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/P46/039

Note

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

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1. Introduction

In the EU, lacosamide (LCM) is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide; previously referred to as harkoseride) is a functionalised amino acid. The precise mechanism of its antiepileptic effects in humans is not fully elucidated, but in vitro electrophysiological studies have indicated a selective enhancement of slow inactivation of voltage-gated sodium channels with ensuing stabilization of hyperexcitable neuronal membranes.

On 13 November 2020, the MAH submitted a Article 46 paediatric dossier for completed study SP0967, 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

SP0967 was a phase 3, multicenter, double-blind, randomized, placebo(PLACEBO)-controlled, parallel-group study to evaluate the efficacy and safety of LCM, given as oral solution, as adjunctive therapy in patients with epilepsy $\geq$1month to <4years of age with uncontrolled POS. SP0967 consisted of predetermined periods (baseline, titration, maintenance, transition, taper, and follow-up) with a maximum exposure to study medication of 55 days. The MAH has provided the final CSR based on the completed study.

The study SP0967 enrolled a total of 255 paediatric patients.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product was provided as oral solution measured and administered via a dosing syringe.

2.3. Clinical aspects

2.3.1. Introduction

For the current report, the MAH submitted a clinical overview addendum, summarizing the disposition and TEAEs for the 255 participants from SP0967, all within the age ranges from 1 month to <4 years old at the time of study entry, in order to fulfil the requirement of reporting paediatric data as outlined in Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The MAH also submitted a final clinical study report for study SP0967 providing data from the overall participant population.

2.3.2. Clinical study

SP0967: A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of lacosamide as adjunctive therapy in subjects with epilepsy ≥1 month to <4 years of age with partial-onset seizures.

Description

A phase 3 multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety and tolerability of LCM as adjunctive therapy administered concomitantly with 1 to 3 antiepileptic drugs in children ≥1 month to <4 years of age with partial-onset epilepsy (POS) and currently uncontrolled seizures.

Methods

Objective(s)

The primary objective was to evaluate the efficacy of LCM administered concomitantly with 1 to 3 antiepileptic drugs (AEDs) in patients ≥1 month to <4 years of age with epilepsy who currently have uncontrolled partial-onset seizures (POS). The secondary objective was to evaluate the safety and tolerability of LCM in patients ≥1 month to <4 years of age with epilepsy who currently have uncontrolled POS. An additional objective was to evaluate the pharmacokinetics (PK) of LCM in children ≥1 month to <4 years of age. There were no specific exploratory objectives.

Study design

The following study periods were identified (Figure 1):

- baseline period of 7 days (baseline Visit 1; video-EEG in inpatient setting; Visit 3 with randomization of eligible patients in 1:2 ratio to parallel treatment arms (LCM vs. placebo).

- titration period of 20 days to attain the target dose (LCM 8 mg/kg/day to 12 mg/kg/day, or matching placebo) of the maintenance period flexibly, based on tolerability. The aim was to achieve the minimum target dose for the final 3 days.

- maintenance period of 7 days with no adjustments to the dosing (blinded)

- transition period of 12 days for patients who completed the maintenance period and wanted to continue and enter the open-label extension study EP0034

Patients who were not eligible or chose not to enter the OLE study EP0034 or did not complete the baseline, titration, and maintenance periods entered the following:

- taper period (from 8 up to 16 days), during which the study medication was withdrawn according to a scheme, allowing addition of AEDs eller VNS adjustment.

- safety follow-up period of 30 days, including a 14-day clinic visit (±2 days) and a telephone contact at 30 days.

Figure 1: Study periods for subjects entering the EP0034 OLE study
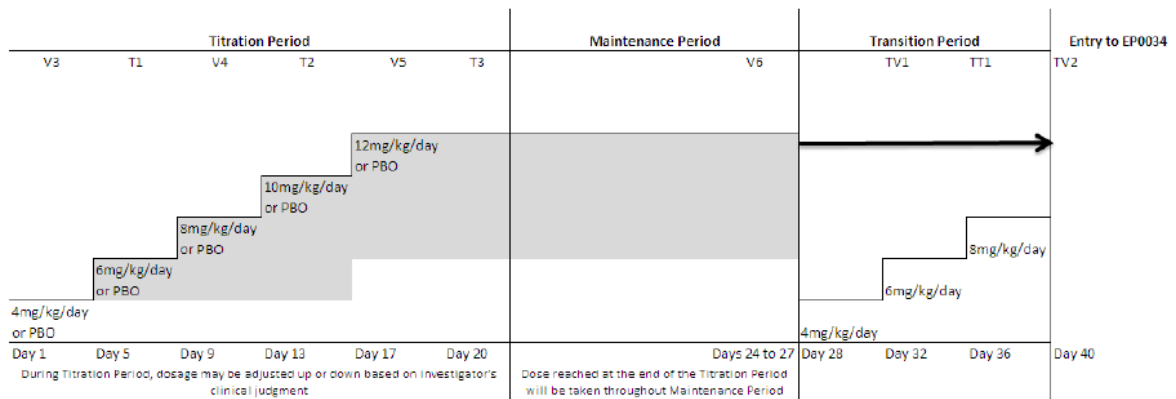
So, if patients were eligible and willing to enter the OLE study EP0034 they either continued on the LCM dose of the maintenance period during the transition period, or in case of placebo, they were transitioned from placebo to LCM according to a set dosing scheme, starting from 4 mg/kg/day and increasing up to 8 mg/kg/day. Those who ineligible or unwilling to enter the OLE study entered the taper period with stepwise reduction and discontinuance, ending with a taper visit (Figure 2).

Figure 2: Study periods for subjects entering the EP0034 OLE study
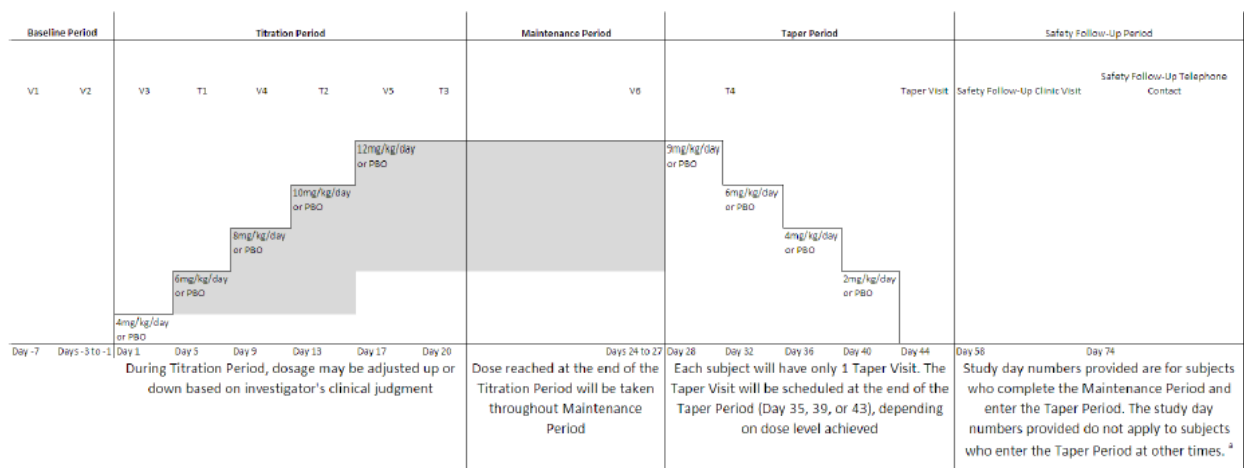
The maximum duration of study medication administration was thus 55 days, and the maximum study duration was 93 days (notwithstanding the set visit windows).

Study population /Sample size

The patient enrolled fulfilled the following main inclusion criteria:

- age ≥ 1 month (4 weeks after full term; corrected gestational age used for preterm children) to <4 years.

- weight ≥4 kg and <30 kg at visit 1.

- diagnosis of epilepsy with POS and ≥2 POS attacks with or without secondary generalization during each consecutive 7-day period during the 2 weeks prior to visit 1 and also during the end-of-baseline video-EEG (ictal patterns involving ≥2 contiguous electrodes).

- a stable dosing regimen of 1-3 AEDs (constant ≥2 weeks before visit 1, including a possible benzodiazepine). Vagus nerve stimulation was allowed if device was implanted at least 6 months and settings had been stable ≥2 weeks prior to visit 1, and settings were kept stable during baseline, maintenance and transition periods.

- given informed consent in writing from parent or legal representative/caregiver, who was deemed reliable and capable of adhering to protocol and medication intake.

The following main exclusion criteria were applied:

- previous randomization into this study, or participation in other investigational medical or device study currently or within two months prior to visit 1.

- nonepileptic events that could be confused with seizures; diagnosis of Lennox-Gastaut or Dravet syndrome, primary generalized epilepsy, epilepsia partialis continua, or non-partial-onset seizures; generalized convulsive status epilepticus within 2 months prior to screening

- acute or subacutely progressive central nervous system disease, or epilepsy secondary to progressing cerebral or neurodegenerative disease

- medical or psychiatric condition deemed jeopardizing or compromising as for participation

- previous LCM treatment terminated due to lack of effect or an AE.

- known hypersensitivity to any component of study drug; history of anaphylaxis secondary to medication or serious blood dyscrasias; renal insufficiency with creatinine clearance <30mL/min; >2x upper limit of normal (ULN) in any of the following: alanine amino transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (>1.5xULN if Gilbert's syndrome).

- hemodynamically significant congenital heart disease, clinically relevant ECG abnormality, or an arrhythmic heart condition requiring medical treatment; known cardiac channelopathy

- previous treatment with felbamate with toxicity issue(s)

The rules for withdrawal of a patient from the study were the following:

- generalized convulsive status epilepticus.

- any intolerable AE precluding further participation, according to investigator judgement.

- QTc interval ≥500ms in ECG, incident second- or third-degree atrioventricular block.

- need for medication not permitted by the protocol, or use of benzodiazepines other than a stable daily dosage within 24 hours prior to video-EEG for any reason.

- unwillingness or inability to continue, clinically relevant change in medical or psychiatric condition or noncompliance of legal representative/caregiver as deemed by investigator.

- request of withdrawal by regulatory agency or sponsor, or investigator's view that withdrawal would be in the patient´s best interest.

The following rules were followed concerning a potential drug-induced liver injury:

- immediate and permanent discontinuation if either ALT/AST ≥5xULN or ALT/AST ≥3xULN and coexisting total bilirubin ≥2xULN

- immediate discontinuation if ALT/AST ≥3xULN with temporally associated symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness) or hypersensitivity (fever, rash, eosinophilia >5%).

- continuation at the discretion of the investigator when ALT/AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, without associated symptoms of hepatitis or hypersensitivity

The planned number of patients to be enrolled was 244 (122 per treatment arm) after determination of sample size, based on an estimated effect size of 0.402, power of 80%, two-sided testing at 5% level of significance, anticipated discrepancy in video-EEG counts, and a potential dropout rate of 14%. The target was held after a preplanned, blinded half-way re-estimation procedure. Overall, 255 patients were randomized: 128 to LCM and 127 to placebo, and all took at least 1 dose of study medication.

Assessor's comment

The study sp0967 was designed as a paediatric study of efficacy and safety of lacosamide as an adjunct for patients with POS, the age range being from one month to 4 years. The number of enrolled patients fulfilling the set inclusion and exclusion criteria carried through the study periods meets the preplanned recruitment as specified by the power analysis.

Notably, the licensing of LCM does not cover children less than 4 years of age. However, considering the complete bioavailability of LCM and the prior PK modelling and simulations, the dose regimen in the age group ≥1 month to 4 years may be considered acceptable.

Treatments

The double-blind randomization into LCM and placebo groups in a 1:1 ratio was done at visit 3 after completion of end-of-baseline video-EEG and ascertainment of met selection criteria. The randomization was stratified by four age categories (≥1 month to <6 months; ≥6 months to <1 year; ≥1 year to <2 years; ≥2 years to <4 years).

Study medication was provided as LCM oral solution (10mg/mL) and matching placebo oral solution similarly packed, measured and administered via a dosing syringe twice a day (with approximately 12-hour intervals). Administration by feeding tube was permitted, if necessary. In cases of incomplete dosing, no readministration was done. The first dose was administered at the clinic on visit 3.

The titration period was started with a dose of LCM 4 mg/kg/day or matching placebo with the following recommended dosing schedule (Table 1).

Table 1: Study periods for subjects entering the EP0034 OLE study

Target LCM (or matching PBO) doses for the Titration Period				
Days 1 to Day 4	**Day 5 to Day 8**	**Day 9 to Day 12**	**Day 13 to Day 16**	**Day 17 to Day 20**
4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/day	12mg/kg/day

LCM=lacosamide; PBO=placebo

Flexibility of dosing was allowed according to tolerability, including back-titration to the minimum of 4mg/kg/day, but at least the minimum target dose of 8 mg/kg/day was to be reached for the final 3 days of the titration period, and no change of dose was allowed after day 20. Patients who did not tolerate the dosage or were not deemed to reach the minimum target were withdrawn and entered the blinded taper period. Those who achieved at least the minimum target dose as planned entered the 7-day blinded maintenance period on the achieved dose without adjustments.

Patients who completed the maintenance period were offered the opportunity to enroll in the open-label extension study EP0034. Eligible patient who chose to continue in EP0034 entered a blinded 12-day transition period, under which patients receiving LCM continued with the maintenance period dose and those receiving placebo were transitioned to LCM 8mg/kg/day, according to the following schedule (Table 2).

Table 2: LCM dosing for the transition period

	LCM doses for the Transition Period		
Maintenance Period	**Day 28 to Day 31**	**Day 32 to Day 35**	**Day 36 to Day 39**
PBO	4mg/kg/day	6mg/kg/day	8mg/kg/day

LCM=lacosamide; PBO=placebo

Patients who did not choose to enter the study EP0034 or did not complete the maintenance period underwent a study medication withdrawal under a blinded taper period of 8 to 16 days. For those who completed the maintenance period, the dosing during the taper period was determined by the achieved maintenance dose, according to the following schedule (Table 3).

Table 3: Study medication dosing for the taper period

LCM (or matching PBO) dose achieved	LCM (or matching PBO) doses for the Taper Period			
	Day 28 to Day 31	**Day 32 to Day 35**	**Day 36 to Day 39**	**Day 40 to Day 43**
11 or 12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9 or 10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7 or 8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day
5 or 6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day	NA
4mg/kg/day	2mg/kg/day	2mg/kg/day	NA	NA

LCM=lacosamide; PBO=placebo

For patients who did not enter EP0034 there was a 30-day safety follow-up period, starting on the day after the last dose of study medication and continuing until the date of last telephone contact and/or 30 days after the last dose of study medication, whichever was later.

Outcomes/endpoints

The efficacy variables were based on video-EEGs (up to 72 hours of continuous recording, with attempt to obtain at least 48 hours of interpretable recording). POS frequency was based on electrographic seizures for infants ≥1 months to ≤6 months, whereas for infants >6 months to <4 years the count was based on electrographic seizures with an accompanying clinical correlate. Electrographic seizures were defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures were initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds. The video-EEG recordings were evaluated locally by the investigator, subinvestigator, or qualified designated reader. The average daily frequency (ADF) of electrographic POS was calculated as (number of POS as recorded on the video-EEG divided by the number of interpretable hours recorded) multiplied by 24.

The primary efficacy variable (US):

- the change in ADF of electrographic POS as measured on the end-of-maintenance period video-EEG compared to the end-of-baseline period video-EEG (on condition that ≤10% of study patients discontinued early; summarized as a secondary efficacy variable if >10% discontinued early).

The primary efficacy variable (EU):

- the proportion of responders, where a responder was a patient who experienced a ≥50% reduction in their ADF of electrographic POS recorded on the end-of-maintenance period video-EEG compared to the end-of-baseline period video-EEG (was to be considered the primary efficacy variable also in the US if >10% of patients discontinued early).

The secondary efficacy variables:

- percent and absolute change in ADF of electrographic POS from the end-of-baseline period video-EEG to the end-of-maintenance period video-EEG

- proportion of patients who achieved "seizure-free" status (yes/no) from all seizure types, and from POS types only for patients who completed at least 48 hours of interpretable video-EEG recording during the end-of-maintenance period video-EEG

- proportion of patients who experienced a ≥25% to <50%, 50% to 75%, or >75% reduction in ADF of electrographic POS from the end-of-baseline period video-EEG to the end-of-maintenance period video-EEG

- proportion of patients who experienced no change in ADF of electrographic POS (between <25% reduction and <25% increase) from the end-of-baseline period video-EEG to the end-of-maintenance period video-EEG

- proportion of patients who experienced an increase in ADF of electrographic POS of ≥25% from the end-of-baseline period video-EEG to the end-of-maintenance period video-EEG

Other efficacy variables:

- Clinical Global Impression of Change (GIC) at the end of the maintenance period

- caregiver's GIC at the end of the maintenance period

- change from baseline in Pediatric Quality of Life Inventory (PedsQL) health summary score at the end of the maintenance period

- healthcare resource use: concomitant medications, medical procedures, healthcare provider consultations not related to the study, and hospitalizations not related to the study

Pharmacokinetic and pharmacodynamic variables

Blood samples were collected according to pre-set schedule, recording the time of collection and the most recent time of study medication dosing. The plasma concentrations of LCM were applied to:

- develop a population PK model of LCM

- investigate the correlation between plasma concentrations and efficacy or safety

The primary safety variables

- adverse events reported spontaneously by the patient's parent(s) and/or legal representative(s)/caregiver(s) or observed by the investigator

- patient withdrawals due to AEs

Other safety variables

- changes in hematological or clinical chemistry parameters

- change in 12-lead ECGs

- changes in vital sign measurements (such as blood pressure and pulse rate)

- physical and neurological examination findings

- changes in body weight, height, and calculated body mass index

The protocol was amended thrice. The first amendment (dated 14 Jan 2015) primarily implemented the contingent primary efficacy variable for the US, include sensitivity analyses for the primary endpoint, clarified the enrolment of subjects <2 years of age, and provided additional detail regarding the sample size re-estimation at the request of FDA. The protocol amendment 2 (09 Aug 2016) clarified the video-EEG recording durations the video-EEG and implemented other minor changes to boost recruitment. The primary purpose of the protocol amendment 3 (05 Aug 2018) was to address the high variability in video-EEG seizure counts between the site and central reader by removing the central reader as proposed by the FDA, as the variability could not be overcome by reasonable corrective actions, e.g. introduction of a second central reader. Before that, consultation with PDCO resulted in an agreement to remove the study SP0967 from a Paediatric Investigation Plan (EMEA 000402 PIP02 11 M05, decision P/0001/2018 on 08 Jan 2018).

Statistical methods

All efficacy, safety and demographic variables were summarized by descriptive statistics. Statistical tests of efficacy variables were presented as 2-sided p-values at the 0.05 level of significance. Baseline values for efficacy and safety variables were generally determined from the last non-missing scheduled or unscheduled assessment prior to the first dose of study medication unless otherwise noted.

The analysis sets were the following:

- the safety set (SS), the primary set for safety variables, included all randomized patients who received at least 1 dose of study medication.

- The full analysis set (FAS), the primary set for efficacy variables, included all patients in the SS.

- The full analysis set source-data verified (FAS-SDV) included all FAS patients who had both their end-of-baseline and end-of-maintenance period video-EEG eCRF pages source data verified at on-site monitoring.

- The per-protocol set (PPS), the secondary analysis set for the efficacy data, included all FAS patients without important protocol deviations related to efficacy

- The pharmacokinetic per-protocol set (PK-PPS) consisted of all patients who provided at least one measurable post-dose plasma sample with recorded sampling time on at least one visit with documented study medication intake times.

Center and age group pooling strategies were applied, as mentioned in the SAP, as determined at the final data evaluation meeting prior to unblinding of the study data. Covariate adjustments were made in the primary efficacy analyses as well as planned sensitivity analyses for log-transformed baseline seizure ADF, age category and center in the ANCOVA models.

The analyses of the primary and secondary efficacy variables were based on the ADF of electrographic POS. All efficacy variables were summarized for the FAS by treatment group. Additional populations were used for sensitivity analyses (including several analyses to address the impact of COVID-19 pandemic on the efficacy results).

For the US primary efficacy variable, seizure ADF was analyzed using ANCOVA with terms for treatment, age stratification categories, and center (pooled appropriately), on log-transformed seizure ADF, and log-transformed baseline ADF as a covariate. The seizure ADF between treatment groups was compared using least squares means (LSMs). The percent reduction over PLACEBO was estimated as $100 \times (1 - \exp[\text{LSM}_{LCM} - \text{LSM}_{placebo}])$. The treatment estimates (LSMs and 95% confidence intervals [CIs]) were back-transformed using the exponential function and subtracting 1. The analysis of this efficacy variable

consisted of all FAS patients with at least 48 hours of interpretable recordings during both the end-of-baseline video-EEG and the end-of-maintenance period video-EEG.

Sensitivity analyses for the US primary efficacy variable were conducted to control for the effects of modified data cleaning and reconciliation processes, protocol deviations, early discontinuations, and operational bias: repeated primary analysis for the PPS, FAS-SDV, for the first 244 patients enrolled for the FAS/FAS-SDV, for the FAS with exclusion of early discontinued patients, and for all patients with at least 24 hours of interpretable recordings at end-of-baseline or end-of-maintenance period video-EEGs.

For the EU primary efficacy variable, patients with a 50% or more reduction in seizure ADF were categorized as responders. This classification required at least 48 hours of interpretable recordings during both the end-of-baseline video-EEG and the end-of-maintenance period video-EEG. Patients with 0 seizures at baseline were considered non-responders. The proportion of responders between LCM and placebo was analysed using logistic regression with treatment, age categories, and center as factors. Odds ratios were presented from this model along with the corresponding 95% CIs and p values. The number and percentage of patients with a 50% or more reduction in seizure ADF were presented by treatment and age groups.

Sensitivity analyses for the EU primary efficacy variable were conducted to control for the effects of modified data cleaning and reconciliation processes, protocol deviations, early discontinuations, and operational bias: repeated primary analysis for the PPS, FAS-SDV, for the first 244 patients enrolled for the FAS/FAS-SDV, for the FAS with patients who discontinued before the end-of-maintenance period video-EEG for reasons related to lack of efficacy designated as non-responders, and for all patients with at least 24 hours of interpretable recordings at end-of-baseline or end-of-maintenance period video-EEGs including those who discontinued for reasons related to lack of efficacy, designated as non-responders.

All safety variables were summarized for the SS. The overall duration of study medication exposure during the titration, maintenance and treatment periods were calculated and summarized. Adverse events were tabulated by MedDRA system organ class (SOC) and preferred term (PT), and the number and percentage of patients experiencing each event at least once were summarized, and summaries repeated by treatment and age groups. Haematology, blood chemistry, urinalysis, endocrinology parameters, vital signs, and 12-lead ECGs were assessed throughout the study locally and at a central laboratory. Treatment-emergent markedly abnormal (TEMA) values were defined as occurring during the defined treatment period.

Plasma concentrations of LCM only were summarized using descriptive statistics by LCM maintenance dose level, by visit, and by age group.

No imputation of missing values for analysis parameters was planned, and only reported data were used in each analysis time interval. AEs with missing intensity were assumed to be severe, and events with missing relationship to treatment to be related. Completely missing dates were not replaced but the corresponding variables were set to missing. Imputation of partially reported dates for the last administration of the study drug followed an algorithm specified in the SAP. When necessary for calculation of derived variables, partial dates were completed with the earliest possible calendar date, apart from dates pertaining to start and stop of AEs, concomitant medication, or study drug.

Data monitoring and interim analyses included a blinded sample re-estimation when 50% of patients had been randomized, interim reviews of safety data by an independent data monitoring committee (IDMC), and the SAE real-time monitoring by the study monitor and the MAH. No interim analyses for efficacy data were planned.

The SAP was amended twice. The first amendment (05 Feb 2019) was to reflect the primary change to the source of seizure data from the central reader's interpretation of EEG to the local investigator's EEG analysis (reflecting protocol amendment 3). The SAP amendment 2 (07 May 2020) was made to include additional analyses to address the impact of COVID-19 pandemic.

Results

Recruitment/ Number analysed

The total number of screened patients was 349 at 89 sites. There were finally 94 screen failures. A total of 255 patients were randomized, 128 to LCM and 127 to placebo. Of these, 242 patients (94.9%) completed the study. There were fewer discontinued patients in the placebo group (3 [2.4%]) than in the LCM group (10 [7.8%]), the most common reason being withdrawn consent (3 in each group). Overall, 249 patients (97.6%) completed the titration period and entered the maintenance period; 245 (96.1%) completed the maintenance period; 244 entered the transition period, and 241 (94.5%) entered the open-label extension study EP0034. The number of patients entering and completing each of the periods was generally similar between the treatment as well as age groups.

The important protocol deviations were considered based on predefined criteria, and the majority of decisions regarding them were based on a review of blinded data prior to database lock; four deviations were adjudicated after database lock but before sponsor unblinding. On the whole, the decision did not affect patient inclusion in the analysis sets. The important protocol deviations and the population sets analysed are given in the tables below.

Table 4: Important protocol deviations (SS)

Category	PBO N=127 n (%)	LCM N=128 n (%)	All study participants N=255 n (%)
No important protocol deviations	80 (63.0)	77 (60.2)	157 (61.6)
At least 1 important deviation	47 (37.0)	51 (39.8)	98 (38.4)
Inclusion criteria	2 (1.6)	4 (3.1)	6 (2.4)
Exclusion criteria	3 (2.4)	5 (3.9)	8 (3.1)
Withdrawal criteria	3 (2.4)	5 (3.9)	8 (3.1)
Prohibited concomitant medication	1 (0.8)	1 (0.8)	2 (0.8)
LCM dosing regimen	10 (7.9)	15 (11.7)	25 (9.8)
Procedural noncompliance	33 (26.0)	40 (31.3)	73 (28.6)
COVID-19-related deviations [a]	1 (0.8)	1 (0.8)	2 (0.8)

Table 5: Disposition of analysis sets (SS)

Analysis set	PBO N=127 n (%)	LCM N=128 n (%)	All study participants N=255 n (%)
SS	127 (100)	128 (100)	255 (100)
FAS	127 (100)	128 (100)	255 (100)
FAS-SDV	123 (96.9)	119 (93.0)	242 (94.9)
PPS	112 (88.2)	107 (83.6)	219 (85.9)
PK-PPS	125 (98.4)	122 (95.3)	247 (96.9)

FAS=Full Analysis Set; FAS-SDV=Full Analysis Set-Source Data Verified; LCM=lacosamide; PBO=placebo;
   PK-PPS=Pharmacokinetic Per Protocol Set; PPS=Per Protocol Set; SS=Safety Set
Note: Percentages were based on the number of study participants in the SS.

Assessor's comment

The analysis sets may be considered sufficiently balanced. The reported rate of protocol violations is relatively high. The class of procedural noncompliance is predominant (mainly, missed assessments, samples, or erroneous sampling). Considering the totality of the trial, its conduct and the clinical conclusions, the violation rate is not deemed clinically significant.

Baseline data

A summary of patient demographics is given in the tables below.

Table 6: Patient baseline characteristic and demographics

Variable Statistic	PBO N=127	LCM N=128	All study participants N=255
Age (months)			
n	127	128	255
Mean (SD)	26.1 (13.4)	25.2 (13.6)	25.6 (13.5)
Median (min, max)	26.0 (2, 47)	24.5 (1, 47)	25.0 (1, 47)
Age (years)			
n	127	128	255
Mean (SD)	2.207 (1.114)	2.134 (1.135)	2.170 (1.123)
Median (min, max)	2.212 (0.25, 3.99)	2.086 (0.11, 3.96)	2.155 (0.11, 3.99)
Age group, n (%)			
≥1 to <6 months	8 (6.3)	8 (6.3)	16 (6.3)
≥6 months to <1 year	13 (10.2)	18 (14.1)	31 (12.2)
≥1 to <2 years	38 (29.9)	36 (28.1)	74 (29.0)
≥2 to <4 years	68 (53.5)	66 (51.6)	134 (52.5)
Randomization age strata (per IXRS), n (%)			
≥1 to <6 months	6 (4.7)	8 (6.3)	14 (5.5)
≥6 months to <1 year	16 (12.6)	18 (14.1)	34 (13.3)
≥1 to <2 years	37 (29.1)	36 (28.1)	73 (28.6)
≥2 to <4 years	68 (53.5)	66 (51.6)	134 (52.5)
Age, n (%) [a]			
28 days to <24 months	59 (46.5)	62 (48.4)	121 (47.5)
≥24 months to <12 years	68 (53.5)	66 (51.6)	134 (52.5)
Gender, n (%)			
Male	75 (59.1)	71 (55.5)	146 (57.3)
Female	52 (40.9)	57 (44.5)	109 (42.7)

Variable Statistic	PBO N=127	LCM N=128	All study participants N=255
Racial group, n (%)			
American Indian/Alaskan Native	5 (3.9)	13 (10.2)	18 (7.1)
Asian	15 (11.8)	14 (10.9)	29 (11.4)
Black	0	2 (1.6)	2 (0.8)
Native Hawaiian or Other Pacific Islander	0	0	0
White	101 (79.5)	94 (73.4)	195 (76.5)
Other/Mixed	6 (4.7)	5 (3.9)	11 (4.3)
Ethnicity, n (%)			
Hispanic or Latino	20 (15.7)	26 (20.3)	46 (18.0)
Not Hispanic or Latino	107 (84.3)	102 (79.7)	209 (82.0)
Region, n (%)			
North America	5 (3.9)	7 (5.5)	12 (4.7)
Latin America	14 (11.0)	22 (17.2)	36 (14.1)
Western Europe	5 (3.9)	7 (5.5)	12 (4.7)
Eastern Europe	86 (67.7)	76 (59.4)	162 (63.5)
Asia/Pacific/Other	17 (13.4)	16 (12.5)	33 (12.9)
Country, n (%)			
Argentina	1 (0.8)	0	1 (0.4)
Brazil	2 (1.6)	4 (3.1)	6 (2.4)
China	7 (5.5)	7 (5.5)	14 (5.5)
Croatia	3 (2.4)	2 (1.6)	5 (2.0)
Czech Republic	2 (1.6)	1 (0.8)	3 (1.2)
France	1 (0.8)	3 (2.3)	4 (1.6)
Georgia	9 (7.1)	12 (9.4)	21 (8.2)
Greece	1 (0.8)	1 (0.8)	2 (0.8)
Hungary	15 (11.8)	11 (8.6)	26 (10.2)
Israel	2 (1.6)	2 (1.6)	4 (1.6)
Italy	4 (3.1)	3 (2.3)	7 (2.7)
Lithuania	1 (0.8)	1 (0.8)	2 (0.8)
Mexico	11 (8.7)	18 (14.1)	29 (11.4)
Philippines	1 (0.8)	1 (0.8)	2 (0.8)
Poland	1 (0.8)	0	1 (0.4)

Variable Statistic	PBO N=127	LCM N=128	All study participants N=255
Portugal	0	1 (0.8)	1 (0.4)
Republic of Korea	5 (3.9)	3 (2.3)	8 (3.1)
Republic of Moldova	0	2 (1.6)	2 (0.8)
Romania	7 (5.5)	3 (2.3)	10 (3.9)
Russia	10 (7.9)	8 (6.3)	18 (7.1)
Serbia	5 (3.9)	3 (2.3)	8 (3.1)
Taiwan	1 (0.8)	2 (1.6)	3 (1.2)
Thailand	1 (0.8)	1 (0.8)	2 (0.8)
Ukraine	32 (25.2)	32 (25.0)	64 (25.1)
United States	5 (3.9)	7 (5.5)	12 (4.7)
Center Pool, n (%)			
Center Pool 1	10 (7.9)	14 (10.9)	24 (9.4)
Center Pool 2	20 (15.7)	13 (10.2)	33 (12.9)
Center Pool 3	14 (11.0)	22 (17.2)	36 (14.1)
Center Pool 4	15 (11.8)	14 (10.9)	29 (11.4)
Center Pool 5	32 (25.2)	32 (25.0)	64 (25.1)
Center Pool 6	15 (11.8)	11 (8.6)	26 (10.2)
Center Pool 7	21 (16.5)	22 (17.2)	43 (16.9)

Variable Statistic	PBO N=127	LCM N=128	All study participants N=255
Weight (kg)			
n	127	128	255
Mean (SD)	11.67 (3.42)	11.34 (3.79)	11.50 (3.61)
Median (min, max)	12.00 (4.1, 21.6)	11.00 (4.0, 22.8)	11.20 (4.0, 22.8)
Height (cm)			
n	127	128	255
Mean (SD)	85.80 (12.30)	84.83 (13.76)	85.31 (13.03)
Median (min, max)	86.00 (54.0, 108.0)	85.50 (49.0, 125.0)	86.00 (49.0, 125.0)
BMI (kg/m^2)			
n	127	128	255
Mean (SD)	15.60 (2.12)	15.42 (2.26)	15.51 (2.19)
Median (min, max)	15.54 (10.7, 22.8)	15.43 (8.4, 23.1)	15.54 (8.4, 23.1)
Head circumference (cm)			
n	127	128	255
Mean (SD)	44.83 (4.20)	44.67 (4.65)	44.75 (4.42)
Median (min, max)	45.00 (25.0, 56.0)	45.00 (30.0, 54.2)	45.00 (25.0, 56.0)
VNS, n (%)			
Active VNS	0	0	0
No VNS or VNS not active	127 (100)	128 (100)	255 (100)
No VNS	127 (100)	128 (100)	255 (100)
VNS not active	0	0	0

BMI=body mass index; EudraCT=European Clinical Trials database; IXRS=interactive voice/web response system; LCM=lacosamide; max=maximum; min=minimum; PBO=placebo; SD=standard deviation; SS=Safety Set; VNS=vagus nerve stimulation

Note: Center Pool: 1=France, Italy, Portugal, US; 2=Croatia, Czech Republic, Greece, Lithuania, Poland, Republic of Moldova, Romania, Serbia; 3=Argentina, Brazil, Mexico; 4=China, Philippines, Republic of Korea/South Korea, Taiwan, Thailand; 5=Ukraine; 6=Hungary; 7=Georgia, Israel, Russia.

Note: Weight, height, and BMI at Visit 1 were summarized.

Note: Percentages were based on the number of study participants in the SS.

[a] EudraCT age categories

The previous and ongoing medical history conditions, other than epilepsy, were prevalent (212 patients [83.1%]) and dominated by nervous system disorders (129 patients [50.6%]) and congenital, familial and genetic disorders (116 patients [45.5%]) representing a severely affected patient population in

general. Overall, there was a higher incidence in the LCM group vs. placebo (87.5% vs. 78.7%), especially higher reported incidence in the SOC of Infections and infestations (25.0% in LCM vs. 15.7% in placebo) but not driven by any particular subcategory.

All patients had a diagnosis of epilepsy with POS. 103 patients (40.4%) experienced simple partial and 176 patients (69.0%) complex partial seizures, and 127 (49.8%) partial seizures evolving into secondarily generalized seizures. Some differences between the treatment groups was observed in the frequency: in simple partial 43.8% vs 37.0%, in complex partial 64.1% vs 74.0%, and in secondarily generalized 49.2% vs 50.4%. A total of 20 patients (7.8%) had also generalized seizures and 14 patients (5.5%) unclassified epileptic seizures with a similar incidence in the LCM and placebo groups.

The number of previous AEDs and those taken on the day of first dose of study medication are given in the tables below.

Table 7: Number of previous AEDs (SS)

Variable	PBO N=127 n (%)	LCM N=128 n (%)	All study participants N=255 n (%)
Number of previous AEDs			
0	74 (58.3)	81 (63.3)	155 (60.8)
1 to 3	45 (35.4)	44 (34.4)	89 (34.9)
4 to 6	8 (6.3)	3 (2.3)	11 (4.3)
≥7	0	0	0

AED=antiepileptic drug; LCM=lacosamide; PBO=placebo; SS=Safety Set
Note: Previous AEDs were defined as AEDs taken and stopped >14 days prior to Visit 1 (ie, prior to entry into the Baseline Period), and not taken during the course of the study.
Note: Percentages were based on the number of study participants in the SS.
Note: Antiepileptic drugs taken as rescue medication were excluded from this summary.

Table 8: Number of the AEDs taken on the day of first dose of study medication (SS)

Variable	PBO N=127 n (%)	LCM N=128 n (%)	All study participants N=255 n (%)
Number of AEDs			
1	36 (28.3)	38 (29.7)	74 (29.0)
2	55 (43.3)	54 (42.2)	109 (42.7)
3	34 (26.8)	34 (26.6)	68 (26.7)
≥4	1 (0.8)	1 (0.8)	2 (0.8)
Missing	1 (0.8)	1 (0.8)	2 (0.8)

AED=antiepileptic drug; LCM=lacosamide; PBO=placebo; SS=Safety Set
Note: Percentages were based on the number of study participants in the SS.
Note: Antiepileptic drugs taken as rescue medication were excluded from this summary.

Table 9: Concomitant AEDs used by the patient in treatment groups and overall (SS)

Medication name	PBO N=127 n (%)	LCM N=128 n (%)	All study participants N=255 n (%)
Any AED	126 (99.2)	127 (99.2)	253 (99.2)
Valproate	71 (55.9)	57 (44.5)	128 (50.2)
Levetiracetam	54 (42.5)	60 (46.9)	114 (44.7)
Topiramate	31 (24.4)	24 (18.8)	55 (21.6)
Carbamazepine	13 (10.2)	28 (21.9)	41 (16.1)
Oxcarbazepine	13 (10.2)	15 (11.7)	28 (11.0)
Clobazam	15 (11.8)	12 (9.4)	27 (10.6)
Vigabatrin	8 (6.3)	14 (10.9)	22 (8.6)
Phenobarbital	10 (7.9)	11 (8.6)	21 (8.2)
Clonazepam	10 (7.9)	8 (6.3)	18 (7.1)
Lamotrigine	8 (6.3)	9 (7.0)	17 (6.7)
Phenytoin	5 (3.9)	1 (0.8)	6 (2.4)

AED=antiepileptic drug; LCM=lacosamide; PBO=placebo; SS=Safety Set
Note: Concomitant AEDs included AEDs taken concomitantly for at least 1 day in common with study medication.
Note: Percentages were based on the number of study participants in the SS.
Note: Phenobarbital use included: phenobarbital, phenobarbital sodium, methylphenobarbital, and primidone.
 Phenytoin use included: phenytoin, phenytoin sodium, ethotoin, fosphenytoin, fosphenytoin sodium, and
 zentronal. Valproate use included: valproic acid, valproate semisodium, valproate sodium, ergenyl chrono, and
 valpromide.
Note: Antiepileptic drugs taken as rescue medication were excluded.

The mean study medication compliance for the SS during the treatment period for LCM and placebo was 101.27% (range: 55.1% to 267.4%) and 101.58 (range: 68.0% to 131.5%), respectively. One patient in the LCM group and one in the placebo group had treatment compliance <75%; 4 patients in the LCM group and 2 patients in the placebo group had treatment compliance >125%. Notably, the single patient in the LCM group with study medication compliance reported as 267.4% discontinued the study early and was tapered off study medication without entering the taper period. The majority of compliance was in the range of 75% to 125% for both LCM (123 patients [96.1%]) and placebo (124 patients [97.6%]).

> **Assessor's comment**
>
> The treatment groups may be considered sufficiently balanced as for their epilepsy and the seizure types. The demographic variables as well as the general morbidity are as expected in the study population over the age range in this study design. The concomitant medications are as expected, provided the study design and entry criteria.
>
> In light of the polypharmacy of the target group, the differences between the treatment groups are potentially challenging. In this context, there are two main differences: the relative predominance of CBZ in the LCM group, and that of VPA in the placebo group. In original dedicated studies, no PK interaction has been reported between LCM and CBZ/VPA (Patsalos, 2013); however, CBZ is known to increase LCM clearance (Nickel et al., 2008), and it is possible that also LCM may lower VPA levels (Tountopolou et al, 2017). All in all, considering their pharmacodynamic action, which is expected to be additive/synergistic, these differences are not expected to have a significant bearing on the study results.
>
> The youngest age group (≥1 month to <6 months) is underrepresented, which undermines the validity of the study in this age cohort, in principle precluding making of any firm conclusions concerning this age group.

Efficacy results

The primary efficacy variable for the US was the change in ADF of electrographic POS as measured on the end-of-maintenance period video-EEG compared to the end-of-baseline video recording, since the early discontinuance rate was 5.1% (7.8% in LCM vs. 2.4% in placebo groups), i.e. remained ≤10%. The summary and analysis are given below (Table 10).

Table 10: Primary efficacy variable (US) - summary and analysis of ADF of electrographic POS by study period (FAS)

Time period Statistic	PBO N=127	LCM N=128
EOB Period		
n	126	128
Mean (SD)	12.4078 (28.8091)	9.6594 (18.0772)
Median (min, max)	3.9877 (0, 246.9247)	3.3977 (0.6589, 153.8237)
EOM Period		
n	123	121
Mean (SD)	7.8274 (15.3810)	7.1472 (13.3917)
Median (min, max)	2.8430 (0, 97.5773)	2.0754 (0, 98.7910)

Statistic	PBO N=127	LCM N=128
n [a]	120	116
Percent reduction vs PBO (95% CI)	-	3.19 (-13.59, 17.50)
p-value	-	0.6895

The sensitivity analyses performed with the sets PPS, FAS-SDV, first enrolled 244 patients (FAS), and first enrolled 244 patients (FAS-SDV) supported the conclusions of the primary analysis. Also multiple imputations for missing data and including all patients with at least 24 hours of interpretable EEG recording supported the primary analysis. When broken down by age groups, a similar decrease in each treatment group was observed in the median ADF of electrographic POS between the timepoints of recording without significant or clinically meaningful differences.

The primary efficacy variable for EU was the proportion of responders, defined as a patient experiencing a reduction of ≥50% in their ADF of electrographic POS as measured on the end-of-maintenance period video-EEG compared to the end-of-baseline video recording. The summary and analysis are presented below (Table 11).

Table 11: Primary efficacy variable (EU) - summary and analysis of responders by study period (FAS)

Statistic	PBO N=127	LCM N=128
n [a]	120	116
Responder, n (%)	45 (37.5)	48 (41.4)
Nonresponder, n (%)	75 (62.5)	68 (58.6)
Odds ratio vs PBO (95% CI)	-	1.163 (0.680, 1.991)
p-value	-	0.5809

One patient in the placebo group had no POS recorded on the end-of-baseline video-EEG and was thus considered a non-responder; no non-responders due to lack of efficacy and subsequent discontinuance were observed.

The sensitivity analyses performed with the sets PPS, FAS-SDV, first enrolled 244 patients (FAS), and first enrolled 244 patients (FAS-SDV) supported the conclusions of the primary analysis. Also inclusion of early discontinuations in the analysis as well as performing multiple imputations for missing data and including all patients with at least 24 hours of interpretable EEG recording supported the primary analysis. When broken down by age groups, a similar decrease in each treatment group was observed in the median ADF of electrographic POS between the timepoints of recording without significant or clinically meaningful differences. In then youngest age cohort, however, the proportion of responders was numerically higher (4 [57.1%] vs. 2 [25%]), but number of patients was obviously very limited.

Assessor's comment

The efficacy results are neutral for the primary variable analysis for both US and EU approaches, and the results are consistently supported by all sensitivity analyses applied.

In secondary efficacy variables, the median percent change from baseline ADF of electrographic POS at the end-of-maintenance-period video-EEG was -40.11% in the LCM group and -32.49 in the placebo group, with the median absolute changes of -1.34 in the LCM group and -1.03 in the placebo group (FAS). The differences were not significant or clinically meaningful. Results with FAS-SDV set were consistent.

The patients who achieved a seizure-free status from all seizures were few (FAS): 20/117 (17.1%) in LCM and 19/120 (15.8%) in placebo group. Likewise, seizure-freedom from POS was not frequent: 22/117 (18.8%) in LCM and 20/120 (16.7%) in placebo group. Results with FAS-SDV set were consistent. The fraction of patients who achieved >75% reduction in ADF of electrographic POS between the timepoints of video-EEG was numerically greater in the LCM group compared to placebo (36/116, [31%]) but lower in the group achieving a response ≥50% to ≤75% (12/116 [10.3%] vs. 21/120 [17.5%]) and slightly so in the group achieving a response ≥25% to <50% (21/116 [18.1%] vs. 22/120 [18.3%]). The results were consistent in the FAS-SDV set.

The proportion of patients (FAS) who experienced no change from baseline ADF of electrographic POS at the end-of-maintenance-period video-EEG was 32(27.6%) in the LCM group and 34(28.3%) in the placebo group. The result was consistent in the FAS-SDV set. The proportion of patients (FAS) who

experienced an increase from baseline ADF of electrographic POS at the end-of-maintenance-period video-EEG was 15 (12.9%) in the LCM group and 18(15.0%) in the placebo group. The result was consistent in the FAS-SDV set.

In other efficacy variables, the clinical GIC at visit 6 (day 27) showed a numerically higher percentage of improved patients in the LCM group in comparison with placebo (87 patients [68.0%] vs. 76 study [59.8%]), including the categories of 'very much improved', 'much improved', and 'minimally improved'. A higher percentage of LCM patients were seen in the 'much improved' category (43 [33.6%] vs. 27 patients [21.3%]).

Assessment by the caregiver's GIC indicated a numerically higher percentage of improved patients in the LCM group in comparison with placebo (98 patients [76.6%] vs. 78 study [61.4%]), including the categories of 'very much improved', 'much improved', and 'minimally improved'. A higher percentage of LCM patients were seen in the 'much improved' category (42 [32.8%] vs. 25 patients [19.7%]).

In PedsQL scale the total and subscale scores for patients aged 2-4 years showed a favourable trend of higher mean scores in patients treated with LCM; however, the amplitude of change was small with no or a very minor shift in median (table). In patients aged 1 to 12 months and 13 to 24 months, there were no meaningful differences between the treatment groups, but a marginal trend in favour of LCM group.

Table 12: Change from baseline at visit 6 in PedsQL subscale and total scores for patients aged 2 to 4 years (FAS).

Score or subscale	Statistic	PBO N=68	LCM N=66
Physical functioning	n	64	63
	Mean (SD)	-0.829 (18.018)	2.742 (15.816)
	Median (min, max)	0.000 (-93.75, 31.25)	0.000 (-40.62, 56.25)
Emotional functioning	n	64	62
	Mean (SD)	1.250 (19.355)	3.367 (16.730)
	Median (min, max)	0.000 (-45.00, 75.00)	0.000 (-35.00, 40.00)
Social functioning	n	63	62
	Mean (SD)	0.714 (23.346)	2.016 (22.222)
	Median (min, max)	0.000 (-100.00, 60.00)	0.000 (-70.00, 60.00)
School functioning	n	27	30
	Mean (SD)	0.308 (22.937)	4.167 (27.919)
	Median (min, max)	0.000 (-91.67, 41.67)	0.000 (-91.67, 100.00)
Psychosocial health summary score	n	63	61
	Mean (SD)	1.081 (15.306)	3.178 (15.087)
	Median (min, max)	0.000 (-50.00, 57.50)	2.500 (-42.50, 47.50)
Physical health summary score	n	64	63
	Mean (SD)	-0.829 (18.018)	2.742 (15.816)
	Median (min, max)	0.000 (-93.75, 31.25)	0.000 (-40.62, 56.25)
Total score	n	64	62
	Mean (SD)	0.300 (12.738)	2.723 (14.163)
	Median (min, max)	0.000 (-51.19, 31.95)	1.885 (-37.50, 42.26)

There were no differences between the healthcare resource use in terms of concomitant medical procedures, healthcare provider consultations, hospitalizations and emergency room visits. The reported numbers were low for both treatment groups. Only two patients had their efficacy assessments impacted by Covid-19 pandemic.

Post hoc-analyses of the available centrally read video-EEG data (90 baseline video-EEGs, prior to removal of the central reader by the protocol amendment 3 as well as 98 end-of-maintenance period video-EEGs) revealed a high variability between the central and the local readers in the interpretation of video-EEG data. As for the POS categories (<2, 2 to 20, and >20), the agreement between the local readers and the central reader was poor at the end-of-baseline period (kappa=0.08 [95% CI: 0.02, 0.15]; weighted Kappa=0.08 [95% CI: 0.01, 0.16]) and fair at the end-of-maintenance period (kappa=0.23 [95% CI: 0.12, 0.35]; weighted kappa=0.24 [95% CI: 0.13, 0.36]), as measured by kappa statistics. The observed difference in reader interpretation of end-of-baseline period video-EEG was 65.7%, instead of the 5% planned based on previous experience. Finally, there was a substantial variability between the local readers' and the central reader's interpretations of the number of seizures observed, particularly in the number of POS seizures but also in the number of primary generalized and unclassified epileptic seizures at both at the end-of-baseline period and end-of-maintenance period, without a difference in the interpretable hours of video recordings between the local and central readers.

> **Assessor's comment**
>
> *The efficacy results fail to show an increase in efficacy when LCM is used concomitantly with 1-3 antiepileptic drugs in paediatric patients ≥1 month to <4 years of age with currently uncontrolled partial-onset epilepsy.*

Safety results

In the overall study period (titration and maintenance), exposure to study medication was similar across age groups (the exposure to study medication is given in the table 13 below). The median duration of treatment in the LCM and placebo groups ranged from 27.0 days to 28.0 days across all age groups. The average of the median daily dose for the LCM and placebo groups ranged from 8.8mg/kg/day (≥1 month to <6 months in the LCM group) to 9.4mg/kg/day (placebo group ≥1 month to <6 months in the placebo group and ≥6 months to <1 year in LCM group).

Table 13: Exposure to study medication (SS)

Treatment Period Statistic	PBO N=127	LCM N=128
Study medication duration (days)		
N	127	128
Mean (SD)	27.4 (2.6)	27.7 (3.8)
Median (min, max)	27.0 (6, 32)	27.0 (3, 44)
Median total daily dose (mg/kg/day)		
N	127	128
Mean (SD)	9.2 (1.4)	9.1 (1.6)
Median (min, max)	10.0 (3, 11)	10.0 (3, 12)
Maintenance Period **Statistic**	**PBO** **N=127**	**LCM** **N=128**
Study medication duration (days)		
n	125	124
Mean (SD)	7.2 (1.7)	7.6 (2.5)
Median (min, max)	7.0 (3, 12)	7.0 (3, 21)
Median total daily dose (mg/kg/day)		
n	125	123
Mean (SD)	10.9 (1.4)	10.8 (1.5)
Median (min, max)	12.0 (8, 12)	12.0 (4, 13)

Summary of TEAEs

A summary of the incidence of TEAEs in all paediatric patients is presented in the table below.

Table 14: Overview of the incidence of TEAEs for the study (SS)

	Overall study	
Category	**PBO** **N=127** **n (%) [#]**	**LCM** **N=128** **n (%) [#]**
Any TEAEs	73 (57.5) [185]	66 (51.6) [174]
Serious TEAEs	6 (4.7) [8]	6 (4.7) [7]
Discontinuations due to TEAEs	0	2 (1.6) [2]
Drug-related TEAEs	19 (15.0) [27]	32 (25.0) [65]
Drug-related serious TEAEs	0	2 (1.6) [2]
Severe TEAEs	4 (3.1) [5]	3 (2.3) [5]
All deaths (AEs leading to death)	0	0
Deaths (TEAEs leading to death)	0	0

Of the total of TEAES during the entire study, most of those reported during the treatment period were mild to moderate in intensity. The majority of TEAEs in both treatment groups were reported during the titration period, with a higher incidence in the ≥2 years to <4 years age group compared with the younger age groups. Most of the TEAEs were reported in the SOCs of Infections and infestations (23.4% in the LCM and 34.6% in the placebo group), Nervous system disorders (19.5% in the LCM and 12.6% in the placebo group), and General disorders and administration site conditions (12.5% in the LCM and 18.1% in the placebo group).

The most commonly reported TEAE in the LCM group during the entire study was somnolence (14.1%), followed by vomiting, pyrexia, and irritability (5.5% each), whereas the most commonly reported TEAEs in the placebo group were pyrexia (12.6%) and upper respiratory tract infection (11.0%). Dose at onset did not appear to have an impact on the expectedly higher incidence of somnolence. The most frequently reported TEAEs considered by the investigator to be related to study medication and reported at a higher incidence in the LCM group were somnolence (10.9% in the LCM, 2.4% in the placebo group), vomiting (4.7% in the LCM, 0.8% in the placebo group), irritability (3.1% in the LCM and none in the placebo group), and abnormal liver function test, dizziness, and aggression, each reported in 1.6% in the LCM group only.

During the titration period, the reported TEAEs with a higher incidence in the LCM group were vomiting (5.5% vs 3.1%), diarrhoea (2.3% vs 1.6%), irritability (4.7% vs 1.6%), somnolence (10.2% vs 2.4%), and cough (1.6% vs 0.8%). During the maintenance period, the TEAEs reported at a higher incidence in the LCM group were somnolence (1.6% vs 0.8%) and cough (1.6% vs 0.8%).

The incidence of serious TEAEs reported during the treatment period was the same between the treatment groups (4 patients [3.1%] in each). Serious TEAEs of vomiting and convulsion were reported in the LCM group (2 patients each), the vomiting episodes being considered related to study medication by the investigator. Serious TEAEs reported in the placebo group included pyrexia, upper respiratory infection, urinary tract infection, thermal burn, and respiratory failure (1 patient each). Of the 8 patients with serious TEAEs, 1 was in the ≥6 months to <1 year age group and 7 were in the ≥2 years to <4 years age group. No serious TEAEs led to study medication discontinuation in the placebo group, whereas in the LCM group there were two TEAEs leading to study medication discontinuation during the maintenance period, mild sinus bradycardia and mild generalized epilepsy. There were no deaths among treated patients during the study.

Five patients, 3 in the LCM group and 2 in the PLACEBO group, experienced other significant events, including decreased appetite (3 patients), and sinus bradycardia and self-injurious behavior (1 patient each). All 5 patients who experienced other significant events were in the ≥2 years to <4 years age group.

<u>TEAEs of Interest</u>

Five patients (3 in the LCM, 2 in the placebo group), experienced other significant TEAEs. In the LCM group, other significant TEAEs reported included decreased appetite, sinus bradycardia, and self-injurious behaviour, all in patients in the ≥2 years to <4 years age group. Decreased appetite was moderate in severity and occurred at on onset dose of 4mg/kg/day and resolved after 17 days without further action. The TEAE of sinus bradycardia was ongoing and resulted in discontinuation from the study. Self-injurious behaviour was mild in severity and occurred at an onset dose of 8mg/kg/day and resolved after 5 days without further action taken. In the placebo group, 2 patients in the ≥2 years to <4 years age group reported decreased appetite, resolving without further action.

A total of 4 TEAEs in the LCM group and 6 in the placebo group were related to seizures. Two events of convulsion required hospitalization. Three patients experienced 3 TEAEs of aggression (2 in the LCM, 1 in the placebo group) during the treatment period and were considered related to study medication by the investigator. All cases of aggression were reported in the ≥2 years to <4 years age group.

No patients experienced TEAEs related to memory impairment, amnesia, or cognitive disorder. Development delay was reported in a 6-month old patient at an onset dose of 8mg/kg/day during the titration period; it was considered mild in severity and not related to study medication.

No AEs were considered related to COVID-19.

Clinical laboratory evaluations

No consistent or clinically relevant mean changes from baseline after onset of treatment were observed for haematology or clinical chemistry parameters that were considered related to LCM. The overall incidence of treatment emergent markedly abnormal (TEMA) values for haematology and clinical chemistry was low for both treatment groups.

TEAEs related to abnormal haematology values reported by ≥2 patients in either treatment group during the treatment period were neutropenia (2 patients in the LCM and one patient in the placebo group), eosinophilia (2 patients in the LCM group, none in the placebo group), and eosinophil count increased (one patient in the LCM group, 2 in the placebo group). The remaining TEAEs were reported by only a single patient each in the placebo group (neutrophil count decreased and white blood cell count decreased).

TEAEs related to clinical chemistry values and liver function tests (LFTs) reported by ≥2 patients in either treatment group during the treatment period were alanine aminotransferase (ALT) increased (3 patients in the LCM and one in the placebo group) and LFT abnormal (2 patients in the LCM and none in the placebo group). The remaining TEAEs were reported by only a single patient each in the LCM group (blood thyroid stimulating hormone [TSH] increased) and placebo group (hypertriglyceridemia and blood alkaline phosphatase [ALP] increased). No patients met PDILI criteria.

Vital signs, physical examination and ECG findings

Overall, no consistent or clinically relevant change from baseline in vital sign parameters was observed. Mean values for systolic and diastolic blood pressure, pulse rate, body weight, height, and head circumference were generally within the expected ranges at baseline and post-baseline visit for both treatment groups. Markedly abnormal vital sign parameter values were the following: systolic BP high (8.6% in LCM, 4.7% in placebo); diastolic BP high (18.0% in LCM, 18.1% in placebo); diastolic BP low (14.1% in LCM, 7.9% in placebo); pulse rate low (20.3% in LCM, 13.4% in placebo).

No clinically relevant changes from baseline were observed for vital signs or 12-lead electrocardiograms (ECGs). 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.

Clinical pharmacology results

Plasma concentrations of LCM were obtained to develop a population PK model of LCM and to investigate the correlation between LCM plasma concentrations and efficacy or safety. Plasma was collected at visit 5 (day 17) of the titration period and at visit 6 (day 27) of the maintenance period. LCM plasma concentrations at each dose level were generally similar at visit 5 and 6, and the mean LCM concentrations generally increased with dose (5.3423 µg/mL at 8mg/kg/day, 9.4100 µg/mL at 10mg/kg/day, and 9.4224 µg/mL at 12mg/kg/day). However, there was substantial interparticipant variability due to the small sample size (n range 1-18) at several of the dose levels. Correlation between plasma concentrations and efficacy or safety was not further explored.

2.3.3. Discussion on clinical aspects

A total of 255 paediatric patients were included in the study SP0967, which was designed to evaluate the efficacy and safety of orally administered lacosamide (LCM) as adjunctive therapy in patients ≥1 month to <4years of age with uncontrolled partial-onset epilepsy. The number of enrolled patients fulfilling the set inclusion and exclusion criteria carried through the study periods meets the preplanned recruitment as specified by the power analysis, and the treatment groups may be considered sufficiently balanced and representative as for their epilepsy, seizure types, demographic variables, and as expected for the general morbidity and concomitant medications. The ensuing analysis sets were sufficiently balanced. Although the licensing of LCM does not cover children less than 4 years of age, considering the complete bioavailability of LCM and the prior PK modelling and simulations, the dose regimen in the age group ≥1 month to 4 years was considered acceptable. However, the youngest age group (≥1 month to <6 months) was underrepresented, undermining the validity of the study in this age cohort.

The main challenge of feasibility turned out to be the unexpectedly high variability in the EEG assessment methodology, dramatically lowering the inter-rater reliability of the interpretation of seizure counts and types, which was crucial for the primary and several secondary variable outcome analyses as well as inclusion in the study. The low reliability could not be compensated by reasonable corrective actions. The study was agreed to be removed from the PIP after PDCO consultation (EMEA 000402 PIP02 11 M05, decision P/0001/2018 on 08 Jan 2018).

The efficacy results were neutral for the primary variable analysis for both US and EU approaches, and the negative results were consistently supported by all sensitivity analyses applied. Finally, the totality of efficacy results failed to show an increased efficacy when LCM is used concomitantly with 1-3 antiepileptic drugs in paediatric patients ≥1 month to <4 years of age with currently uncontrolled partial-onset epilepsy. In the post-hoc analyses, the agreement between local and central readers as for the seizure frequency and classification was poor to fair at best. This overshadowing methodological issue largely obviates discussion on the other minor potential issues in the efficacy assessment (e.g. protocol violations, differences in concomitant medications).

The safety profile of lacosamide in the paediatric population is currently reflected in the SmPC. The overall incidence of drug-related TEAEs appears to be as expected, consistent with the known safety

profile of LCM in adults and children ≥4 years of age, which appears acceptable. No new safety concerns were identified, and consequently, there is no need to update the product information based on this dataset at present.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of sp0967 in order to fulfil the requirement of reporting paediatric data as outlined in accordance with Article 46 of regulation (EC) no 1901/2006, as amended.

The MAH determines that the benefit-risk profile of LCM remains unchanged and positive despite the failure to show improved efficacy, which is acceptable. The MAH does not propose any changes of the currently approved SmPC based on the present data, which is supported.

MS comments were received by MS1 and MS2.
MS1 supported the Rapporteur's conclusions with no additional comments.
MS2 suggested the inclusion of a statement of the design and negative results of study SP0967 in section 5.1 to inform the prescribers about this study in this specific 1 month-4-year population.

The Rapporteur would however propose not to include a statement on this study in the SmPC. The safety profile of lacosamide in the paediatric population is currently already sufficiently reflected in the SmPC and no new safety concerns were identified. The efficacy results failed to show an increased efficacy when LCM was used in the studied population. However, as stated in the discussion, there were significant methodological issues with the study rendering any results difficult to interpret. Therefore, a summary of the findings of this study is not considered to be of informative value to the prescriber.

☒ **Fulfilled:**