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Committee for Medicinal Products for Human Use (CHMP)

# 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/P46/028

## Note

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

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# 1. Introduction

On 15 of August, 2017, the MAH submitted the results of SP0969 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation), which requires the MAH to submit information on studies conducted in children (<18 years of age) treated with lacosamide (LCM; VIMPAT®; SPM 927, previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037).

Based on the new data presented in this Clinical Overview Addendum and the corresponding SP0969 clinical study report (CSR), the MAH is not seeking to expand the label in pediatrics with this submission. Furthermore, the benefit-risk balance of LCM remains positive.

At a later date, proposed labeling changes based on SP0969 results will be submitted as part of a Type II variation.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that "SP0969 is a multicenter, double blind, randomized, placebo controlled, parallel group study that evaluated the efficacy and safety of lacosamide as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial onset seizures" study is a stand-alone study.

## *2.2. Information on the pharmaceutical formulation used in the study*

The study medication was provided as LCM oral solution (syrup) (LCM 10mg/mL), LCM tablets (LCM 50mg and LCM 100mg), and matching placebos.

The LCM 10mg/mL oral solution and matching placebo oral solution were colorless to pale yellow in appearance. Both oral solutions were packaged in amber polyethylene terephthalate bottles. Oral solution doses were measured and administered via a dosing syringe.

The LCM 50mg tablets and matching placebo were pinkish, oval tablets debossed with "SP" on 1 side and "50" on the other side. The LCM 100mg tablets and matching placebo were dark yellow, oval tablets debossed with "SP" on one side and "100" on the other side. Tablets were packaged in high density polyethylene bottles.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- "SP0969 is a multicenter, double blind, randomized, placebo controlled, parallel group study that evaluated the efficacy and safety of lacosamide as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial onset seizures"

Lacosamide was first approved by the European Medicines Agency in 2008 and is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy.

SP0969 was a Phase 3, multicenter, double-blind, randomized, placebo controlled, parallel-group study to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day [oral solution] for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day [oral solution] for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day [tablets] for subjects weighing ≥50kg, or matching placebo) as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled partial onset seizures. Subjects weighing ≥50kg who were unable or unwilling to swallow tablets may have received LCM oral solution; however, they were not permitted to exceed the maximum dose of LCM 400mg/day. SP0969 included a Baseline Period, Titration Period, Maintenance Period, Transition Period, Taper Period, and Safety Follow-up Period.

Subjects with uncontrolled partial-onset seizures were enrolled into an 8-week Baseline Period. At the end of the Baseline Period, subjects were randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or placebo in a 1:1 ratio. Eligible subjects entered a 6-week Titration Period (with study medication dosing flexibility allowed based on tolerability) to achieve the target Maintenance Period dose. Subjects who achieved at least the minimum target study medication (LCM or matching placebo) dose for the final 3 days of the Titration Period entered a 10-week Maintenance Period on the study medication dose achieved on the final day of the Titration Period. Lacosamide dose (or matching placebo) remained stable throughout the Maintenance Period. Subjects who completed the Maintenance Period and planned to participate in the open-label extension study (EP0034) entered the 4-week blinded Transition Period.

## 2.3.2. Clinical study

## SP0969 is a multicenter, double blind, randomized, placebo controlled, parallel group study that evaluated the efficacy and safety of lacosamide as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial onset seizures

## Description

## Methods

### *Objective(s)*

#### Primary objective

The primary objective of this study was to evaluate the efficacy of LCM administered concomitantly with 1 to ≤3 AEDs in subjects with epilepsy ≥4 years to <17 years of age who currently had uncontrolled partial-onset seizures.

#### Secondary objective

The secondary objective was to evaluate the safety and tolerability of LCM in subjects ≥4 years to <17 years of age.

#### Additional objective

An additional objective was to evaluate the PK of LCM in subjects ≥4 years to <17 years of age.

***Study design***

SP0969 was a Phase 3, multicenter, double-blind, randomized, placebo controlled, parallel-group study to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day [oral solution] for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day [oral solution] for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day [tablets] for subjects weighing ≥50kg, or matching placebo) as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled partial onset seizures. Subjects weighing ≥50kg who were unable or unwilling to swallow tablets may have received LCM oral solution; however, they were not permitted to exceed the maximum dose of LCM 400mg/day. SP0969 included a Baseline Period, Titration Period, Maintenance Period, Transition Period, Taper Period, and Safety Follow-up Period.

Subjects with uncontrolled partial-onset seizures were enrolled into an 8-week Baseline Period. At the end of the Baseline Period, subjects were randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or placebo in a 1:1 ratio. Eligible subjects entered a 6-week Titration Period (with study medication dosing flexibility allowed based on tolerability) to achieve the target Maintenance Period dose. Subjects who achieved at least the minimum target study medication (LCM or matching placebo) dose for the final 3 days of the Titration Period entered a 10-week Maintenance Period on the study medication dose achieved on the final day of the Titration Period. Lacosamide dose (or matching placebo) remained stable throughout the Maintenance Period. Subjects who completed the Maintenance Period and planned to participate in the open-label extension study (EP0034) entered the 4-week blinded Transition Period.

There was a 30-day Safety Follow-up Period for subjects not entering the open-label extension study (EP0034).

***Study population /Sample size***

To be eligible to participate in this study, all of the following **inclusion criteria** must have been met:

1. An IRB/IEC approved written ICF was signed and dated by the parent(s) or legal representative. The ICF or a specific Assent form, where required, was signed and dated by minors.

2. Subject/legal representative was considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.

3. Subject was male or female from ≥4 years to <17 years of age.

4. Subject had a diagnosis of epilepsy with partial-onset seizures. The results of ≥1 prior electroencephalogram AND 1 prior magnetic resonance imaging/computerized tomography scan were to be consistent with the above diagnosis.

5. Subject had been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with ≥2 AEDs (concurrently or sequentially).

6. Subject must have been observed to have on average ≥2 partial-onset seizures per 28 days with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the Baseline Period. During this study, subjects must have reported ≥2 partial-onset seizures during the 8-week prospective Baseline Period to be eligible for randomization at Visit 2. (Note: In the case of simple partial-onset seizures, only those seizures with motor signs were counted towards meeting the inclusion criterion.)

7. Subject was on a stable dosage regimen of 1 to ≤3 AEDs. The daily dosage regimen of concomitant AED therapy was to be kept constant for a period of ≥4 weeks prior to the Baseline Period.

8. Vagal nerve stimulation was allowed and was not counted as a concomitant AED. The VNS device must have been implanted for ≥6 months before Visit 1, and the device settings must have been stable for ≥4 weeks before Visit 1 and have been kept stable during the Baseline Period. Use of the VNS device magnet was allowed.

***Treatments***

Based on the currently available LCM pediatric safety and PK data from SP847 and SP1047, as well as on information available in the medical literature, the dosing recommendations for SP0969 were as follows to achieve LCM plasma concentrations corresponding to the average steady-state LCM plasma concentration (Css) reached after a LCM 400mg/day dose administration in adult studies, which is approximately 8µg/mL:

- A weight-based dosing scheme was recommended for the Maintenance Period:
    - Subjects <30kg: LCM 8mg/kg/day to 12mg/kg/day
    - Subjects ≥30kg to <50kg: LCM 6mg/kg/day to 8mg/kg/day
    - Subjects ≥50kg: LCM 300mg/day to 400mg/day
- The LCM (or matching placebo) dose was to otherwise remain fixed over the Maintenance Period.
- To provide dosing flexibility and optimized tolerability for each subject during titration, flexible study medication dosing achieved a minimum target dose for entry into the Maintenance Period. The dosing flexibility during the Titration Period included 4 key elements:
    - A Titration Period of 6 weeks allowed sufficient time to achieve the minimum target dose for entry into the Maintenance Period for subjects who required study medication dosing flexibility based on tolerability.
    - Allowed investigators to hold a subject's study medication dose constant at any time during the Titration Period and allowed for multiple holds if needed.
    - Allowed investigators to back titrate a subject's study medication dose by full-step or half-step increments, with asymmetric dosing as needed for tablets.
    - Allowed flexibility in the duration a subject was to remain on a back-titrated study medication dose before a subsequent increase.
- Administration of oral solution by feeding tube was permitted for subjects who were unable to swallow the oral solution; however, they were not permitted to exceed the maximum dose of LCM 400mg/day.
- Dosing with oral solution was permitted for subjects weighing ≥50kg who were unable or unwilling to swallow tablets.

***Outcomes/endpoints***

*Primary efficacy variable*

- The primary efficacy variable was the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period.

*The secondary efficacy variables are described below:*

- Proportion of responders, where a responder was a subject who experienced a 50% or greater reduction in partial-onset seizure frequency from Baseline to the Maintenance Period
- Proportion of subjects who experienced a ≥25% to <50%, ≥50% to ≤75%, or >75% reduction in partial-onset seizure frequency from Baseline to the end of the Maintenance Period
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects who experienced a ≥25% to <50%, ≥50% to ≤75%, or >75% reduction in partial-onset seizure frequency from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects who experienced no change in partial-onset seizure frequency (between <25% reduction and <25% increase) from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects who experienced an increase in partial-onset seizure frequency of ≥25% from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods) by seizure type
- Proportion of seizure-free days during the Maintenance Period for subjects who entered the Maintenance Period
- Proportion of subjects who achieved “seizure-free” status (yes/no) for subjects who completed the Maintenance Period

*Safety and tolerability were assessed using the following primary variables:*

- Adverse events reported spontaneously by the subject and/or caregiver (including parent/legal guardian) or observed by the investigator
- Subject withdrawals due to AEs

*Other safety variables*

Other safety variables included:

- Changes in hematology, clinical chemistry, and endocrinology parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate)
- Physical and neurological examination findings
- Changes in body weight, height, and calculated body mass index
- Behavioral assessments (Achenbach CBCL/1½-5 or CBCL/6-18)
- Cognitive function assessments (BRIEF-P/ Behavior Rating Inventory of Executive Function [BRIEF®])

Plasma concentrations of LCM and concomitant AEDs were obtained in order to:

- Develop a population PK model of LCM
- Investigate the effect of LCM on the steady-state plasma concentrations of concomitant AEDs
- Investigate the correlation between LCM plasma concentrations and efficacy or safety

***Statistical Methods***

Descriptive statistics were displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category were presented. The denominator for percentages was based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics included number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.

Decimal places for descriptive statistics always applied the following rules:

- "n" was an integer.
- Mean, SD, and median used 1 additional decimal place compared with the original data.
- Coefficient of variation (CV[%]) was presented with 1 decimal place.
- Minimum and maximum had the same number of decimal places as the original value.

Statistical tests of efficacy variables were presented as 2-sided p-values rounded to 4 decimal places. Statistical comparison was performed at the 0.0500 level of significance.

A complete set of data listings containing all documented data and all calculated data (eg, change from Baseline) were generated, and were sorted by site, subject number and visit (where applicable).

The analysis sets defined for this study were the Safety Set (SS), Full Analysis Set (FAS), Per-Protocol Set (PPS), and Pharmacokinetic Per-Protocol Set (PK-PPS).

The primary analysis set for the efficacy data was the FAS. The secondary analysis set for the efficacy data was the PPS. The primary analysis set for the safety parameters was the SS. The primary analysis set for the PK parameters was the PK-PPS.

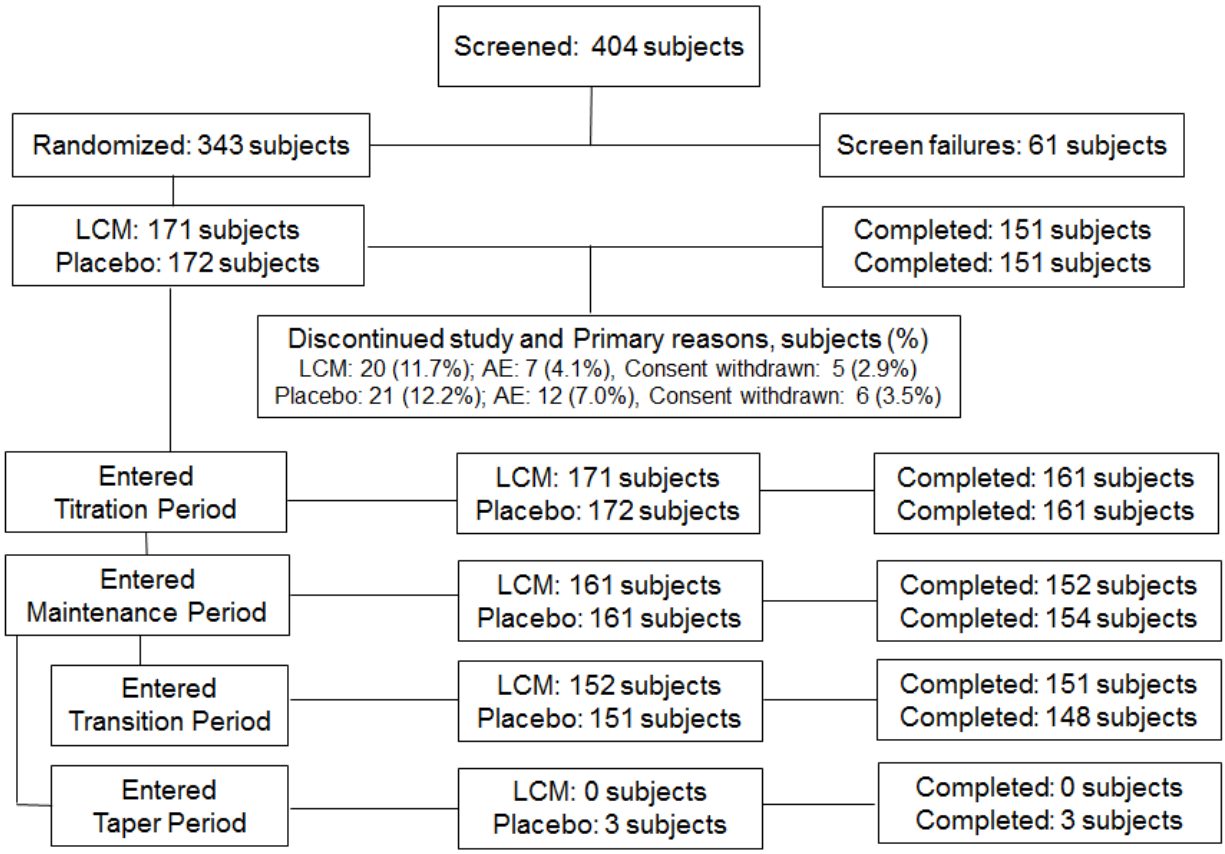
Age at enrollment was categorized into the subgroups: ≥4 to <12 years and ≥12 to <17 years, and used within summaries of disposition, demography, exposure, AEs, and certain efficacy analyses. Weight at Baseline was categorized into the subgroups: <30kg, ≥30kg to <50kg, and ≥50kg, and used within summaries of exposure and AEs.

## Results

***Recruitment/ Number analysed***

A summary of subject disposition and reasons for discontinuation is presented in Figure 7-1.

Figure 7-1: Subject disposition and reasons for discontinuation (All Subjects Screened and SS)




Overall, 404 subjects were screened at 114 sites. There were 61 screen failures (15.1%) primarily attributed to ineligibility (9.2%) and consent withdrawn (3.2%). A total of 343 subjects were randomized: 171 subjects to LCM and 172 subjects to placebo; 151 subjects in each treatment group completed the study (88.3% and 87.8% of subjects in LCM and placebo groups, respectively).

Overall, of the 343 subjects who started the study, 302 subjects (88.0%) completed the study. The most common reason for discontinuation from the study was AE (19 subjects [5.5%]) followed by consent withdrawn (11 subjects [3.2%]); the reasons for discontinuation were generally similar between the LCM and placebo groups.

Overall, 322 subjects (93.9%) completed the Titration Period and entered the Maintenance Period; 306 subjects (89.2%) completed the Maintenance Period. Of the 303 subjects who entered the Transition Period, 299 subjects (87.2%) completed and moved to the open-label extension study, EP0034.

***Baseline data***

Overall, the mean age of subjects was 10.7 years (range: 4 to 16 years). A slightly greater proportion of the subjects comprised the ≥4 to <12 years age group compared with the ≥12 to <17 years age group (53.1% vs 46.9%). Overall, the proportion of males was higher compared with females (55.4% and 44.6%, respectively). The mean weight was 41.48kg and the subjects were approximately evenly divided among the 3 weight bands: 32.9%, 30.9%, and 36.2% in the <30kg, ≥30kg to <50kg, and ≥50kg bands, respectively. The mean height, BMI, and head circumference were 143.03cm, 19.16kg/m2, and 52.61cm, respectively. The majority of subjects were white (267 subjects [77.8%]) and not of Hispanic or Latino ethnicity (315 subjects [91.8%]). Subjects in the LCM and placebo

groups had generally similar demographics. Notably, there were fewer Asian subjects in the LCM group compared with the placebo group (25 subjects [14.6%] vs 35 subjects [20.3%]).

The majority of subjects had not used vagus nerve stimulation (VNS) (335 subjects [97.7%]). A total of 8 subjects (2.3%) were VNS users, 6 subjects (3.5%) and 2 subjects (1.2%) in the LCM and placebo groups, respectively.

In the ≥4 to <12 years and ≥12 to <17 years age group, the mean age and weight of subjects were 7.9 years and 14.0 years, and 28.92kg and 55.76kg, respectively.

A total of 239 subjects (69.7%) had any previous and ongoing medical history conditions, with the LCM and placebo groups having similar incidence (71.3% and 68.0%, respectively). Overall, the most common system organ classes (SOCs) in which medical history findings were noted were Nervous system disorders (143 subjects [41.7%]), Congenital, familial, and genetic disorders (97 subjects [28.3%]), and Psychiatric disorders (54 subjects [15.7%]), and Infections and infestation (49 subjects [14.3%]). Mental retardation was the most common condition (50 subjects [14.6%]). The medical history conditions were generally similar in the LCM and placebo groups.

All subjects participating in the study had a diagnosis of epilepsy with partial-onset seizures. Overall, 179 subjects (52.2%), 265 subjects (77.3%), and 215 subjects (62.7%) experienced simple partial (IA), complex partial (IB), and partial evolving to secondarily generalized (IC) seizures, respectively. Subjects in the LCM and placebo groups had generally similar seizure history; simple partial (IA), complex partial (IB), and partial evolving to secondarily generalized (IC) seizures diagnosed in the LCM group compared with the placebo group were 55.0% vs 49.4%, 78.4% vs 76.2%, and 64.9% vs 60.5%, respectively. A total of 5 subjects (1.5%) and 2 subjects (0.6%) also had generalized seizures or unclassified epileptic seizures, respectively.

The mean time of epilepsy duration was 6.58 years (range: 0.4 to 16.2 years) and the mean age at diagnosis was 4.72 years (range: 0.0 to 15.6 years). Epilepsy duration and age at diagnosis were similar between the LCM and placebo groups (6.57 years vs 6.59 years and 4.54 years vs 4.90 years, respectively).

Overall, the subjects had a history of low incidence of withdrawal seizures and status epilepticus (18 subjects [5.2%] and 30 subjects [8.7%], respectively); these incidence were generally similar between the LCM and placebo groups.

The median partial-onset seizure frequency per 28 days at Baseline was 10.41 in the LCM group and 8.77 in the placebo group.

Overall, the number of subjects taking 1, 2, or 3 AEDs on the day of the first dose of study medication was 59 subjects (17.2%), 160 subjects (46.6%), and 124 subjects (36.2%), respectively.

Overall, the most common concomitant AEDs used by >5% of subjects in any treatment group was valproate (166 subjects [48.4%]), levetiracetam (142 subjects [41.4%]), and carbamazepine and lamotrigine (89 subjects [25.9%] each). The use of concomitant AEDs was generally similar between the LCM and placebo groups.

Overall, the concomitant use of the enzyme-inducing AEDs carbamazepine, phenobarbital, and phenytoin were reported by 89 subjects (25.9%), 20 subjects (5.8%), and 8 subjects (2.3%), respectively

***Efficacy results***

This double-blind, placebo-controlled Phase 3 study supports that LCM is efficacious as an adjunctive therapy in subjects ≥4 years to <17 years of age with epilepsy with uncontrolled partial-onset seizures.

- Statistically significant and clinically relevant reduction in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period was observed between the LCM and placebo group (p=0.0003). Similar results were observed from Baseline to entire Treatment Period (p<0.0001).
- The percent reduction in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period in the LCM group over the placebo group was 31.72% (95% CI: 16.342, 44.277). The percent reduction in partial-onset seizure frequency per 28 days from Baseline to entire Treatment Period in the LCM group over the placebo group was 30.18% (95% CI: 17.490, 40.919).
- Subgroup analyses by age group demonstrated similar reduction in the LCM group for subjects ≥4 to <12 years and ≥12 to <17 years in median partial-onset seizure frequency per 28 days for both periods of Baseline to the Maintenance Period and Baseline to entire Treatment Period.
- The magnitude of reduction in partial-onset seizure frequency per 28 days from Baseline increased in the LCM group over the placebo group during the visits in the Titration Period and achieved statistical significance as early as Visit 4. The percentage reduction at Visit 3, Visit 4, and Visit 5 were 13.94% (p=0.0852), 29.78% (p=0.0006), and 33.87% (p=0.0006), respectively.
- The percentage of responders, subjects experiencing a ≥50% reduction in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period, was higher in the LCM group compared with the placebo group (52.9% vs 33.3%); the difference was statistically significant based on odds ratio (2.17, p=0.0006).
    - In the group of responders, the percent reduction by seizure types, simple partial (IA), complex partial (IB), or secondary generalized (IC) seizures, were similar between the LCM and the placebo groups.
- The proportion of subjects experiencing a >75% reduction in partial-onset seizure frequency per 28 days from Baseline to end of the Maintenance Period was higher in the LCM group compared with the placebo group.
- The proportion of subjects experiencing a >75% reduction in partial-onset seizure frequency per 28 days from Baseline to end of entire Treatment Period was higher in the LCM group compared with the placebo group, however, the proportion of subjects experiencing a ≥50% to ≤75% reduction in the LCM and placebo groups were comparable.
- The proportion of subjects experiencing no change in partial-onset seizure frequency per 28 days from Baseline to entire Treatment Period was lower in the LCM group compared with the placebo group (20.6% vs 32.0%); the difference was statistically significant based on odds ratio (0.56, p=0.0220).
- The proportion of subjects experiencing an increase in partial-onset seizure frequency per 28 days from Baseline to entire Treatment Period was comparable between the LCM and the placebo groups (18.8% and 23.1%, respectively).

- Statistically significant reductions in seizure frequency per 28 days from Baseline to entire Treatment Period were observed by seizure type between the LCM and placebo group: 30.82% (p=0.0255) for simple partial seizures (IA), 32.41% (p=0.0004) for complex partial seizures (IB), and 23.35% (p=0.0390) for secondary generalized seizures (IC).
- The proportion of seizure-free days during the Maintenance Period was higher in the LCM group compared with the placebo group (0.71 vs 0.65); the difference in LS Mean between the LCM and placebo groups was statistically significant (0.07, p=0.0011).
- The percentage of subjects who completed the Maintenance Period and achieved seizure-free status was 15.1% and 9.7% in the LCM and placebo groups, respectively.
- The overall Clinical Global Impression of Change response value at the end of the Maintenance Period, in the Improved category was higher for subjects in the LCM group compared with the placebo group (80.0% vs 64.7%).
- The overall Caregiver's Global Impression of Change response value at the end of the Maintenance Period, in the Improved category was higher for subjects in the LCM group compared with the placebo group (79.4% vs 67.1%).
- The overall Pediatric Quality of Life Inventory (PedsQL) scores from Baseline to Last Visit indicated similar and stable health related quality of life (HRQoL) for subjects in both the LCM and placebo groups.
- Health care resource uses were:
    - Concomitant antiepileptic drugs (AEDs): The most frequently used AEDs were valproate (48.4%), levetiracetam (41.4%), carbamazepine and lamotrigine (25.9% each), and topiramate (23.9%); their usage was similar between the LCM and placebo groups.
    - Concomitant medical procedures: Few subjects reported concomitant medical procedures with onset during the Baseline Period or the entire Treatment Period.
    - Health care provider consultations: More subjects reported consultations with health care providers with onset during the entire 16-week Treatment Period compared with onset during the 8-week Baseline Period; the subjects most commonly consulted with their general practitioner or the specialist physician.
    - Hospitalizations: Few subjects reported hospitalizations; the number of hospitalization was higher with onset during the entire 16-week Treatment Period compared with onset during the 8-week Baseline Period; most hospitalizations were related to adverse events (AEs) and lasted 1 to 5 days. Few subjects reported ER visits.

***Safety results***

**Extent of exposure**

In the overall LCM and placebo groups, and by subgroups (age and weight bands), the subjects had very similar median durations of treatment during the Titration, Maintenance, and entire Treatment Period: 43.0, 70.0, and 113.0 days, respectively, in both groups.

The average of the median daily dose for LCM during the Titration, Maintenance, and entire Treatment Period was 5.5mg/kg/day, 8.0mg/kg/day, and 7.7mg/kg/day, respectively. The majority of the

subjects in the LCM group (83.0%) tolerated the doses and did not require any back titration during the Titration Period.

**Summary of Safety**

The MAH concluded that safety observations in SP0969 were consistent with the known safety profile of LCM in adults. Observations in SP0969 were as expected for the pediatric population (e.g., high incidence of infections and associated symptoms). No new safety concerns were identified in this study.

- A total of 122 subjects (71.3%) in the LCM group and 112 subjects (65.1%) in the placebo group experienced treatment-emergent adverse event (TEAEs) during the study. Treatment emergent AEs were most frequently reported in the SOCs of Infections and infestations (37.4% in the LCM group and 32.6% in the placebo group), Nervous system disorders (34.5% in the LCM group and 28.5% in the placebo group), and Gastrointestinal disorders (22.8% in the LCM group and 18.0% in the placebo group).
    - In the ≥4 to <12 years age group, TEAEs were reported with a higher frequency in the LCM group compared with the placebo group, 73.6% vs 59.3%.
    - In the ≥12 to <17 years age group, TEAEs were reported with a similar frequency in the LCM and placebo groups, 68.8% and 71.6%, respectively.
- The most common TEAEs (reported by ≥3% of subjects) that occurred at a higher incidence in the LCM group compared with the placebo group were: somnolence (16.4% vs 6.4%), nasopharyngitis (11.7% vs 5.8%), pyrexia (9.9% vs 5.8%), and tremor (3.5% vs 0%).
    - the ≥4 to <12 years age group, the most common TEAEs that occurred at a higher incidence in the LCM group compared with the placebo group were: somnolence (18.7% vs 6.6%), nasopharyngitis (12.1% vs 4.4%), and pyrexia (12.1% vs 5.5%).
    - In the ≥12 to <17 years age group, the most common TEAEs that occurred at a higher incidence in the LCM group compared with the placebo group were: dizziness (17.5% vs 8.6%), somnolence (13.8% vs 6.2%), and nasopharyngitis (11.3% vs 7.4%).
- In the LCM group, higher incidence of TEAEs were reported during the Titration Period in the SOC of Nervous system disorders compared with the Maintenance Period (25.7% vs 10.6%); the incidence were similar in the SOCs of Infections and infestations (21.6% vs 19.3%) and Gastrointestinal disorders (15.2% vs 12.4%). The most common TEAE that occurred during the Titration Period was somnolence (11.7%) and during Maintenance Period were pharyngitis and vomiting (4.3% each).
    - In the ≥4 to <12 years age group, the most common TEAEs during the Titration Period and Maintenance Period were somnolence (12.1%) and pharyngitis (7.0%), respectively.
    - In the ≥12 to <17 years age group, the most common TEAEs during the Titration Period and Maintenance Period were dizziness (17.5%) and vomiting (4.0%), respectively.
- The most common TEAEs considered related to LCM by the investigator (reported by ≥3% of subjects) that occurred at a higher incidence in the LCM group compared with the placebo group were: somnolence (14.0% vs 5.8%) and dizziness (8.8% vs 5.8%).

- In the ≥4 to <12 years age group, the TEAEs considered related to LCM by the investigator that occurred at a higher incidence in the LCM group compared with the placebo group were: somnolence (15.4% vs 6.6%), diplopia (4.4% vs 0%), and fatigue (4.4% vs 1.1%).
- In the ≥12 to <17 years age group, the TEAEs considered related to LCM by the investigator that occurred at a higher incidence in the LCM group compared with the placebo group were: dizziness (13.8% vs 7.4%) and somnolence (12.5% vs 4.9%).

- No deaths were reported during the study.
- The incidence of serious adverse events (SAEs) was similar between the LCM and placebo groups, 6.4% and 7.6%, respectively. The most common SAE was convulsion: 1.2% and 2.3% in the LCM and placebo groups, respectively. One subject in the LCM group, experienced an SAE of vomiting that was considered related to study medication by the investigator.
- The incidence of TEAEs leading to discontinuation of study medication was lower in the LCM group compared with the placebo group, 4.1% vs 7.0%.
    - In the LCM group, of the TEAEs leading to discontinuation of study medication, 11 of the 13 events were considered related to study medication by the investigator (2 events each of diplopia and vertigo; and 1 event each of abnormal coordination, ALT increased, migraine, nystagmus, somnolence, vision blurred, and vomiting).
    - In the placebo group, of TEAEs leading to discontinuation of study medication, 12 of the 22 events were considered related to study medication by the investigator (2 events of rash, and 1 event each of aggression, balance disorder, convulsion, dizziness, emotional disorder, eosinophilia, nausea, prolonged corrected QT interval (QTc), vision blurred, and vomiting).
    - In the ≥4 to <12 years and ≥12 to <17 years age groups, there were similar incidence of TEAEs leading to discontinuation of study medication.
- Other significant AEs, as defined in the protocol, were reported by 6 subjects (3.5%) in the LCM group and no subjects in the placebo group. The AEs were suicidal ideation (4 events; 2 events for the same subject), syncope (2 events for the same subject), and bradycardia and sinus bradycardia (1 event each). The event of sinus bradycardia was considered related to LCM by the investigator; none of these AEs led to study discontinuation.
- Few TEAEs of relevance to the partial-onset seizure population were observed. A total of 7 TEAEs in the LCM group and 11 TEAEs in the placebo group were related to seizures.
    - Four subjects (2.3%) in the LCM group and 8 subjects (4.7%) in the placebo group experienced TEAEs of convulsion. Treatment-emergent AEs of complex partial seizures, partial seizures, and simple partial seizures were experienced by 1 subject each in the LCM group; TEAEs of complex partial seizures, partial seizures with secondary generalization, and seizure cluster were experienced by 1 subject each in the placebo group.
    - One subject (0.6%) in the LCM group and 2 subjects (1.2%) in the placebo group experienced TEAEs of weight increased. Two subjects (1.2%) in the LCM group and no subjects in the placebo group experienced TEAEs of weight decreased. No subjects in the LCM group and 1 subject (0.6%) in the placebo group experienced TEAEs of obesity.

    - No TEAEs related to memory impairment, amnesia, cognitive disorders, or psychotic disorders were observed.
- A total of 13 TEAEs in the LCM group and 14 TEAEs in the placebo group were related to pediatric growth, neurodevelopment, behavior, or endocrine function.
    - Four subjects (2.3%) in the LCM group and 1 subject (0.6%) in the placebo group experienced TEAEs of irritability.
    - Two subjects (1.2%) each in the LCM and placebo groups experienced TEAEs of aggression.
    - Two subjects (1.2%) in the LCM group experienced TEAEs of hypothyroidism.
    - Two subjects (1.2%) in the placebo group experienced TEAEs of emotional disorder.
- There were no pregnancies reported during the study.
- No consistent or clinically relevant mean changes from Baseline after onset of treatment were observed for hematology, clinical chemistry, or endocrinology parameters.
- No clinically relevant changes from Baseline were observed for vital signs or 12-lead ECGs.
- The incidence of TEAEs related to abnormal hematology, clinical chemistry, endocrinology, vital signs, or ECGs was low (≤3.0%).
- The incidence of shifts in neurological examination findings from normal at Baseline to abnormal, clinically significant at the Last Visit was low overall and similar for both the LCM and the placebo groups.
- Few subjects shifted from their Tanner stage at study entry to the end of treatment; no subject regressed in either the LCM or the placebo group.
- The Achenbach Child Behavior Checklist (CBCL)/1½-5 and CBCL/6-18 scores for behavioral and emotional functioning were stable overall and showed no worsening for subjects in the LCM group over the placebo group.
- There were no actual suicide attempts during the course of the study.
- The Behavior Rating Inventory of Executive Function Preschool Version (BRIEF-P) and Behavior Rating Inventory of Executive Function (BRIEF) scores for cognitive development and functioning were stable overall and showed no worsening for subjects in the LCM group over the placebo group.

### 2.3.3. Discussion on clinical aspects

The MAH submitted the results of the study SP0969 evaluating LCM efficacy as an adjunctive therapy in subjects ≥4 years to <17 years of age with epilepsy with uncontrolled partial-onset seizures. This study provides efficacy and safety data from 343 randomized patients to lacosamide (n=171) and placebo (n=172) treatments. Majority of patients completed the study (LCM n= 151, placebo n=151). The reported efficacy was in line with the efficacy known from studies in adult population. The safety profile observed in the SP0969 study was also consistent with the well-known safety profile of LCM in adults. No new safety concerns were identified in this study.

Although the drug is already licensed in children from 4 years of age, it is useful for the prescriber to know the basis and robustness of the data supporting the efficacy of Vimpat as an adjunctive therapy

in children. This is a positive large phase 3 double blind, randomized, placebo controlled study and currently in section 5.1 only the following is mentioned: “The efficacy of lacosamide in children aged 4 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures.”

Moreover, it is important that the SmPC provides the most accurate dosing recommendations to ensure effective and safe use in the paediatric population. It is noted that the paediatric posology mentioned in the SmPC partly differs from the one used in this trial, e.g. the SmPC proposes a maximum recommended dose in patients ≥ 20 kg to < 30 kg: up to 10 mg/kg/day, whereas in the clinical trial subjects below 30kg received a maximum dose of 12mg/kg. Therefore, it is important that the MAH discusses whether changes in the recommended posology should be made based on the efficacy/safety and PK results of this paediatric study.

Since the MAH is planning to propose the update of the SmPC at the later date through type II variation the aspects regarding dosing and updates of the 5.1 section mentioned above should be taken into account.

# 3. Rapporteur’s overall conclusion and recommendation

The results of SP0969 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The MAH proposed no changes to the approved EU Summary of Product Information for VIMPAT with this submission based on SP0969 results. The MAH proposed that at later date labeling changes based on SP0969 results will be submitted as part of a Type II variation. The MAH proposal is supported by the Rapporteur.

## ☒ Fulfilled:

No regulatory action required.