the time of entry in SP848 was ≥18 years of age.

Treatments

Study participants who completed SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or study participants from another applicable LCM pediatric clinical study in epilepsy (ie, SP0966 and EP0060) began with a LCM dose equivalent to the one they last received in the primary study and were able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators were allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each study participant. The investigator could have titrated/adjusted the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the study participant's body weight exceeded 50kg.

The maximum permitted LCM dose in SP848 was 12mg/kg/day or 600mg/day, whichever was lower. Increases in the LCM dose were to occur only during office visits. If needed to optimize tolerability and seizure reduction in selected study participants, concomitant AEDs could have been carefully tapered and discontinued to achieve LCM monotherapy. New concomitant AEDs may have been introduced and should have been added only when the study participant had not optimally or adequately responded to a maximum tolerated dose of LCM.

Objective(s)

The objectives of this study were:

- To obtain information about the safety, tolerability, and PK of LCM during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long-term exposure

- To allow study participants who had participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow study participants who had participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric study participants ≥4 to ≤17 years of age who had not previously received LCM to begin receiving LCM. Protocol Amendment 5.2 allowed approximately 46 additional eligible pediatric study participants ≥4 to ≤17 years of age with POS who had not previously received LCM to enroll directly at approximately 9 sites in Japan. Protocol 5.4 allowed approximately 60 additional eligible pediatric study participants ≥4 to ≤17 years of age with POS who had not previously received LCM to enroll directly at sites in China.

Outcomes/endpoints

The primary safety variables were:

• Incidence of TEAEs

• Incidence of SAEs

• Study participant withdrawal from the study due to TEAEs

Other safety variables

The other safety variables were:

• Hematology, blood chemistry, endocrinology, and urinalysis parameters

• 12-lead ECGs

• Vital sign measurements (blood pressure and pulse)

• Physical and neurological examination findings

• Body weight, height, and calculated body mass index (BMI)

• Tanner Stage (if applicable)

• Achenbach CBCL at Baseline for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior

• Bayley-III scales at Baseline for children <18 months of age at time of enrollment (applicable only to study participants enrolled in English-speaking countries)

• Cognitive function assessments BRIEF/BRIEF-P (if applicable)

• LCM palatability and ease of use questionnaire

Primary efficacy variables

No primary efficacy variables were defined for this study.

Secondary efficacy variables

The secondary efficacy variables, based on daily seizure diaries, were:

• Percent change from Baseline in 28-day POS frequency

· ≥50% reduction in 28-day POS frequency

· ≥75% reduction in 28-day POS frequency

• Seizure days per 28 days (study participants with generalized seizures only)

• Seizure-free status

Other efficacy variables

• Clinical Global Impression of Change

• Caregiver Global Impression of Change

• Quality of life assessments (PedsQL) (if applicable)

• Health care resource use (concomitant AEDs, medical procedures, health care provider (HCP) consultations not related to study, hospitalizations not related to study)

• All seizure frequency analyses as described in the secondary efficacy variables (presented for the overall Treatment Period only) may have been additionally presented by modal daily dose group, seizure type, seizure classification subgroup, time interval, visit or time period, or completer cohort

Sample size

Approximately 42 study participants from SP847 were eligible to enroll in this open-label study. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric study participants ≥4 to ≤17 years of age who had not previously participated in a LCM clinical study were permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric study participants ≥4 to ≤17 years of age with POS who had not previously received LCM enrolled directly at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric study participants with POS aged ≥4 to ≤17 years who had not previously participated in a LCM clinical study enrolled directly into SP848.

Beginning with Protocol Amendment 6, up to 75 eligible pediatric study participants ≥4 to <17 years of age who participated in EP0060 were permitted to enroll into SP848. Protocol Amendment 8 allowed an enrollment increase from 75 to 100 eligible pediatric study participants ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of study participants down to 1 month of age.

In total, up to approximately 400 study participants may have been eligible to participate in SP848.

Randomisation and blinding (masking)

This was an open-label study. No randomization or blinding was performed.

Statistical Methods

Descriptive statistics were displayed to provide an overview of the study results. For categorical parameters, the number and percentage of study participants in each category were presented.

Results

Recruitment

A total of 391 study participants were screened at 69 sites. There were 25 screen failures (6.4%), which were primarily attributed to ineligibility (18 study participants [4.6%]).

A total of 365 study participants were treated with LCM and started the study, including 45 study participants aged ≥1 month to <4 years, 319 study participants aged ≥4 to <18 years, and 1 study participant aged ≥18 years.

Baseline data

Study participant demographics are summarized for the SS for pediatric study participants in Table 1.

Table 1: Pediatric study participant (<18 years of age) demographics by age group (SS)

Variable Statistic	≥1 month to <4 years N=45	≥4 to <18 years N=319	All pediatric study participants N=364
Age (years), n [a]	45	319	364
Mean (SD)	1.95 (1.25)	10.21 (3.86)	9.19 (4.54)
Median	1.92	10.10	9.32
Min, Max	0.2, 3.9	3.6, 17.9	0.2, 17.9
Age (years), n [b]	45	319	364
Mean (SD)	2.06 (1.27)	10.27 (3.85)	9.26 (4.53)
Median	2.10	10.10	9.45
Min, Max	0.2, 3.9	4.0, 17.9	0.2, 17.9
Age, n (%) [c]			
≥28 days to <24 months	21 (46.7)	0	21 (5.8)
≥24 months to <12 years	24 (53.3)	205 (64.3)	229 (62.9)
≥12 years to <18 years	0	114 (35.7)	114 (31.3)
Age, n (%) [d]			
≤18 years	45 (100)	319 (100)	364 (100)
19 years to <65 years	0	0	0
Gender, n (%)			
Male	22 (48.9)	170 (53.3)	192 (52.7)
Female	23 (51.1)	149 (46.7)	172 (47.3)
Weight (kg), n [e]	45	319	364
Mean (SD)	11.15 (3.83)	37.60 (19.61)	34.33 (20.36)
Median	12.00	31.80	28.55
Min, Max	5.0, 18.8	10.2, 139.5	5.0, 139.5
Weight band (kg), n (%) [e]			
<30	45 (100)	146 (45.8)	191 (52.5)
≥30 to <50	0	96 (30.1)	96 (26.4)
≥50	0	77 (24.1)	77 (21.2)
Height (cm), n	45	318	363
Mean (SD)	83.06 (13.76)	136.56 (21.35)	129.93 (27.09)
Median	87.00	136.50	131.00
Min, Max	57.0, 101.6	89.0, 189.2	57.0, 189.2
BMI (kg/m^2), n	45	318	363
Mean (SD)	15.39 (2.21)	18.67 (4.75)	18.26 (4.64)

Table 1: Pediatric study participant (<18 years of age) demographics by age group (SS)

Variable Statistic	≥1 month to <4 years N=45	≥4 to <18 years N=319	All pediatric study participants N=364
Median	15.50	17.40	17.10
Min, Max	11.0, 19.2	10.3, 39.0	10.3, 39.0
Racial group, n (%)			
American Indian/Alaskan native	0	1 (0.3)	1 (0.3)
Asian	0	111 (34.8)	111 (30.5)
Black	0	26 (8.2)	26 (7.1)
Native Hawaiian or other Pacific Islander	0	0	0
White	36 (80.0)	164 (51.4)	200 (54.9)
Other/mixed	9 (20.0)	17 (5.3)	26 (7.1)
Ethnicity, n (%)			
Hispanic or Latino	14 (31.1)	42 (13.2)	56 (15.4)
Not Hispanic or Latino	31 (68.9)	277 (86.8)	308 (84.6)
Active VNS, n (%)	0	16 (5.0)	16 (4.4)
No VNS or VNS not active	45 (100)	302 (94.7)	347 (95.3)
No VNS	45 (100)	302 (94.7)	347 (95.3)
VNS not active	0	0	0
Missing	0	1 (0.3)	1 (0.3)

BMI=body mass index; EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; max=maximum; min=minimum; SD=standard deviation; SS=Safety Set, VNS=vagus nerve stimulation
Note: Percentages were based on the number of study participants in the SS.
[a] Age at entry into previous pediatric study for rollover study participants and age at entry into SP848 for directly enrolled study participants.
[b] Age at entry into SP848.
[c] EudraCT age categories at entry into SP848.
[d] Clinicaltrials.gov age categories at entry into SP848.
[e] Weight at entry into SP848.

Of the 364 pediatric study participants in the SS, 311 study participants had a history of POS and 46 study participants had a history of generalized seizures.

Overall, the most common seizure types in POS pediatric study participants were complex partial (IB; presently called focal impaired awareness) seizures (210 study participants [67.5%]), followed by partial, secondary generalized (IC; presently called focal to bilateral tonic-clonic) seizures (190 study participants [61.1%]) and simple partial (IA; presently called focal aware) seizures (108 study participants [34.7%]). Complex partial (IB) seizures in POS pediatric study participants were most commonly characterized by impairment of consciousness at onset with no other features (IB2a; presently called focal impaired awareness) (67 study participants [21.5%]), simple partial onset followed by impairment of consciousness with simple partial features (IB1a; presently called focal

impaired awareness) (63 study participants [20.3%]), and impairment of consciousness at onset with automatism (IB2b; presently called focal impaired awareness) (62 study participants [19.9%]). Partial, secondary generalized (IC) seizures in POS pediatric study participants were most commonly characterized as complex partial evolving to generalized (IC2; presently called focal to bilateral tonic-clonic) (113 study participants [36.3%]). Simple partial (IA) seizures in POS study participants were most commonly characterized by motor signs (IA1; presently called focal aware motor-onset) (87 study participants [28.0%]).

Comparing between age groups, a greater proportion of pediatric study participants had complex partial (IB) seizures in the ≥4 to <18 years age group (190 study participants [69.3%]) than in the ≥1 month to <4 years age group (20 study participants [54.1%]); a greater proportion of pediatric study participants had simple partial (IA) seizures in the ≥4 to <18 years age group (103 study participants [37.6%]) than in the ≥1 month to <4 years age group (5 study participants [13.5%]); and similar proportions of study participants had partial, secondary generalized (IC) seizures in the ≥4 to <18 years (169 study participants [61.7%]) and ≥1 month to <4 years (21 study participants [56.8%]) age groups.

Generalized seizures were most commonly characterized as tonic (IID; presently called generalized tonic) (23 pediatric study participants [50.0%]), myoclonic (IIB; presently called generalized myoclonic) (21 pediatric study participants [45.7%]), and tonic clonic (IIE; presently called generalized tonic-clonic) (16 pediatric study participants [34.8%]). A minority of generalized seizure pediatric study participants (9 study participants [19.6%]) also reported a history of POS. Partial-onset seizures were characterized as partial, secondary generalized (IC) (5 pediatric study participants [10.9%]), complex partial (IB) (3 pediatric study participants [6.5%]), and simple partial (IA) (2 pediatric study participants [4.3%]).

Overall, the mean epilepsy duration for POS pediatric study participants was 5.163 years (range: 0.13 to 17.67 years), and the mean age at diagnosis of the disease was 4.157 years (range: 0.00 to 16.23 years). As expected, both the mean epilepsy duration and the mean age at diagnosis of the disease for POS pediatric study participants were higher in the ≥4 to <18 years age group (5.692 years and 4.603 years, respectively) than in the ≥1 month to <4 years age group (1.248 years and 0.853 years, respectively).

Overall, the mean epilepsy duration for generalized seizure pediatric study participants was 6.292 years (range: 0.34 to 16.21 years), and the mean age at diagnosis of the disease was 3.497 years (range: 0.00 to 16.59 years). As expected, both the mean epilepsy duration and the mean age at diagnosis of the disease for generalized seizure pediatric study participants were higher in the ≥4 to <18 years age group (7.023 years and 3.969 years, respectively) than in the ≥1 month to <4 years age group (2.217 years and 0.869 years, respectively).

Overall, 119 pediatric study participants (32.7%) had taken 1 to 3 previous AEDs, 53 pediatric study participants (14.6%) had taken 4 to 6 previous AEDs, and 49 pediatric study participants (13.5%) had taken ≥7 previous AEDs. A total of 143 pediatric study participants (39.3%) had not previously taken any AEDs.

The majority of study participants in the ≥1 month to <4 years age group (35 study participants [77.8%]) had no prior AED use. The percentages of study participants who had taken 1 to 3, 4 to 6, and ≥7 previous AEDs were higher in the ≥4 to <18 years age group (34.8%, 16.0%, and 15.4%, respectively) than in the≥1 month to <4 years age group (17.8%, 4.4%, and 0%, respectively).

The majority of pediatric study participants were taking concomitant AEDs at the start of the SP848 Treatment Period. Most of pediatric study participants were taking 2 (169 pediatric study participants [46.4%]) followed by 3 (122 pediatric study participants [33.5%]) concomitant AEDs at the start of

SP848 Treatment Period. Sixty-eight pediatric study participants (18.7%) were taking 1 concomitant AED, and 2 pediatric study participants (0.5%) were not taking any concomitant AED at the start of SP848 Treatment Period.

In the ≥1 month to <4 years age group, a majority of study participants (27 study participants [60.0%]) were taking 2 concomitant AEDs, followed by 1 concomitant AED (11 study participants [24.4%]) at the start of the SP848 Treatment Period. In the ≥1 month to <4 years age group, 7 (15.6%) study participants were taking 3 concomitant AEDs and no study participants were taking 0 or ≥4 concomitant AEDs at the start of the SP848 Treatment Period. In the ≥4 to <18 years age group, a majority of study participants (142 study participants [44.5%]) were taking 2 concomitant AEDs, followed by 3 concomitant AEDs (115 study participants [36.1%]) at the start of the SP848 Treatment Period. In the ≥4 to <18 years age group, 57 study participants (17.9%) were taking 1 concomitant AEDs, 3 study participants (0.9%) were taking ≥4 concomitant AEDs, and 2 study participants (0.6%) were taking 0 concomitant AEDs at the start of SP848 Treatment Period.

Overall, the most common concomitant AEDs taken at the start of the SP848 Treatment Period were levetiracetam (157 pediatric study participants [43.1%]), valproate (147 pediatric study participants [40.4%]), and oxcarbazepine (84 pediatric study participants [23.1%]).

Levetiracetam and valproate were the most common concomitant AEDs taken at the start of SP848 in the ≥1 month to <4 years age group and ≥4 to <18 years age group. Oxcarbazepine was taken by 3 study participants (6.7%) in the ≥1 month to <4 years age group and 81 study participants [25.4%]) in the ≥4 to <18 years age group.

Antiepileptic drugs taken concomitantly for at least 1 day in common with LCM in SP848 during the SP848 Treatment Period, were taken by all pediatric study participants. Overall, the most common were levetiracetam (167 pediatric study participants [45.9%]), valproate (159 pediatric study participants [43.7%]), diazepam (87 pediatric study participants [23.9%]), and oxcarbazepine (86 pediatric study participants [23.6%]).

In the ≥1 month to <4 years age group, the most common concomitant AEDs taken during the SP848 Treatment Period were levetiracetam (25 study participants [55.6%]), valproate (23 study participants [51.1%]), and diazepam (11 study participants [24.4%]). In the ≥4 to <18 years age group, the most common concomitant AEDs taken during the SP848 Treatment Period were levetiracetam (142 study participants [44.5%]) and valproate (136 study participants [42.6%]), followed by oxcarbazepine (81 study participants [25.4%]) and diazepam (76 study participants [23.8%]).

A total of 22 pediatric study participants (6.0%) were recorded as taking LCM as a concomitant AED during the study.

Clinical pharmacology

The pharmacology results for the overall SP848 population are presented in detail within the full SP848 CSR.

For all pediatric study participants, following administration of LCM 6mg/kg/day, LCM 8mg/kg/day, and LCM 12mg/kg/day, the geometric mean LCM plasma concentration remained relatively stable over the course of the study (at Visit 7, Visit 9, and Visit 13).

Overall, the geometric mean LCM plasma concentrations generally increased with increasing LCM actual dose level; however, there was substantial interparticipant variability due to the small sample sizes at several of the dose levels.

At a designated dose and visit, geometric mean LCM plasma concentrations were slightly lower in the ≥ 1 month to <4 years age group than in the ≥4 to <18 years age group.

These results are in line with the previous knowledge of LCM plasma concentration levels.

Efficacy results

Seizure counts

Percent change from Baseline in 28-day partial-onset seizure frequency

The mean percent change in 28-day POS frequency from Baseline to the end of the Treatment Period was -24.13% for pediatric study participants overall, -27.63% in the ≥1 month to <4 years age group, and -23.67% in the ≥4 to <18 years age group.

Overall, the percent reduction in 28-day POS frequency from Baseline to the end of the Treatment Period was greatest for partial secondary generalized seizures (-47.62%), followed by simple partial seizures (-12.57%), and complex partial seizures (-4.40%). The percent reduction from Baseline in 28-day POS frequency was generally greater in the ≥1 month to <4 years age group than in the ≥4 to <18 years age group for all 3 seizure types during most time intervals up to 30 months.

≥50% reduction in 28-day POS frequency from Baseline to the end of each time interval during the Treatment Period

Overall, the proportion of ≥50% responders increased through 30 months (range: 48.4% to 74.7%) and then decreased slightly for the subsequent time intervals which were assessed for Japanese direct enrollers in the ≥4 to <18 years age group only (range: 54.8% to 62.5%). The proportion of ≥50% responders from Baseline to the end of the Treatment Period was 53.6% in POS pediatric study participants overall, with a greater proportion in the ≥1 month to <4 years age group (77.8%) than in the ≥4 to <18 years age group (50.4%).

Seizure days per 28 days for pediatric study participants with generalized seizures

In the ≥4 to <18 years age group, the number of seizure days per 28 days decreased from Baseline to Visit 8 (Week 44) and then remained stable. In the ≥1 month to <4 years age group, the number of seizure days per 28 days generally remained stable.

The mean number of seizure days per 28 days at the Last Visit was 11.86 for pediatric study participants overall, 17.70 in the ≥1 month to <4 years age group, and 10.81 in the ≥4 to <18 years age group.

Seizure-free status

During the Treatment Period, seizure free status was achieved by 24 (7.5%) pediatric study participants overall, with a greater proportion in the ≥1 month to <4 years age group (6 study participants [13.3%]) than in the ≥4 to <18 years age group (18 study participants [6.5%]).

Clinical global impression of change

At the Last Visit, 76.7% of pediatric study participants overall were considered by the investigator to have improved, 17.5% of pediatric study participants were considered to have had no change, and 5.8% of pediatric study participants were considered to have worsened. At the Last Visit, a higher proportion of study participants were considered by the investigator to have improved in the ≥1 month to <4 years age group (88.9%) than in the ≥4 to <18 years age group (74.9%), a lower proportion of study participants were considered to have had no change in the ≥1 month to <4 years age group (6.7%) than in the ≥4 to <18 years age group (19.0%), and similar proportions of study participants were considered to have worsened in both the ≥1 month to <4 years (4.4%) and ≥4 to <18 years (6.0%) age groups.

Caregiver global impression of change

At the Last Visit, 74.9% of pediatric study participants overall were considered by their caregivers to have improved, 16.2% of pediatric study participants were considered to have had no change, and 8.9% of pediatric study participants were considered to have worsened. At the Last Visit, a higher proportion of study participants were considered by their caregivers to have improved in the ≥1 month to <4 years age group (84.4%) than in the ≥4 to <18 years age group (73.6%), a lower proportion of study participants were considered to have had no change in the ≥1 month to <4 years age group (6.7%) than in the ≥4 to <18 years age group (17.5%), and an identical proportion of study participants (8.9%) were considered to have worsened in both the ≥1 month to <4 years and ≥4 to <18 years age groups.

The PedsQL results support that study participants' health-related quality of life (HRQoL) remained stable over the course of the study.

Safety results

Extent of exposure

Overall, 364 pediatric study participants were exposed to at least 1 dose of LCM for a total exposure of 625.5 participant years. Of these, 321 study participants (88.2%) were exposed to LCM for >6 months, 295 study participants (81.0%) were exposed to LCM for >12 months, 276 study participants (75.8%) were exposed to LCM for >18 months, and 239 study participants (65.7%) were exposed to LCM for >24 months. For pediatric study participants in Japan, where the study duration was longer than the 2-year duration at other sites, 32 study participants (8.8%) were exposed to LCM for >30 months, 31 study participants (8.5%) were exposed to LCM for >36 months, 31 study participants (8.5%) were exposed to LCM for >42 months, and 16 study participants (4.4%) were exposed to LCM for >48 months.

The mean duration of exposure was 627.6 days for pediatric study participants overall, the mean maximum daily LCM dose was 9.2mg/kg/day, and the mean modal daily dose was 8.1mg/kg/day.

The mean duration of exposure, mean maximum daily LCM dose, and mean modal daily LCM dose were similar across the ≥1 month to <4 years and ≥4 to <18 years age groups (646.0 days and 625.0 days, respectively; 9.5mg/kg/day and 9.2mg/kg/day, respectively; and 9.3mg/kg/day and 8.0mg/kg/day, respectively).

Adverse events

Overall summary of TEAEs

An overall summary of treatment emergent adverse events (TEAEs) is presented for the SS for pediatric study participants in Table 2.

Table 2: Overview of the incidence of TEAEs by age group for pediatric study participants (<18 years of age) (SS)

Category	≥1 month to <4 years N=45 n (%) [#]	≥4 to <18 years N=319 n (%) [#]	All pediatric study participants N=364 n (%) [#]
Any TEAEs	41 (91.1) [334]	294 (92.2) [3011]	335 (92.0) [3345]
Serious TEAEs	15 (33.3) [41]	67 (21.0) [179]	82 (22.5) [220]
Study participant discontinuations due to TEAEs	1 (2.2) [1]	26 (8.2) [33]	27 (7.4) [34]
Drug-related TEAEs	2 (4.4) [2]	169 (53.0) [636]	171 (47.0) [638]
Drug-related serious TEAEs	0	13 (4.1) [27]	13 (3.6) [27]
Severe TEAEs	4 (8.9) [9]	40 (12.5) [68]	44 (12.1) [77]
All deaths	0	1 (0.3) [1]	1 (0.3) [1]
Deaths (TEAEs leading to death)	0	1 (0.3) [1]	1 (0.3) [1]

SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n was the number of study participants reporting at least 1 TEAE in that category.
Note: [#] was the number of individual occurrences of the TEAE in that category.
Note: Drug-related TEAEs were determined as per the investigator.
Note: Percentages were based on the number of study participants in the SS.

The incidence of TEAEs was similar in the ≥1 month to <4 years (91.1%) and ≥4 to <18 years (92.2%) age groups. The incidence of drug-related TEAEs was lower in the ≥1 month to <4 years age group (4.4%) than in the ≥4 to <18 years age group (53.0%). The incidence of serious TEAEs was higher in the ≥1 month to <4 years age group (33.3%) than in the ≥4 to <18 years age group (21.0%).

The most common TEAEs (≥5% of all pediatric study participants) by age group for the SS for pediatric study participants are summarized in Table 3.

Table 3: Incidence of most common TEAEs during the Treatment Period (≥5% of all study participants) by age group for pediatric study participants (<18 years of age) (SS)

MedDRA v16.1 SOC PT	≥1 month to <4 years N=45 n (%) [#]	≥4 to <18 years N=319 n (%) [#]	All pediatric study participants N=364 n (%) [#]
Any TEAEs	41 (91.1) [334]	294 (92.2) [3011]	335 (92.0) [3345]
Gastrointestinal disorders	14 (31.1) [31]	156 (48.9) [421]	170 (46.7) [452]
Vomiting	5 (11.1) [14]	75 (23.5) [152]	80 (22.0) [166]
Diarrhoea	3 (6.7) [3]	39 (12.2) [51]	42 (11.5) [54]
Constipation	3 (6.7) [3]	25 (7.8) [34]	28 (7.7) [37]
Nausea	1 (2.2) [1]	23 (7.2) [33]	24 (6.6) [34]
Abdominal pain	1 (2.2) [1]	22 (6.9) [33]	23 (6.3) [34]
General disorders and administration site conditions	15 (33.3) [26]	110 (34.5) [205]	125 (34.3) [231]
Pyrexia	12 (26.7) [18]	70 (21.9) [113]	82 (22.5) [131]
Fatigue	0	21 (6.6) [31]	21 (5.8) [31]
Infections and infestations	30 (66.7) [142]	211 (66.1) [846]	241 (66.2) [988]
Nasopharyngitis	10 (22.2) [28]	81 (25.4) [225]	91 (25.0) [253]
Upper respiratory tract infection	11 (24.4) [23]	75 (23.5) [147]	86 (23.6) [170]
Pharyngitis	6 (13.3) [9]	31 (9.7) [39]	37 (10.2) [48]
Gastroenteritis	6 (13.3) [8]	25 (7.8) [30]	31 (8.5) [38]
Bronchitis	3 (6.7) [3]	26 (8.2) [41]	29 (8.0) [44]
Influenza	3 (6.7) [4]	26 (8.2) [34]	29 (8.0) [38]
Urinary tract infection	3 (6.7) [5]	19 (6.0) [22]	22 (6.0) [27]
Viral infection	1 (2.2) [2]	21 (6.6) [36]	22 (6.0) [38]
Sinusitis	1 (2.2) [1]	19 (6.0) [28]	20 (5.5) [29]
Ear infection	3 (6.7) [6]	16 (5.0) [21]	19 (5.2) [27]
Injury, poisoning and procedural complications	11 (24.4) [51]	74 (23.2) [159]	85 (23.4) [210]
Contusion	4 (8.9) [19]	21 (6.6) [36]	25 (6.9) [55]
Metabolism and nutrition disorders	7 (15.6) [8]	53 (16.6) [68]	60 (16.5) [76]
Decreased appetite	1 (2.2) [1]	26 (8.2) [29]	27 (7.4) [30]
Nervous system disorders	16 (35.6) [26]	191 (59.9) [562]	207 (56.9) [588]
Somnolence	3 (6.7) [5]	72 (22.6) [96]	75 (20.6) [101]
Dizziness	0	69 (21.6) [114]	69 (19.0) [114]
Headache	1 (2.2) [2]	46 (14.4) [90]	47 (12.9) [92]

Table 3: Incidence of most common TEAEs during the Treatment Period (≥5% of all study participants) by age group for pediatric study participants (<18 years of age) (SS)

MedDRA v16.1 SOC PT	≥1 month to <4 years N=45 n (%) [#]	≥4 to <18 years N=319 n (%) [#]	All pediatric study participants N=364 n (%) [#]
Convulsion	4 (8.9) [5]	30 (9.4) [41]	34 (9.3) [46]
Tremor	0	21 (6.6) [23]	21 (5.8) [23]
Respiratory, thoracic and mediastinal disorders	7 (15.6) [8]	82 (25.7) [143]	89 (24.5) [151]
Cough	2 (4.4) [2]	34 (10.7) [41]	36 (9.9) [43]

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n was the number of study participants with at least 1 TEAE within the SOC/PT.
Note: [#] was the number of individual occurrences of the TEAE.
Note: Percentages were based on the number of study participants in the SS.

Most study participants experienced TEAEs during the first 3 months of treatment. Overall, 268 pediatric study participants (73.6%) experienced TEAEs during this time interval, with a lower incidence in the ≥1 month to <4 years age group (57.8%) than in the ≥4 to <18 years age group (75.9%).

Deaths

One study participant had 1 fatal TEAE of sudden death on Day 145 while at a dose level of LCM 8mg/kg/day. This event was severe in intensity, was considered serious, and was considered not related to the study medication by the investigator.

The MAH states that full narrative for the death has been produced.

Serious TEAEs

Overall, 82 pediatric study participants (22.5%) experienced a total of 220 serious TEAEs, and 13 pediatric study participants (3.6%) experienced a total of 27 serious TEAEs that were considered related or possibly related to study medication by the investigator. The most common serious TEAEs (by PT) were convulsion (21 pediatric study participants [5.8%]), status epilepticus (11 pediatric study participants [3.0%]), and vomiting (8 pediatric study participants [2.2%]).

The incidence of any serious TEAE was higher in the ≥1 month to <4 years age group (15 out of 45 study participants [33.3%]) than in the ≥4 to <18 years age group (67 out of 319 study participants [21.0%]).

Overall, the incidence of serious TEAEs up to 30 months ranged from 2.1% to 7.2%. During time intervals beyond 30 months, which were assessed for Japanese direct enrollers in the ≥4 to <18 years age group only, the incidence of serious TEAEs ranged from 3.1% to 12.9%. Of note, the small sample sizes at later time points make it difficult for meaningful comparisons to be made.

Discontinuation due to TEAEs

Overall, 27 pediatric study participants (7.4%) experienced a total of 34 TEAEs leading to study discontinuation. The most common TEAEs leading to study discontinuation overall (by PT) were

dizziness and vomiting (4 pediatric study participants [1.1%] each), and convulsion and somnolence (3 pediatric study participants [0.8%] each).

The incidence of TEAE leading to study discontinuation was higher in the ≥4 to <18 years age group (26 study participants [8.2%]) than the ≥1 month to <4 years age group (1 study participant [2.2%]; PT: status epilepticus).

Overall, the incidence of TEAEs leading to study discontinuation was highest in the first 3 months of the study (15 pediatric study participants [4.1%]) and was then consistently low for the remaining time intervals, up to 30 months (range: 0% to 1.2%).

Other significant AEs

Four pediatric study participants (1.1%) experienced TEAEs of bradycardia, 2 pediatric study participants (0.5%) each experienced TEAEs of syncope and electrocardiogram (ECG) QT prolonged, and 1 pediatric study participant (0.3%) each experienced a TEAE of self-injurious behavior, defect conduction intraventricular, and suicidal ideation.

The incidence of other significant TEAEs was similar in the ≥1 month to <4 years age group (1 pediatric study participant [2.2%]) and the ≥4 to <18 years age group (10 pediatric study participants [3.1%]).

AEs of relevance to the participant population

The most frequently reported seizure related TEAE was convulsion (34 pediatric study participants [9.3%]) which is not unforeseen given the pediatric population living with epilepsy included in this study. The incidences of TEAEs related to memory impairment, amnesia, or cognitive disorder were low; these TEAEs occurred in only 1 study participant each, except for aggression (8 study participants), agitation (3 study participants), and memory impairment (2 study participants). No events of cognitive disorder were reported. The incidences of TEAEs related to psychotic disorders were low; these TEAEs occurred in only 1 study participant each, except for hallucination, visual (2 study participants). The incidences of TEAEs related to body weight change were low; these TEAEs occurred in only 1 study participant each, except for weight decreased (5 study participants), obesity (4 study participants), and weight increased (2 study participants).

Pediatric growth-, neurodevelopment-, behavior-, and endocrine related TEAEs

Overall, 87 pediatric study participants (23.9%) experienced a total of 142 TEAEs related to pediatric growth, neurodevelopment, behavior, or endocrine function; which were not unforeseen given the rate of cerebral palsy, developmental delay, and genetic disorders typically observed in this pediatric population of study participants. Treatment-emergent AEs related to pediatric growth, neurodevelopment, behavior, or endocrine function observed in more than 1 pediatric study participant included the following: irritability (18 study participants); lethargy (12 study participants); aggression (8 study participants); abnormal behavior (7 study participants); blood testosterone increased (6 study participants), anger, blood testosterone decreased, hypothyroidism, psychomotor hyperactivity, salivary hypersecretion, and tri iodothyronine decreased (4 study participants each); attention deficit/hyperactivity disorder, enuresis, and incontinence (3 study participants each); and blood luteinising hormone decreased, blood thyroid stimulating hormone decreased, cryptorchism, fecal incontinence, and memory impairment (2 study participants each).

Clinical laboratory evaluation, vital signs and ECG

Overall, no consistent or clinically relevant mean or median changes from Baseline after LCM treatment were observed for hematology, clinical chemistry, endocrinology parameters, or vital sign parameters.

None of the relatively small changes from Baseline in ECG parameters appeared to be clinically relevant according to the MAH. The incidences of TEAEs related to abnormal 12-lead ECG values were low in pediatric study participants overall (range: 0.3% to 0.8%) and in both the ≥1 month to <4 years (range: 0% to 2.2%) and ≥4 to <18 years (range: 0.3% to 0.9%) age groups. Overall, the most common TEAEs related to abnormal 12-lead ECG values (by PT) were AV block first degree, ECG abnormal, and tachycardia (3 pediatric study participants [0.8%] each). The remaining TEAEs related to 12 lead ECG findings were observed in ≤2 study participants each.

Two pediatric study participants experienced 3 events of ECG QT prolonged. One participant had 2 events of ECG QT prolonged which were mild in intensity, not considered serious, considered not related to study medication by the investigator, did not lead to study discontinuation, and resolved. One participant had an event of ECG QT prolonged which was moderate in intensity, was not considered serious, considered possibly related to study medication by the investigator, did not result in study discontinuation, and resolved.

All other TEAEs related to abnormal 12-lead ECG findings were mild or moderate in intensity, were considered not serious, and did not lead to study discontinuation. The 4 events of AV block first degree; 2 events of ECG T wave abnormal; and 1 event each of ECG abnormal, defect conduction intraventricular, ECG PR prolongation, nodal arrhythmia, and ventricular extrasystoles were considered possibly related to study medication. The majority of TEAEs related to abnormal 12-lead ECG findings resolved by the end of the study except for the following events that were ongoing: 2 events each of bundle branch block right and ECG T wave abnormal; 1 event each of AV block first degree, bundle branch block left, and ECG PR prolongation; and 1 event of ventricular extrasystoles that was resolving at the end of the study.

Achenbach Child Behavior Checklist

Overall, study participants assessed with the Achenbach Child Behavior Checklist for Ages 1.5 to 5 years (CBCL/1.5-5) showed very small mean negative change values (negative change representing improvement) from Baseline to the Last Visit (n=60) for all scores (aggressive behavior, anxious/depressed, emotionally reactive, sleep problem, somatic complaints, withdrawn, and other problems), except for attention problems which presented a mean (SD) change of 0.3 (2.3).

Overall, study participants assessed with the Achenbach CBCL for Ages 6 to 18 years (CBCL/6 18) (including the 1 study participant aged ≥18 years old at the time of entry in SP848) showed small mean negative change values (negative change representing improvement) from Baseline to the Last Visit (n=228) for all scores (aggressive behavior, anxious/depressed, attention problems, rule breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed).

BRIEF-P and BRIEF

Overall, study participants assessed with the Behavior Rating Inventory of Executive Function® Preschool Version (BRIEF®-P) showed small mean positive change values (positive change representing worsening) from Baseline to the Last Visit (n=34) for all 3 indexed scores (inhibitory self-control, flexibility, and emergent metacognition) (range: 1.1 to 2.1) and the Global Executive Composite (GEC) score (4.3), but these were based on small sample sizes and were associated with large SDs (SD range for the 3 indexed scores: 8.0 to 12.1; GEC score SD: 24.1).

Overall, study participants assessed with the Behavior Rating Inventory of Executive Function® (BRIEF®) (including the 1 study participant aged ≥18 years old at the time of entry in SP848) showed small mean negative change values (negative change representing improvement) from Baseline to the Last Visit for all scores, but these mean changes were associated with large SDs: Behavioral Regulation

Index (BRI) score (-2.7, SD=11.1, n=205), the Metacognition Index (MI) score (-3.8, SD=20.0, n=201), and the GEC score (-6.7, SD=28.9, n=201).

2.3.3. Discussion on clinical aspects

Lacosamide is indicated as monotherapy in the treatment of partial-onset seizures (POS, presently called focal onset seizures) with or without secondary generalization in patients from 4 years of age with epilepsy. Lacosamide is also indicated as adjunctive therapy in the treatment of POS with or without secondary generalization in adults, adolescents, and children from 4 years of age with epilepsy; and in the treatment of primary generalized tonic-clonic seizures in adults, adolescents, and children from 4 years of age with idiopathic generalized epilepsy.

The MAH submitted the results of SP848 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). SP848 was an open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children with epilepsy. The study enrolled totally 364 patients ≥1 month to ≤18 years of age, including 45 study participants aged ≥1 month to <4 years and 319 study participants aged ≥4 to <18 years. It is noted that only patients older than ≥4 years are covered by currently approved indication. Meanwhile, the positive benefit/risk balance is not established for patients aged ≥1 month to <4 years. The study design due to e.g. lack of control arm and open label, does not allow to perform a proper assessment of efficacy of LCM and consequently establish benefit/risk balance for this age group either.

It is noted that even if the incidence of TEAE is rather similar between the patients aged ≥1 month to <4 years and patients aged ≥4 to <18 years, more serious TEAEs are observed in the younger patients' group (33.3% vs 21% respectively). No other clear differences were observed between these two patients' groups except for irritability – patients aged ≥1 month to <4 years (n=4, 8.9%) vs aged ≥4 to <18 years (n=14, 4.4%).

In general, the safety observations in SP848, especially in patients aged ≥4 to <18 years, were consistent with the known safety profile of LCM in adults. Observations in SP848 were as expected for the paediatric population (e.g., high incidence of infections and associated symptoms). No consistent or clinically relevant worsening in neurocognition or behavior, as assessed with CBCL/1.5-5, CBCL/6-18, and BRIEF/BRIEF-P, were observed after LCM treatment according to the MAH. This is agreed. No new safety concerns were identified in this study.

The MAH stated that "at a later date, proposed labelling changes based on SP848 results may be submitted as part of a Type II variation." The Rapporteur considers that the presented safety and efficacy data of LCM treatment in paediatric patients aged ≥1 month to ≤18 years from study SP848 are not sufficient to justify any changes in the product information. Therefore, no changes in the product information are proposed.

3. CHMP overall conclusion and recommendation

The results of SP848 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation).

No new safety concerns were identified in SP848. The safety findings, especially in patients aged ≥4 to <18 years, were consistent with the known safety profile of LCM in adults. Therefore, the benefit risk balance in this patients' population remains favourable. No changes to the approved EU Summary of Product Characteristics for VIMPAT are being proposed with this submission based on SP848 results.