27 January 2022
EMA/99116/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Procedure No. EMEA/H/C/WS2049/G

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name:	Product-specific application number
Vimpat	lacosamide	EMEA/H/C/000863/WS2049/0091/G
Lacosamide UCB	lacosamide	EMEA/H/C/005243/WS2049/0009/G

Worksharing applicant (WSA) UCB Pharma S.A.

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List of abbreviations

ADF	Average Daily Frequency
AED	Antiepileptic drug
AHEG	Ad Hoc Expert Group
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice a day
CBZ	carbamazepine
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	Clearance
CL/F	apparent clearance
C_{max}	Maximum (peak) plasma concentrations
CNS	central Nervous System
C_{ss}	Steady-state plasma concentrations
CYP	Cytochrome P
DDI	Drug-drug interaction
ECG	Electrocardiogram
EEG	Electroencephalogram
EMA	European Medicines Agency
ERA	Environmental risk assessment
F	Bioavailability
FAS	Full Analysis Set
IIV	inter-individual variability
iv	intravenous(ly)
ka	absorption rate constant
ke	elimination rate constant
MAA	Marketing authorisation application
LCM	Lacosamide
LSM	Least Squares Means
PB	Phenobarbital
PCA	Post conceptual age
PD	Pharmacodynamic
PHT	Phenytoin
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic per-protocol set
popPK	Population pharmacokinetic

POS	Partial-onset seizures
PPS	Per Protocol Set
PSUR	Periodic Safety Update Reports
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SS	Safety Set
t½	Plasma elimination half-life
TEAE	Treatment-Emergent Adverse Events
ULN	Upper Limit of Normal
TID	Three times a day
Vc	central Volume
Vd	Volume of distribution
V/F	apparent volume of distribution
VPA	Valproic acid
VPCs	Visual predictive checks

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, UCB Pharma S.A. submitted to the European Medicines Agency on 9 March 2021 an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.IV.1.a.1	Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IB	I, IIIA, IIIB and A
B.II.f.1.b.2	Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	Type IB	I, IIIA and IIIB

Extension of indication to include patients from 1 month to 4 years of age for treatment of partial-onset seizures with or without secondary generalisation as monotherapy and adjunctive therapy for Vimpat/Lacosamide USB. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Version 16.0 of the RMP has also been submitted.
B.IV.1.a.1 - type IB - Medical Devices - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking
B.II.f.1.b.2 - type IB - FINISHED PRODUCT - Stability - Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - After first opening (supported by real time data)
The Package Leaflet and labelling are updated in accordance.

The grouped worksharing procedure requested amendments to the Summary of Product Characteristics (SmPC), Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0001/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0001/2018 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA received Scientific Advice from the CHMP in 21 July 2011 (EMA/CHMP/SAWP/528383/2011). The Scientific Advice pertained to quality and clinical aspects and was given in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	9 March 2021
Start of procedure:	27 March 2021
CHMP Rapporteur Assessment Report	26 May 2021
PRAC members comments	2 June 2021
Updated PRAC Rapporteur Assessment Report	3 June 2021
PRAC Outcome	10 June 2021
CHMP members comments	16 June 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 June 2021
1st Request for supplementary information (RSI)	24 June 2021
WSA's responses to RSI	15 July 2021
CHMP Rapporteur Assessment Report	27 August 2021
PRAC Outcome	2 September 2021
CHMP members comments	9 September 2021
Updated CHMP Rapporteur Assessment Report	10 September 2021
2nd Request for supplementary information (RSI)	16 September 2021
Ad Hoc Expert Group meeting to address questions raised by the CHMP	7 October 2021
WSA's responses to RSI	11 October 2021
CHMP Rapporteur Assessment Report	28 October 2021
CHMP members comments	3 November 2021
Updated CHMP Rapporteur Assessment Report	5 November 2021
3rd Request for Supplementary Information (RSI)	11 November 2021
WSA's responses responses to RSI	21 December 2021
CHMP Rapporteur assessment report	12 January 2022
PRAC Rapporteur assessment report	7 January 2022
PRAC outcome	13 January 2022
CHMP members comments	20 January 2022
Updated CHMP Rapporteur assessment report	20 January 2022

Timetable	Actual dates
CHMP opinion	27 January 2022

2. Scientific discussion

2.1. Introduction

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

Lacosamide (LCM) was first approved on 29 August 2008 in the EU as adjunctive therapy in the treatment of POS with or without secondary generalization in adult and adolescent from 16 years of age with epilepsy. Monotherapy indication in study participants ≥16 years of age was approved on 12 December 2016 in the EU.

The initial scope applied for this variation was the extension of LCM indication as monotherapy and adjunctive therapy in the treatment of POS with or without secondary generalisation to patients from 1 month to <4 years of age.

2.1.1. Problem statement

The previous extension of indication to paediatric patients ≥4 years of age was based on extrapolation of adult efficacy data from adjunctive therapy studies (SP667, SP754, and SP755) and monotherapy studies (SP0993 and SP902) and supported by weight-based paediatric dosing adaptations targeting similar exposures as those in adults at therapeutic LCM doses (CL0177 and CL0266), and long-term safety of adjunctive LCM in paediatric study participants (Pool SPX-1) (EMEA/H/C/000863/II/0065/G, approved in the EU on 14 September 2017).

The present extension of indication, aiming to extend the POS indication as monotherapy or adjunctive treatment to paediatric patients under the age of 4 years, is based on efficacy extrapolation from older patient groups and the available clinical efficacy, safety, and pharmacology data.

2.1.2. About the product

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In July 2011, the MAH received advice from the Committee for Medicinal Products for Human Use (CHMP) concerning the proposed extrapolation strategy for LCM as an adjunctive therapy for partial-onset seizures in children with epilepsy in the age group from 2 to 16 years, the definition of target dose range, and

adequacy of the proposed bridging strategy combined with literature review in filing for LCM as monotherapy in the treatment of POS with or without secondary generalizations in the age group ≥ 1 month and < 18 years (EMA/CHMP/SAWP/528383/2011).

The CHMP agreed that extrapolation of adult efficacy data is partly possible but pointed out that extrapolability down to 2 years did not seem sufficiently supported by the available data. Although there is support from clinical experience, data from confirmatory trials would need to be considered. As for the definition of target dose range, the CHMP pointed out the preferential need for actual data in addition to physiological PK modelling. The possibility of a bridging strategy was agreed on down to the age of 4 years, but the need for data on short-term efficacy, PK and safety in the very young paediatric population (≥1 month to 2 years) was recognized.

2.2. Quality aspects

The currently approved formulations, 10 mg/ml syrup and film coated tablets 50, 100, 150 and 200 mg and 10 mg/ml solution for infusion, were initially proposed to be used in children from 1 month of age. No new formulation was developed for the lower age group applied.

The current approved dosing devices for Vimpat 10 mg/ml syrup and Lacosamide UCB 10 mg/ml syrup drug products are a 30 ml measuring cup and 10 ml dosing syringe and a bottle adaptor.

The MAH initially proposed to register an additional 5 ml syringe, as a consequence of the initial proposed extension of indication to patients from 1 month of age and to allow accurate dosing in the youngest paediatric population initially proposed in this application. In view of the final revised extension of indication to children from 2 years of age, the MAH has justified that the new 5 ml oral syringe will not be included in the packaging and is no longer applied for.

The syrup contains the excipients glycerol, carmellose sodium, sorbitol liquid (crystallizing), macrogol, sodium chloride, anhydrous citric acid, acesulfame potassium, sodium methyl parahydroxybenzoate, strawberry flavour (contains propylene glycol, maltol), masking flavour (contains propylene glycol, aspartame, acesulfame potassium, maltol, deionised water) and purified water.

The syrup is filled in amber glass bottles with a screw cap (polypropylene). The bottle, filled with 200 ml syrup, will be provided with a 30 ml measuring cup and a 10 ml oral syringe (black graduation marks) with an adaptor.

Suitability of the formulation for the paediatric population.

In line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2, the suitability of the proposed formulation in the proposed age group has been satisfactorily addressed considering the safety profile of the excipients for children in the target age groups in relation to exposure.

For aspartame the MAH refers to the ADI of 40 mg/kg bw/day as established by EFSA. However, ADI values established by EFSA, do not apply to infants below 12 weeks of age [EFSA, Scientific Opinion, 'Guidance for submission for food additive evaluations', ANS, EFSA Journal, Vol. 10(7), 2012, p. 2760.]. Given that extrapolation of efficacy below 2 years of age is not supported, the use of aspartame in the formulation for infants below 12 weeks is not further assessed at this stage. The use of aspartame for infants above 12 weeks is judged acceptably justified.

The addition of the warning "Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age." in section 4.4 of the SmPC is agreed.

Suitability of the Container closure system, including the additional dosing device

The same container closure system as already on the market, is intended to be used in all age groups. The current approved dosing devices are a 30 ml polypropylene measuring cup and 10 ml dosing syringe (comprising a polypropylene barrel and a high-density polyethylene plunger) and a bottle adaptor (low-density polyethylene).

As a consequence of the lower dose for younger children, more than 2 months in-use shelf-life will be needed to allow these younger children to consume the full content of a Vimpat 10 mg/ml syrup or Lacosamide UCB 10 mg/ml syrup bottle. It is therefore proposed to increase the in-use shelf life from 2 months to 6 months. 6 months in-use stability data is provided in support of this change.

Dosing device

The already approved package contains a 30 ml measuring cup, a 10 ml dosing syringe and a bottle adaptor which is considered sufficient to cover the recommended doses from 2 years of age.

Due to the recommendation to use the 30 ml measuring cup when the required dose is more than 200 mg (20 mL), uniformity of dose data has been added for the 25 ml and 30 ml doses in section 3.2.P.2.4. Previously data has been presented for the 5 ml, 10 ml, 15 ml and 20 ml doses. The measuring cup with graduation markings of 5 ml, 10 ml, 15 ml, 20 ml, 25 ml and 30 ml complies with acceptance criteria of Ph.Eur. 2.9.27.

Extension of the in-use shelf-life of Vimpat 10 mg/ml syrup and Lacosamide UCB 10 mg/ml syrup

As a consequence of the lower dose for younger children, more than 2 months in-use shelf-life will be needed to allow these younger children to consume the full content of a Vimpat 10 mg/ml syrup or Lacosamide UCB 10 mg/ml syrup bottle. It is therefore proposed to increase the in-use shelf life from 2 months to 6 months. 6 months in-use stability data for the syrup is provided in support of this change.

The MAH also took the opportunity to provide the full shelf life 36 months long term stability data for three batches, manufactured by Istituto De Angeli S.r.l.

In-use testing was performed on two batches - one aged and one freshly manufactured. Both batches were manufactured approximately 4 months prior to the start of the study. The packaged product was stored upright at 30°C/75% RH and was sampled twice a day (weekdays only) for 6 months and each time, 0.7 mL of the contents was removed to mimic patient use. One batch was tested at 0, 1, 2, 3, 4, 5 and 6 months whilst the other batch was tested at 30, 31, 32, 33, 34, 35 and 36 months. All results were within specifications and confirms that a repeated withdrawal of syrup, from the container and the resulting contact with air and the dosing device during a typical in-use-period had no significant impact on the product quality once the closure system has been opened.

Based on the submitted in-use stability results the increase of the in-use shelf life from 2 months to 6 months is acceptable.

IV formulation

The currently approved formulation, 10 mg/ml Solution for infusion for children from 4 years of age, is intended also to be used in children from 2 years of age. The excipients in the solution for infusion are water for injections, sodium chloride and hydrochloric acid (for pH adjustment).

The solution is filled in type 1 glass vials with an extractable volume of not less than 20 ml. The same vial size 20 ml as already approved is intended to be used for all age groups.

Suitability of the formulation for the paediatric population.

The excipients, as described above, included in the current formulation are commonly used and of no safety concern for the use in children from 1 months of age.

The solution for infusion is not supplied with a measuring device and based on the dosing regimen 1 ml syringes with 0.01 increments, commonly available in hospitals and pharmacies, are suitable for dosing. No issues with regards to accuracy and precision are expected.

The need and possibility to develop a smaller presentation, suitable for children has been addressed. The conclusion not to develop a smaller presentation for children is acceptable since it is a temporary replacement from oral administration, handled and administered by highly trained medical professionals in hospital.

2.3. Non-clinical aspects

No new clinical data have been submitted in this paediatric extension of indication, which was considered acceptable by the CHMP.

The previously submitted reproductive and developmental toxicity studies, including juvenile toxicity studies, included and reviewed in the Vimpat marketing authorisation application (MAA), are summarised below. The relevant findings are reflected in the Product Information.

An updated environmental risk assessment (ERA) has been provided in this submission.

2.3.1. Introduction

A comprehensive non-clinical development program has been conducted in adult and juvenile animals. The juvenile studies (see below) were presented and evaluated the first extension of indication to include monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in children from 4 to less than 16 years old with epilepsy (EMEA/H/C/000863/II/0065/G).

Table 1. Lacosamide pre-and post-natal development and juvenile toxicity studies in support of paediatric clinical development.

Type of study (study number)	Species	Age at study start	Dosage period	Dose (mg/kg/day)
Developmental and pre- and postnatal development (1108-004)	Pregnant rat	NA	GD 6 - LD 20	25, 70, 200 by gavage
Pre- and postnatal development DRF (NCD2008)	Pregnant rat	NA	GD 6 - day of delivery	50, 150, 250 twice daily 10 hours apart by gavage
Pre- and postnatal development study (NCD2103)	Pregnant rat	NA	GD 6 - LD 20	25, 50, 100 twice daily 10 hours apart by gavage
Juvenile DRF (LPT 18601/04)	Juvenile rat	7 days	6 weeks	0, 30, 100, 300 once daily by gavage
6-week juvenile + 4-week recovery (LPT 18602/04)	Juvenile rat	7 days	6 weeks	0, 30, 90, 180 once daily by gavage
Juvenile DRF (LPT 20614/06)	Juvenile dog	7-8 weeks	6 weeks	0, 5, 10, 25 once daily by capsule
33-week juvenile + 4-week recovery (LPT 20615)	Juvenile dog	7-8 weeks	33 weeks	0, 3, 10, 25/30/35 once daily and 25/30/35 twice daily 10 hours apart by capsule

GD = gestation day; LD = lactation day

As further discussed in EMEA/H/C/000863/II/0065/G, the types of toxicity observed in juvenile rats and dogs do not differ qualitatively from that observed in adult animals. In juvenile dogs, central nervous system (CNS) clinical signs such as tonic convulsions, emesis, lateral position, staggering gait, and tremor were

considered dose-limiting. In contrast, only few clinical signs were observed in the juvenile rats and despite initially higher exposure these were less severe than at comparable dose levels in adult rats.

Potential effects of long-term treatment with LCM on the developing brain were assessed in a pre- and post-natal study in rats and repeat-dose toxicity studies in juvenile rats and dogs. These studies included detailed CNS histopathology after perfusion fixation as well as observational neurological screening, reflex testing and a series of neurofunctional tests. There were no significant effects in any of the investigated parameters with exception of findings in the open field test at 8 days after cessation of dosing in the juvenile rat study; a slightly decreased latency time to move from the centre sector suggesting a potential anxiolytic effect of LCM. In previous secondary pharmacology studies, LCM was active in the stress-induced hyperthermia model for stress-related anxiety in mice but not in two other models for anxiety in rats, the social interaction and the elevated plus maze tests. Thus, the relevance of potential anxiolytic-like effects of LCM in rats remains equivocal. In juvenile dogs with start of dosing at an age of 7-8 weeks, there were no LCM-related findings upon reflex and neurofunctional testing with exception of increased salivation. No macroscopic or histopathological findings were noted in the brains of juvenile rats or dogs.

In the juvenile dogs, there was no LCM-related effect on body weight, body weight gain or growth parameters. In contrast, in juvenile rats, marked reductions in body weight and/or body weight gain were dose-limiting. As a secondary effect to this, a slightly delayed development of the high-dose groups in general was observed but appeared not to result in any functional consequences. The body weight changes were considered likely a consequence of general toxicity due to high plasma exposure observed at young rat age and not a specific effect on juvenile growth. A contribution of CNS effects resulting in reduced suckling was considered plausible.

In safety pharmacology studies, transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardio depressive action were observed after intravenous administration in anesthetized adult dogs. In anesthetized adult dogs and monkeys, at intravenous doses of 15 to 60 mg/kg, slowing of atrial and ventricular conductivity, AV block and AV dissociation were seen. Electrocardiograms (ECGs) were recorded in the juvenile dog studies with no significant abnormalities observed. Further, there were no LCM-related findings in the heart upon macroscopical or histopathological examination neither in the dog nor in the rat.

In juvenile rats, LCM-treatment caused dose-related increased levels of plasma alkaline phosphatase, cholesterol as well as alanine transaminase activity. These changes were reversible within the 4-week recovery period. Compared to studies with adult rats, the changes were milder and liver weights were not increased. No effects on liver parameters were noted in juvenile or adult dogs.

2.3.2. Ecotoxicity/environmental risk assessment

The MAH has submitted an updated ERA in this application which accounts for the extended paediatric indication. The potential environmental impact was performed using refined market penetration data (FPEN) based on published epilepsy prevalence information.

The revised risk characterisation for LCM has been carried out by comparing the PEC/PNEC ratios against respective triggers given in section 5.2 of CHMP/SWP/4447/00 corr 1 (June 2006). The results are presented in the table below:

Summary of fate and effect analysis:

Risk Characterisation			
PEC (mg/L)	**PNEC (mg/L)**	**PEC/PNEC ratio**	**Criterion for Tier B Evaluation**
$PEC_{SURFACEWATER}$ = 0.0057	$PNEC_{WATER} \geq 1$	≤ 0.0057	PEC/PNEC Ratio ≥ 1
$PEC_{SURFACEWATER}$ = 0.0057	$PNEC_{MICROORGANISM} \geq 100$	$\leq 5.7 * 10^{-5}$	PEC/PNEC Ratio > 0.1
$PEC_{GROUNDWATER}$ = 0.0014	$PNEC_{GROUNDWATER}$ = 3.2	$4.4 * 10^{-4}$	PEC/PNEC Ratio > 1
Physico-chemical Properties, Fate Analysis			
Kow (mean) = 1.78			$Kow > 10^3$
Koc (mean) = 9 L/kg			$Koc > 10^4$ L/kg
Water sediment study: 14% for sediment on Day 14 (a waiver was granted by rapporteur, EMEA/CHMP/628025/2008)[6] (see Annex)			> 10%

Based on worst case market penetration values, the revised PEC/PNEC ratios are lower than the ERA guideline Tier B trigger values. Therefore, the use of LCM, in the current agreed indications and in the proposed extension of indication, is unlikely to present a risk to the terrestrial and aquatic environments.

2.3.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this procedure. The non-clinical data submitted and assessed in the original MAA and in the previous paediatric extension of indication (EMEA/H/C/000863/II/0065/G) are considered adequate to support the extension of the LCM indication.

The main targets of toxicity in adult animals were the cardiovascular system and liver where effects were seen at no or low margins of exposure. In juvenile rats and dogs, the types of toxicity do not differ qualitatively from those observed in adult animals. In juvenile rats, a reduced body weight was observed at systemic exposure levels similar to the expected clinical exposure. In juvenile dogs, transient and dose-related CNS clinical signs started to be observed at systemic exposure levels below the expected clinical exposure.

In the juvenile rat study, dosing was initiated at an age of 7 days. A 7-days-old rat corresponds (approximately) to a term neonate based on overall CNS and reproductive development. In the juvenile dog study, dosing was initiated at an age of 7 to 8 weeks corresponding (approximately) to a 2-year-old child. The MAH also refers to pre- and post-natal studies in rats with administration of LCM *in utero* and via milk for up to 3 weeks, corresponding to a human age of 0-2 years. The exposure of the F_1 pups was ~ 6% to 8% of the exposure of the lactating F_0 females, whatever the dose. In summary, the available non-clinical studies are considered appropriate to cover the age of the intended patient population.

The findings are adequately reflected in the SmPC and the CHMP agreed that no further updates are needed.

2.3.4. Conclusion on the non-clinical aspects

From a non-clinical point of view, the CHMP agreed that there are no objections regarding the proposed extension of the indication.

The CHMP agrees with the ERA conclusions that the extended indication does not lead to a significant increase in environmental exposure to LCM. LCM is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study/ Status	Study Description	Efficacy data	Safety data	PK data
SP0967/ Completed	A Phase 3, multicenter, double-blind, randomized, PBO-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in study participants with epilepsy ≥1 month to <4 years of age with POS	X	X	X
EP0034/ Ongoing[a]	A Phase 3, multicenter, open-label, long-term extension study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric study participants (≥1 month to ≤17 years of age) with POS	X	X	-
SP847/ Completed	A Phase 2, multicenter, open-label, dose-titration study investigating the safety, tolerability, and PK of LCM oral solution (syrup) (2mg/kg/day to up to 12mg/kg/day) as adjunctive therapy in children ≥1month to ≤17 years of age with uncontrolled POS	-	X	X
SP848/ Ongoing[a]	A Phase 2, open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children (≥1 month to ≤18 years of age) with epilepsy	X	X	X
EP0060/ Completed	A Phase 2/3, multicenter, open-label study to investigate the safety and tolerability of iv LCM in children (≥1 month to <17 years of age) with epilepsy	-	X	X
EP0147/ Completed	RWE based study to examine the safety and tolerability of a loading dose in neonates of <1 month and in pediatric patients of ≥1 month to <17 years of age	-	X	-
Pool SPX-1[a]	A single pediatric safety data pool combining SP847, SP848, and EP0034 using data from all study participants receiving a least one dose of LCM	-	X	-
CL0447 Part IV/ Completed	Population Pharmacokinetic Model for LCM	-	-	X

LCM=lacosamide; PBO=placebo; PK=pharmacokinetic(s); POS partial-onset seizure; RWE=real world evidence
[a] For this variation application, an interim analysis was performed on data from study start until 06 Mar 2020.

2.4.2. Pharmacokinetics

The main PK support for the extension of indication comes from the results of the simulations using an existing population PK (popPK) model of LCM (CL0447).

CL0447-Part I was developed with data from study participants with primary generalised tonic-clonic seizures (PGTCS) from SP0982. CL0447-Part II included data from 9 orally dosed studies (EP0008, SP754, SP755, SP847, SP1047, SP848, SP0969, SP0966, SP0982) in paediatric study participants with epilepsy ranging from ≥1 month to <18 years of age. In CL0447-Part III, the final datasets of EP0060, a study that investigated the safety and tolerability of iv LCM in children ≥1month to <17 years of age with epilepsy, were combined with CL0447-Part II to assess the degree of similarity in exposures for the iv and oral routes of administration. The PK model CL0447-Part III was submitted part of response to questions on EP0060 Article 46 submission (procedure EMEA/H/C/000863/P46/037). CL0447-Part IV was developed for this submission to support LCM indication extension to children 1 month of age and older. CL0447-Part IV includes data from the recently completed study of LCM as adjunctive therapy in study participants ≥1month to <4years of age who had epilepsy with uncontrolled POS (SP0967).

Summary of LCM PK profile in adults (≥ 18 years of age)

The PK of LCM has been studied in healthy adult study participants, as well as adult study participants with epilepsy, neuropathic pain, and renal and/or hepatic impairment. The characterization of the PK and pharmacodynamic (PD) of LCM in clinical studies for POS with the adult and paediatric population was provided in the initial MAA.

Healthy adults

Results from the Phase1 studies in healthy study participants showed that LCM is rapidly and completely absorbed after oral administration with negligible first-pass effect. The high oral bioavailability (F) of approximately 100% is not affected by food. Maximum (peak) plasma concentrations (C_{max}) occur between 0.5 and 4 hours postdose after oral administration under fasted and fed conditions. Exposure is proportional to dose, with low intraparticipant and interparticipant variability. Plasma elimination half-life ($t_{½}$) of the unchanged drug is approximately 13 hours and is dose-and time-invariant. Steady-state plasma concentrations (C_{ss}) are achieved after 3 days.

The volume of distribution (Vd) is approximately 0.6L/kg. LCM is less than 15% bound to plasma proteins. LCM is eliminated from the systemic circulation by renal excretion and biotransformation. About 40% of the dose is renally excreted as unchanged compound.

The major metabolic pathway of LCM is demethylation. The O-desmethyl metabolite (referred to as SPM12809) is excreted in the urine and represents about 30% of dose. This metabolite has no known pharmacological activity. *In vitro* results showed that major cytochrome P-450 isoenzymes (CYP) involved in the formation of SPM12809 are CYP2C19, CYP2C9, and CYP3A4. Results from clinical studies in poor metabolizers and extensive metabolizers for CYP2C19 and a drug-drug interaction (DDI) study with omeprazole (CYP2C19 inhibitor) demonstrated that the formation of SPM12809 in humans is mediated by CYP2C19.

LCM is not an inducer or inhibitor of CYPs, except for *in vitro* inhibition of CYP2C19 that was clinically irrelevant. *In vitro*, using Caco-2 monolayer cell systems, LCM was not a substrate for P-glycoprotein or other active transporters and did not modulate the transport of digoxin at concentrations up to 3mmol/L (750µg/mL).

There were no clinically relevant differences in the LCM PK among Asian, Black, and Caucasian study participants. No clinically relevant difference in LCM exposure was observed between CYP2C19 EMs and PMs.

During clinical development, *in vivo* bioequivalence studies were performed to demonstrate the bioequivalence of the LCM oral solution with the tablet. In SP657, bioequivalence was shown between 2 tablets of LCM 100mg and an oral solution containing LCM 200mg (10mg/mL) after oral single-dose administration.

LCM PK in adults with POS

A comparative summary of the PK of LCM in study participants with POS was submitted in the MAA. Overall, the PK of LCM were considered equivalent in study participants with POS compared with healthy study participants.

LCM plasma concentrations showed dose-proportionality after oral administration in study participants with POS. PopPK modelling in study participants with POS showed that the typical PK parameter estimates for elimination rate constant (ke), t½, and apparent volume of distribution (V/F) were comparable with PK parameters determined in Phase1 studies in healthy study participants (by noncompartmental analysis and by popPK modelling). The LCM popPK parameters showed low and comparable interindividual variability in study participants with POS as well as in healthy study participants, indicating that LCM plasma concentrations are highly predictable.

A pooled analysis of antiepileptic drug (AED) plasma concentrations in study participants with POS from SP667, SP754, and SP755 showed that there was no evidence for any relevant DDI of LCM with common AEDs.

To evaluate any differences in LCM exposure between LCM monotherapy and LCM adjunctive therapy in study participants with POS, LCM plasma concentrations from controlled studies were compared. The LCM C_{ss} observed during LCM monotherapy in SP902 were similar to C_{ss} observed during adjunctive LCM therapy in SP754 and SP755.

LCM PK in adults with renal or hepatic impairment

Compared with healthy study participants, the area under the plasma concentration-time curve (AUC) of LCM was increased by approximately 30% in study participants with mild and moderate renal impairment, and by 60% in study participants with severe renal impairment or with end-stage renal disease requiring haemodialysis, whereas Cmax was unaffected.

Study participants with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of LCM (approximately 50% higher weight-normalized AUC). The higher exposure was partly due to a reduced renal function in the study participants. The decrease in non-renal (metabolic) clearance in the study participants was estimated to increase the AUC of LCM by 20%. The PK of LCM was not evaluated in study participants with severe hepatic impairment.

Loading dose in adults

Simulations were performed based on the PK characteristics of LCM to generate the expected LCM plasma concentration-over-time-profiles. The results showed that the LCM 200mg loading dose (oral or iv) followed by multiple-dose administration of LCM 100mg twice a day (bid) (oral or iv) resulted in plasma concentrations comparable to those achieved over time with bid administration of LCM 100mg. Furthermore, data from selected Phase1 studies in healthy study participants after single-dose administration of LCM 200mg (which corresponds to an "initial" or "loading dose") compared with multiple-dose administration of LCM 100mg (which corresponds to maintenance dosing) were in line with the simulated plasma-concentration curves.

These data and results of simulations (along with data pertaining to the safety of a loading dose) resulted in approval for the initiation of oral and iv LCM in patients weighing 50 kg or more with a single loading dose of 200mg, followed approximately 12hours later by 100mg bid (200mg per day), continued for 1week, and then titrated by 50mg bid (100mg per day) every week.

Summary of LCM PK profile in paediatric study participants with epilepsy ≥4 to <16 years of age

Based on the popPK model (CL0177), the Vd/F of LCM in the paediatric population was estimated to be 50.6L for a body weight of 70kg, or approximately 0.7L/kg (95% confidence interval [CI]: 0.6 to 0.8L/kg),

consistent with the value reported in adults (0.6L/kg). Plasma protein binding of LCM is insignificant in adults (<15%), and no change is expected to occur in paediatric patients.

Using the data from the paediatric popPK analysis (CL0177), the typical apparent clearance (CL/F) was 1.36L/h (0.79mL/min/kg) at the mean population body weight of 28.9kg in the absence of inducer AEDs. It ranged from 0.70L/h (1.17mL/min/kg) for a body weight of 10kg to 2.37L/h (0.56mL/min/kg) for a body weight of 70kg. The typical t½ derived from CL/F and Vd/F in the absence of other effects was predicted to reach 7.2 hours, 10.6 hours, and 14.8 hours at body weights of 10, 28.9, and 70kg, respectively. The predicted value for 70kg was consistent with the t½ values of 13 to 16 hours reported in adults (Cawello et al, 2014).

Graphical analyses and visual predictive checks (VPCs) indicated that the final 1-compartment popPK model (with oral first-order and iv zero-order input) was appropriate for describing the available oral and iv LCM PK data.

Bioavailability was estimated at 89.9% (95% CI: 72.1%, 96.8%) indicating a close correspondence in exposure between oral-and iv-dosed study participants. Simulations of the proposed maximum LCM doses of 6mg/kg bid (12mg/kg/day) for patients weighing 11kg to<30kg, 4mg/kg bid (8mg/kg/day) for patients weighing ≥30kg to <50kg, and 200mg bid (400mg/day) for patients weighing ≥50kg, resulted in pediatric exposures consistent with adult exposures.

The oral dosing scheme positioned the model predicted paediatric C_{ss} values in the adult range; iv dosing resulted in slightly higher exposures due to the oral bioavailability of 89.9%. Individual predictions for paediatric study participants were mostly contained within the model-predicted range, illustrating the adequacy of the individual model predictions.

Based on these data, the maximum recommended iv dosing adaptations in paediatric patients ≥4 to <16 years of age are the same as those approved for oral treatment in this age group. It is proposed that oral dosing can be replaced with iv dosing without further dose adaptation.

A covariate analysis of the paediatric popPK data did not detect a significant effect of gender, age, or race on clearance (CL) in paediatric study participants.

The effect of genetic polymorphisms was not evaluated in the paediatric studies. However, based on results of PK in studies in healthy adults, no dose adjustment is expected to be needed in paediatric patients who are CYP2C19 PMs or paediatric patients who receive a concomitant CYP2C19-inhibiting drug.

Lacosamide PK in paediatric study participants with epilepsy ≥1 month to <4 years of age

Study SP0967

One of the objectives of this study was to evaluate the PK of LCM (as adjunctive therapy) in study participants ≥1 month to <4 years of age who had epilepsy with uncontrolled POS.

LCM dosing

Study participants were titrated over 20 days (*Table 1*), with dosing flexibility allowed based on tolerability, to attain the target dose of 4mg/kg bid (8mg/kg/day) to 6mg/kg bid (12mg/kg/day). LCM was administered as an oral solution.

Table 1 Recommended dosing schedule for LCM (or matching PBO) during the Titration Period of SP0967

Target LCM (or matching placebo) doses for the Titration Period				
Day 1 to Day 4	**Day 5 to Day 8**	**Day 9 to Day 12**	**Day 13 to Day 16**	**Day 17 to Day 20**
2mg/kg bid (4mg/kg/day)	3mg/kg bid (6mg/kg/day)	4mg/kg bid (8mg/kg/day)	5mg/kg bid (10mg/kg/day)	6mg/kg bid (12mg/kg/day)

bid=twice daily; LCM=lacosamide; PBO=placebo

Study participants who achieved an LCM dose of at least 4mg/kg bid (8mg/kg/day) for the final 3 days of the Titration Period entered a 7-day Maintenance Period on the dose achieved on the final day of the Titration Period. No adjustments to study medication dose were allowed during the Maintenance Period.

Timing of PK sampling

Blood samples for the determination of LCM plasma concentrations were to be obtained on Day17 (Visit 5) of the 20-day Titration Period and Day 27 (Visit 6), the final day of the 7-day Maintenance Period.

PK results

Descriptive statistics of LCM plasma concentrations by maintenance dose levels at Day27 (Visit 6), overall and by age group, for the pharmacokinetic per-protocol set (PK-PPS) are presented in *Table 2*.

Table 2 LCM plasma concentration (µg/mL) by maintenance dose level -overall and by age group (PK-PPS)

Statistic	Actual LCM (oral solution) dose at Day 27 (Visit 6)		
	4mg/kg bid (8mg/kg/day)	5mg/kg bid (10mg/kg/day)	6mg/kg bid (12mg/kg/day)
Overall			
n	13	35	58
Mean (CV%)	5.3423 (59.8)	9.4100 (37.9)	9.4224 (52.8)
≥1 to <6 months			
n	2	2	1
Mean (CV%)	2.3700 (138.4)	9.8000 (26.0)	6.7300 (-)
≥6 months to <1 year			
n	1	6	9
Mean (CV%)	4.0800 (-)	8.9867 (54.3)	6.3600 (48.2)
≥1 year to <2 years			
n	2	9	19
Mean (CV%)	8.7100 (1.6)	9.4400 (23.4)	9.7384 (53.7)
≥2 years to <4 years			
n	8	18	29
Mean (CV%)	5.4013 (58.5)	9.4928 (41.7)	10.2586 (49.7)

bid=twice daily; CV=coefficient of variation; LCM=lacosamide; PK-PPS=Pharmacokinetic Per Protocol Set
Note: Last Visit was the last nonmissing assessment (scheduled or unscheduled) during the Treatment Period.
Note: Maintenance doses ending in 0.5mg/kg/day were rounded up to the nearest integer dose; doses >12mg/kg/day were rounded down to 12mg/kg/day.

Overall, LCM plasma concentrations at each dose level were generally similar at Day17 (Visit 5) and Day27 (Visit 6). The mean LCM plasma concentrations generally increased with dose (5.3423 µg/mL at 8mg/kg/day, 9.4100 µg/mL at 10 mg/kg/day, and 9.4224 µg/mL at 12 mg/kg/day); however, there was substantial interparticipant variability due to the small sample size at several of the dose levels.

Population PK Analysis

The main PK support for the extensions of indication comes from the results of the simulations using an existing popPK model of LCM (CL0447). An overview of the previously developed popPK models and the corresponding modelling and simulation and clinical studies is provided in *Table 4*. Data from Phase 3 study SP0967 (≥1 month to <4 years) were included popPK analysis CL0447-Part IV which is further described below.

Table 3 Overview of previously developed population PK models and corresponding clinical studies

UCB code	Model type	Treatment type	Population	Clinical studies
CL0261	**Population PK**: 1-compartment model with first order oral absorption in adolescents and adults. Weight, Asia, and inducer AED coadministration as covariates (21% higher AUC in Asians)	Adjunctive	Chinese, Japanese, and Western study participants with partial onset seizures > 16 years	EP0008, SP754, SP755
CL0430	**Population PK:** 1-compartment model with first order oral absorption in pediatric study participants. Race effect not significant	Adjunctive	Asian and Western, pediatric study participants >4 years	SP847, SP848, SP969, SP1047
CL0447-Part I	**Population PK:** 1-compartment model with first order oral absorption in pediatric study participants; Joint analysis of data used in CL0430 combined with data from SP0966	Adjunctive	Asian and Western, pediatric >4 years (CL0430), and Western pediatric ≥1 month (SP0966) study participants	SP847, SP848, SP969, SP1047, SP0966
CL0447-Part II	**Population PK**: 1-compartment model with first order oral absorption in adult and pediatric study participants; Weight, Japan/China, and inducer AED coadministration as covariates	Adjunctive	Asian and Western, pediatric and adult study participants	EP0008, SP754, SP755, SP847, SP1047, SP848, SP0969, SP0966, SP0982
CL0447 Part III	**Population PK**: 1-compartment model with first order oral absorption and iv administration in adult and pediatric study participants; Weight only as covariate	Adjunctive	Asian and Western, pediatric and adult study participants	EP0008, SP754, SP755, SP847, SP1047, SP848, SP0969, SP0966, SP0982, EP0060

AED: anti-epileptic drug, AUC: area under the plasma-concentration versus time curve

Source: CL0447-Part IV, Table 2.

CL0447–Part IV

CL0447-Part IV is provided as part of this submission package; it represents an update of CL0447-Part III, which includes data from SP0967, a study of LCM conducted in study participants ≥1month to <4years of age who had epilepsy with uncontrolled POS.

The objectives of CL0447–Part IV were to:

- Update a previously developed LCM paediatric PK model (CL0447–Part III, WS1782 procedure and submitted via sequence LC0257) adding available LCM PK data from study SP0967
- Perform simulations to:

- Support and evaluate dosing recommendations in patients ≥1month to <4years age
- Support and evaluate a monotherapy scenario in patients ≥1month to <4years of age
- Support and evaluate weight-dependent loading doses across the entire paediatric age range (≥1month to <4years and ≥4years to <17years)

Data

PK data from 11 studies (*Table 4*) were combined and analysed. The full LCM Part IV PK data file contained a total of 7114 LCM concentration records from 1884 study participants. The SP0967 data were examined for concentrations with extreme residuals (absolute value of conditional weighted residual |CWRESI|>4) and four data points were excluded from analysis for this reason. Records with a missing time since last dose were excluded from analysis. In total 6 patients including 10 PK samples were excluded from the SP0967 data. After application of the data exclusion flags, 6490 quantifiable LCM concentration records remained for analysis in 1655 study participants, including 231 concentration records in 122 study participants for SP0967.

Table 4 Clinical studies contributing data to population PK study CL0447

Study	Age, Population	Study participants/ PK samples (n)	PBO or LCM treatment regimen [a]
EP0008	Adults, uncontrolled POS	363[b]/1903[c]	PBO, 200, and 400mg/day bid (tablets)
SP754	Adults, POS	301[b]/1322[c]	PBO, 400, and 600mg/day bid (tablets)
SP755	Adults, POS	322[b]/1007[c]	PBO, 200, and 400mg/day bid (tablets)
SP0982	≥4 years, uncontrolled PGTCS in IGE	98[c]/159[c]	PBO <30kg: 8 to 12mg/kg/day (solution) ≥30kg and <50kg: 6 to 8mg/kg/day (solution) ≥50kg: 300 to 400mg/day (oral solution-syrup or tablet), bid
SP847	≥1 month to ≤17 years, uncontrolled POS	47[b]/311[c]	2 to 12mg/kg/day as bid (oral solution-syrup)
SP1047	≥1 month to ≤17 years, prescribed LCM for epilepsy	32[b]/90[c]	15mg/mL (syrup), 50 to 200mg (tablet), or 10mg/mL (solution) bid at the clinically prescribed dose
SP848	≥1 month to ≤18 years, POS and other epilepsy syndromes	263[b]/933[c]	2 to 12mg/kg/day (syrup), 100 to 600mg/day (tablet) bid
SP0969	≥4 to <17 years, POS	171[b]/356[c]	6 to 12mg/kg/day (syrup), 300 to 400mg/day (tablet) bid
SP0966	≥1 month to <18 years, epilepsy syndromes associated with generalized (Type II) seizures	55[b]/53[c]	2 to 12mg/kg/day (syrup), 100 to 600mg/day (tablet) bid
EP0060[e]	≥1 month to <17 years, epilepsy	95[d]/125[d]	If switching from oral to iv: 2 to 12mg/kg/day or 100 to 600mg/day (same as current oral dose) If initiating LCM treatment: <50kg: 1mg/kg bid or ≥50kg: 50mg bid
SP0967	≥1 month to <4 years (approximately 50% <2 years), POS	122/231	PBO 8 to 12mg/kg/day with titration starting at 4mg/kg/day

bid=twice daily; IGE=idiopathic generalized epilepsy; LCM=lacosamide; NONMEM=nonlinear mixed effects modeling; PBO=placebo; PGTCS=primary generalized tonic-clonic seizure; PK=pharmacokinetic; POS=partial-onset seizure

[a] Doses mentioned are intended doses that may have been adjusted if clinically indicated.

[b] Source: Investigator's Brochure.

[c] Numbers in the PK analysis data selection of the NONMEM file for CL0447–Part II.

[d] Numbers in the PK analysis data selection of the NONMEM file for CL0447–Part III.

[e] EP0060 CSR was submitted to EMA via Article 46, sequence LC0255

Summary measures describing the distribution of body weight, age, and AED coadministration, are provided in Table 4 to Table 8 for both the full LCM Part IV PK and PK analysis data selection data files.

Table 5 Summary of weight, by study and overall, for all study participants in the PK analysis data selection data file

Weight (kg)	N	Mean	SD	Median	Min	Max
EP0008	342	61.5	13.4	60.0	39.8	119
SP754	276	83.8	21.5	81.9	39.0	188
SP755	284	73.6	17.2	71.0	39.0	149
SP847	47	26.8	17.7	20.9	5.90	72.9
SP1047	32	32.0	19.4	28.8	6.50	75.6
SP848	166	36.8	20.6	32.8	5.70	140
SP0969	143	40.9	19.3	40.0	11.5	95.0
SP0966	50	29.1	18.4	23.7	10.5	97.8
EP0060	95	33.3	23.7	26.5	4.80	112
SP0982	98	69.8	21.1	70.0	20.0	127
SP0967	122	11.4	3.86	11.0	4.10	23.8
Overall	1655	55.7	28.5	57.5	4.10	188

Table 6 Summary of age, by study and overall, for all study participants in the PK analysis data selection data file

Age (years)	N	Mean	SD	Median	Min	Max
EP0008	342	32.6	11.9	30.0	16.0	67.0
SP754	276	38.2	12.4	38.0	16.0	71.0
SP755	284	36.7	12.1	36.0	16.0	67.0
SP847	47	7.04	5.12	6.00	0.500	17.0
SP1047	32	8.94	5.32	9.30	0.600	17.3
SP848	166	10.1	4.45	10.4	0.600	17.9
SP0969	143	10.6	3.64	11.0	4.00	16.0
SP0966	50	9.00	4.84	7.46	1.58	17.8
EP0060	95	8.25	4.99	8.42	0.167	16.6
SP0982	98	27.8	13.6	25.0	4.00	66.0
SP0967	122	2.11	1.15	2.08	0.0800	3.92
Overall	1655	24.3	16.7	22.0	0.0800	71.0

Table 7 AED coadministration distribution, by study and overall, for all study participants in the PK analysis data selection data file

Study	Carbamazepine	Phenytoin	Phenobarbital/Primidone	Inducer AEDs	Valproate
EP0008	162 (47.4%)	41 (12%)	32 (9.4%)	203 (59.4%)	160 (46.8%)
SP754	68 (24.6%)	54 (19.6%)	13 (4.7%)	126 (45.7%)	45 (16.3%)
SP755	140 (49.3%)	23 (8.1%)	15 (5.3%)	161 (56.7%)	89 (31.3%)
SP847	4 (8.5%)	4 (8.5%)	4 (8.5%)	12 (25.5%)	10 (21.3%)
SP1047	1 (3.1%)	0 (0%)	1 (3.1%)	2 (6.2%)	3 (9.4%)
SP848	72 (43.4%)	42 (25.3%)	39 (23.5%)	99 (59.6%)	100 (60.2%)
SP0969	71 (49.7%)	5 (3.5%)	15 (10.5%)	82 (57.3%)	96 (67.1%)
SP0966	1 (2%)	1 (2%)	2 (4%)	3 (6%)	27 (54%)
EP0060	17 (17.9%)	3 (3.2%)	5 (5.3%)	23 (24.2%)	37 (38.9%)
SP0982	11 (11.2%)	3 (3.1%)	6 (6.1%)	19 (19.4%)	51 (52%)
SP0967	51 (41.8%)	4 (3.3%)	26 (21.3%)	66 (54.1%)	67 (54.9%)
Overall	598 (36.1%)	180 (10.9%)	158 (9.5%)	796 (48.1%)	685 (41.4%)

Methods

An existing LCM popPK 1-compartment model (CL0447–Part III) that comprised first-order absorption (oral)/zero-order input (iv) was extended with data from study participants from SP0967.

The developed final popPK model comprised first order absorption, single compartment distribution, and first order elimination components, where CL, central volume (Vc), and absorption rate constant (Ka) were estimated with exponential inter-individual variability (IIV). Offdiagonal IIV elements were assessed but led to highly over-parameterized models and therefore only diagonal IIV estimates were estimated. The effect of weight on CL and Vc was quantified using allometric equations where the exponent for weight on CL was freely estimated, and the exponent for weight on Vc was fixed to the theoretical value of 1. With the inclusion of data from SP0967 the suitability of the previously developed structural model was reassessed and updated. In addition, it was reassessed whether allometric exponents should be estimated to adequately describe the data, or whether they could be fixed to theoretical values.

A stepwise covariate modelling search was performed to assess potential covariates associated with the CL of LCM. Forward covariate selection was performed using a p-value of $p<0.05$ ($\chi^2_{p=0.05,v=1}=3.84$) as the selection criterion. Subsequently, backwards deletion was performed using a p-value of $p<0.001$ ($\chi^2_{p=0.001,v=1}=10.83$) as the selection criterion. The following covariates were identified to influence CL in the previous modelling, and hence were also included in the current analysis: Asian race, inducer coadministration (carbamazepine [CBZ], phenytoin [PHT], phenobarbital [PB]), valproic acid (VPA) coadministration, post conceptual age (PCA), sex, eGFR.

The effect of PCA on the exposure was of special interest for the paediatric population, and the applicability of a sigmoid-Emax maturation function of PCA on CL was investigated. Body weight (at baseline) was included a priori in the base model according to allometric theory on CL and Vc, scaled to a typical adult male value of 70 kg.

Goodness of fit plots and VPCs were used to ascertain the ability of the final popPK model to adequately describe and simulate observed LCM concentrations. Parameter precision and derive confidence intervals the SIR procedure as implemented in Perl-speaks-Nonmem was applied to provide an estimate of parameter precision.

Simulations were performed to assess if predicted LCM paediatric C_{ss} fall within the range of adult values (without any comedication), and if these values are comparable between oral and iv dosing in children for the same dosing regimen. In addition, the impact of comedication was investigated, comparing a monotherapy setting (by switching off any covariate related to comedication with AEDs) with the results of simulations of the whole population with add-on treatment including subjects with and without inducer AED coadministration. The NHANES DXA database [18] was used to provide linked demographic variables (age and weight) to drive the simulations (*Figure 1*).

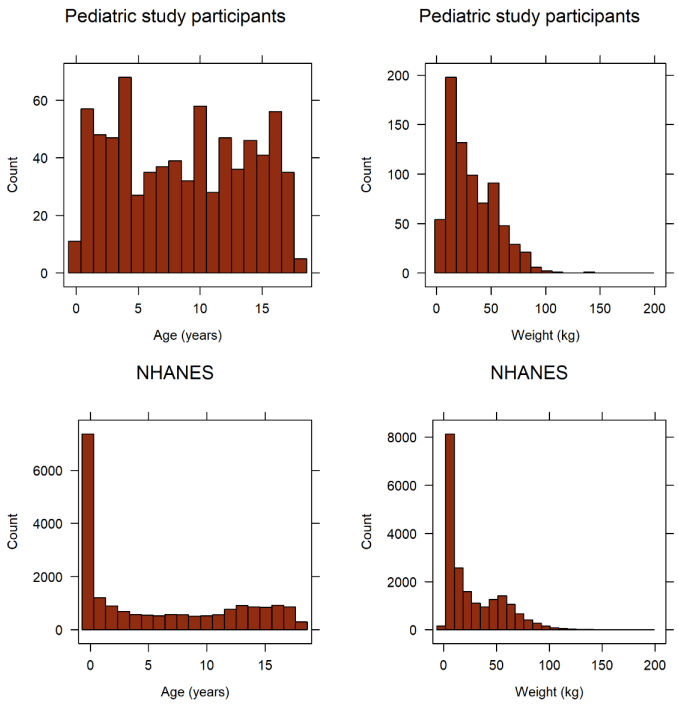


Figure 1 Distribution of weight (right) and age (left) in the children from CL0447-Part IV (top) and from the NHANES database (bottom)

Results

Observed LCM plasma concentrations used in the popPK analysis is presented in *Figure 2*.

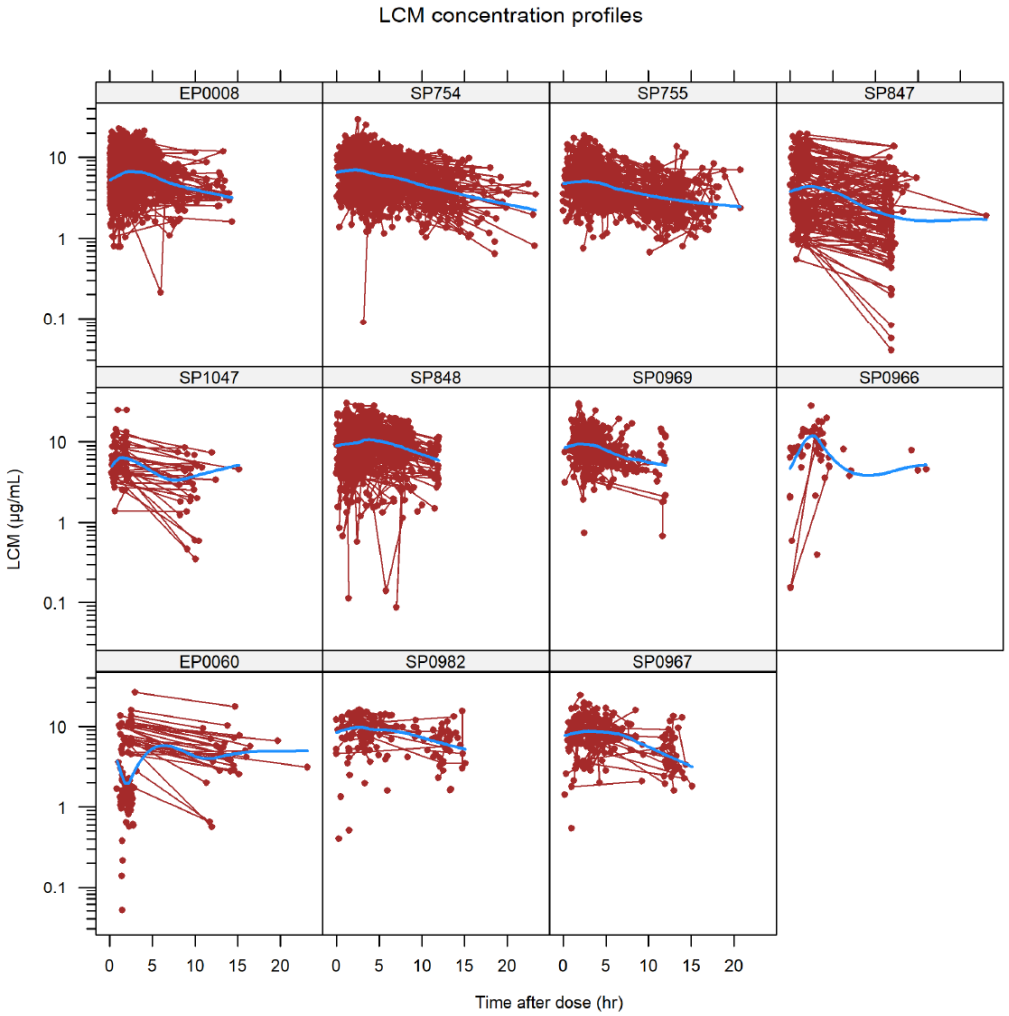


Figure 2 Overlaid LCM concentration profiles by time after dose on logarithmic scale stratified by Study. Red lines and dots: individual connected observations, blue lines: loess smooths though the data.

Graphical analyses (*Figure 3* and *Figure 4*) and VPCs (*Figure 5*) indicated that the 1-compartment popPK model with first-order absorption (oral)/zero-order input (iv) was appropriate for describing the available LCM PK data. Nonlinear Mixed Effects Modelling parameter estimates for the final PK model are provided in *Table 8*.

Table 8 NONMEM parameter estimates for the final population PK model

Parameter	Estimate (95% CI)	IIV (%)	Shrinkage[a] (%)
CL (L/hr)	1.74 (1.50, 1.99)	26.0	15.7
Vc (L)	45.4 (40.1, 50.7)	48.6	51.5
Ka (1/hr)	1.50 (1.27, 1.73)	63.8	74.5
F (fraction)	0.847 (0.707, 0.927)	-	-
Allometric scaling CL	0.467 (0.407, 0.528)	-	-
Allometric scaling Vc	1.00 Fixed	-	-
Hill coefficient age on CL	0.732 (0.501, 0.962)	-	-
Age (year) at 50% maturation on CL	0.709 (0.124, 1.29)	-	-
Change in CL (%) with China on CL	-15.1 (-18.3, -11.8%)	-	-
Change in CL (%) with Japan on CL	-12.1 (-16.4, -7.6)	-	-
Change in CL (%) with IND on CL	28.6 (24.7, 32.6)	-	-
Proportional RUV (fraction)	0.211 (0.198, 0.224	-	12.8
Additive RUV (µg/mL)	0.340 (0.222/0.459)	-	12.8

CI=confidence interval; CL=clearance; F=bioavailability; IIV=inter-individual variability; IND=inducer coadministration; Ka=absorption constant; NONMEM=nonlinear mixed effects modeling; PK=pharmacokinetic; RUV=residual unexplained variability; Vc=central volume

[a] Shrinkage calculated using the standard deviation.

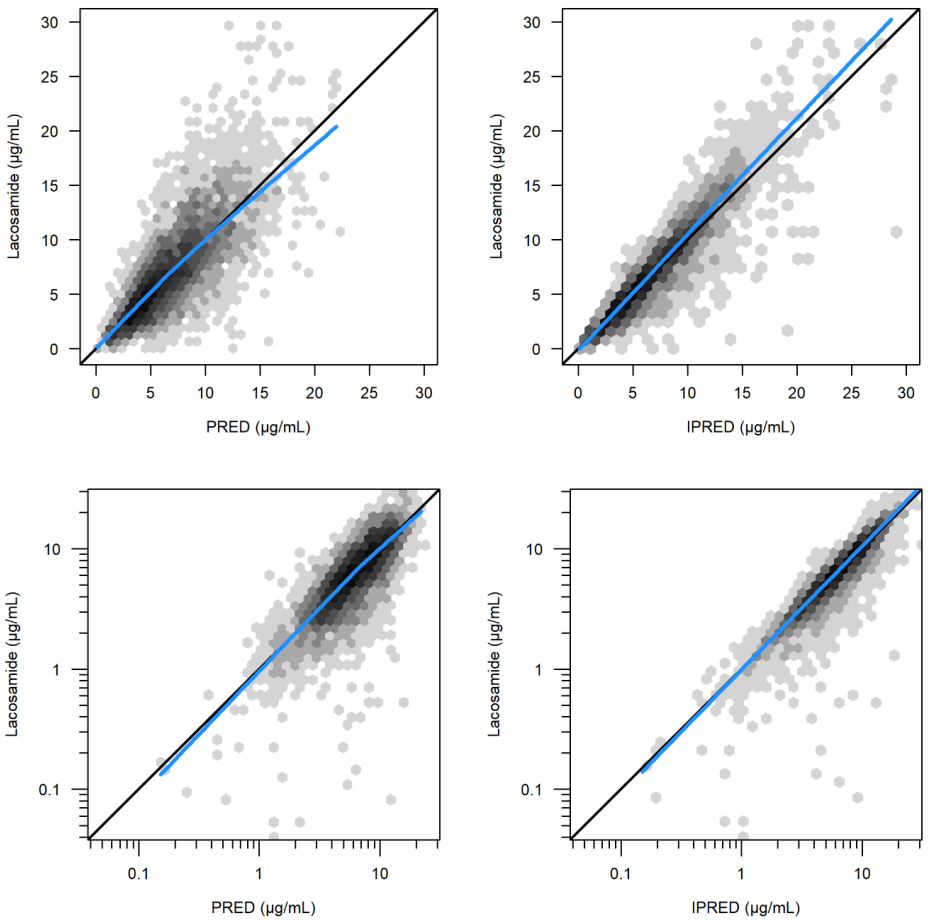


Figure 3 Lacosamide goodness of fit plots for the final population PK model. The black lines are lines of identity, the blue lines are loess smoothers through the data. PRED: population predictions, IPRED: individual predictions. The darkness of the hexagons corresponds to the data density at that location.

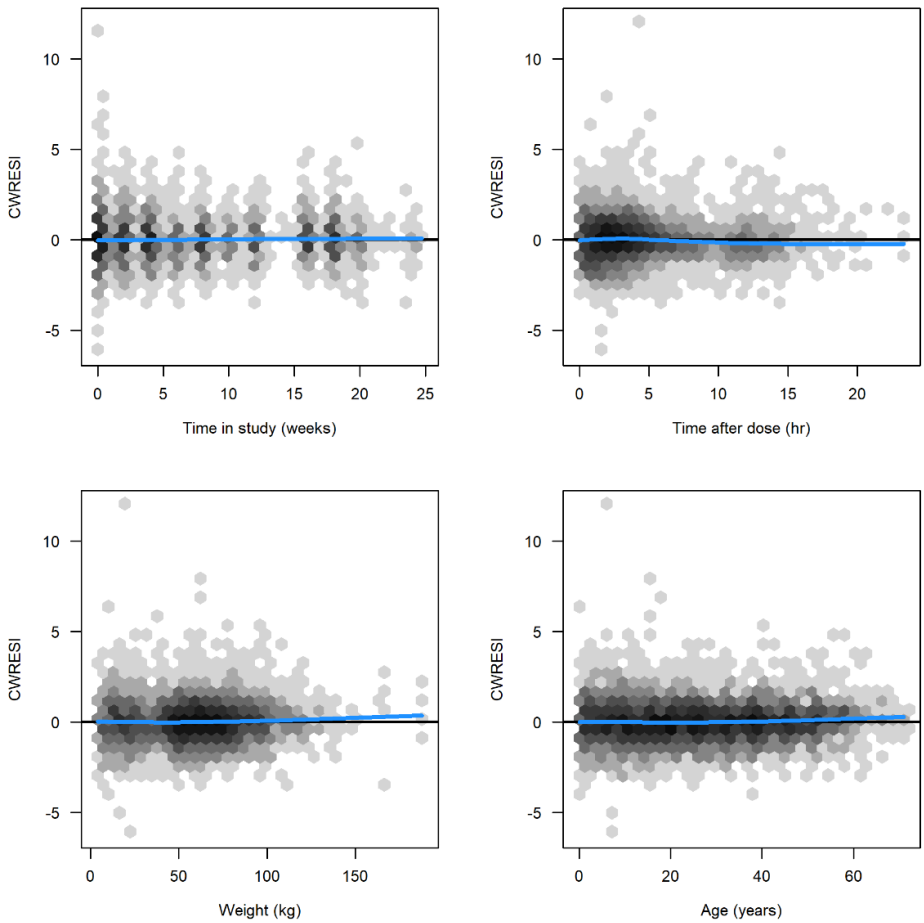


Figure 4 Lacosamide goodness of fit plots using conditional weighted residuals for the final population PK model. The black lines are zero lines, the blue lines are loess smoothers through the data. Conditional weighted residuals (CWRESI) vs time in study, time after dose, body weight, and age. The darkness of the hexagons corresponds to the data density at that location.

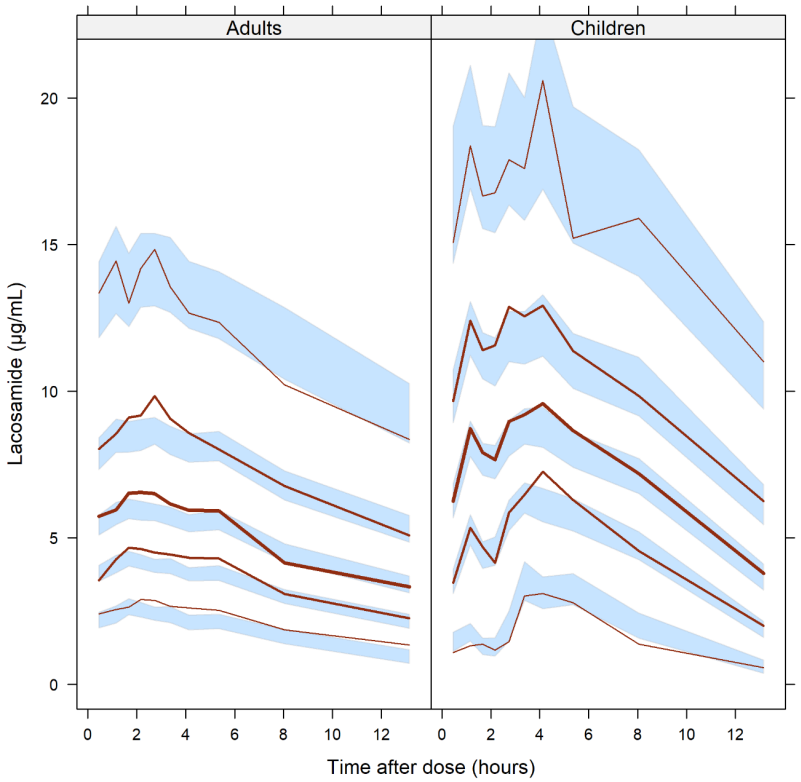


Figure 5 VPCs for the final population PK model split by adults and children. Red lines are the 5th, 25th, 50th (median), 75th and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles.

Figure 6 shows the pronounced association between CL and weight, age, and eGFR, but also shows that incorporation of the few covariate effects in the final model effectively removes the need for incorporation of further covariates like eGFR.

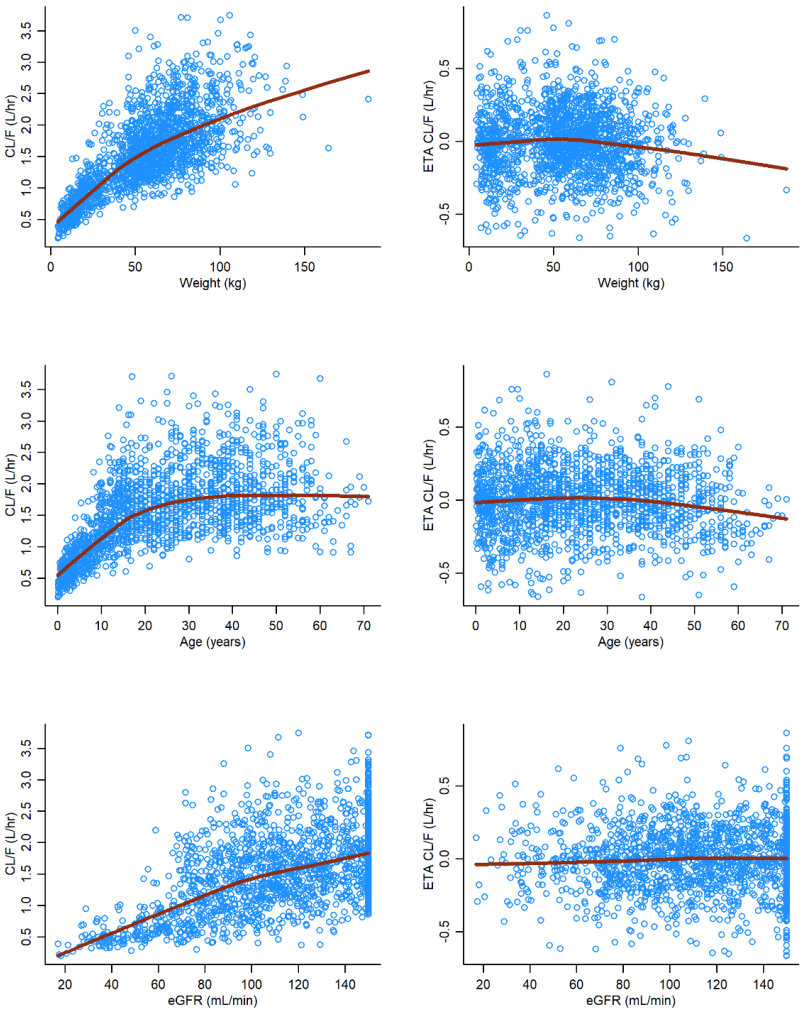


Figure 6 Relationship between the continuous covariates weight (top row), age (middle row), and eGFR (bottom row), and EBEs for CL (left column) and ETAs for CL (right column) for the final population PK model (run118)Blue markers: individual empirical Bayes estimates, red line: loess smooth

Simulations to support dose selection

Paediatric maintenance doses

The population estimates from the final popPK model were used to simulate Css values for all study participants in the NHANES database with the following dosing schedule:

- 7.5 mg/kg bid (oral) or 5 mg/kg tid (three times a day) (iv) for weight <6 kg
- 6 mg/kg bid (oral) dose for ≥6 kg and weight <30kg
- 4 mg/kg bid (oral) dose for ≥30 kg and weight <50 kg
- 200 mg bid (oral) dose for weight ≥50 kg

Simulations of the proposed weight-based doses to produce exposure equivalent to 200mg bid in adults resulted in paediatric exposures in line with adult exposures after oral and iv dosing as illustrated in *Figure 7* and *Figure 8*, respectively. Intravenous dosing resulted in slightly higher exposures due to the bioavailability of 84.7%. In all panels of the figures, the pink shaded area depicts 90% of the simulated average LCM Css over 24 hours in adults receiving LCM 200mg bid orally (without inducer AED-coadministration), and the red line and blue shaded area depict the median and 90% of the simulated paediatric Css values for monotherapy (left) and add-on therapy with inducer AEDs (right) by age (top

panels) and by weight (bottom panels). The orange circles indicate the predicted C_{ss} values for the paediatric individuals in all studies. The concentrations also fell within the same range for monotherapy and for add-on therapy with inducing AEDs; therefore, the same doses can be used regardless of concomitant inducer AED therapy.

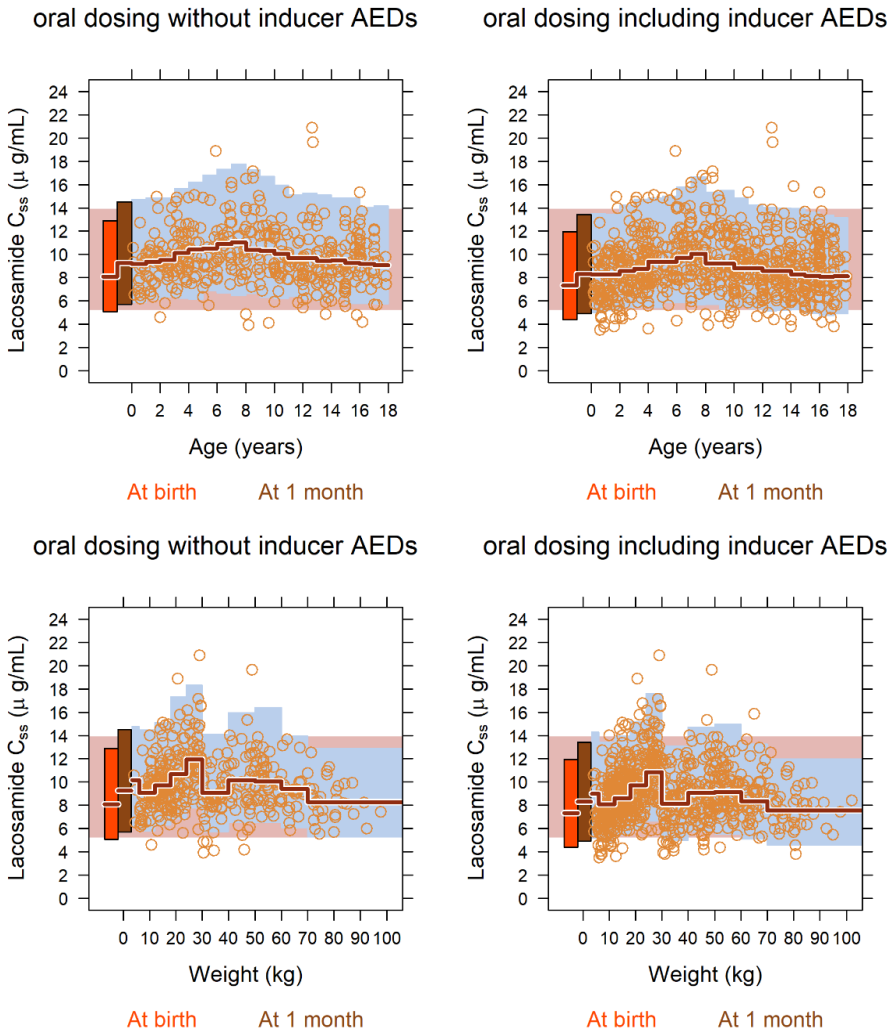


Figure 7 Predicted LCM steady state concentrations after oral administration. Bars at the left of the graphs indicate predictions at birth and at 1month. Red line and blue area: median and 90% of simulated LCM Css values for study participants <18 years of age sampled from the Nhanes database. Orange circles: individual predicted pediatric LCM Css values.

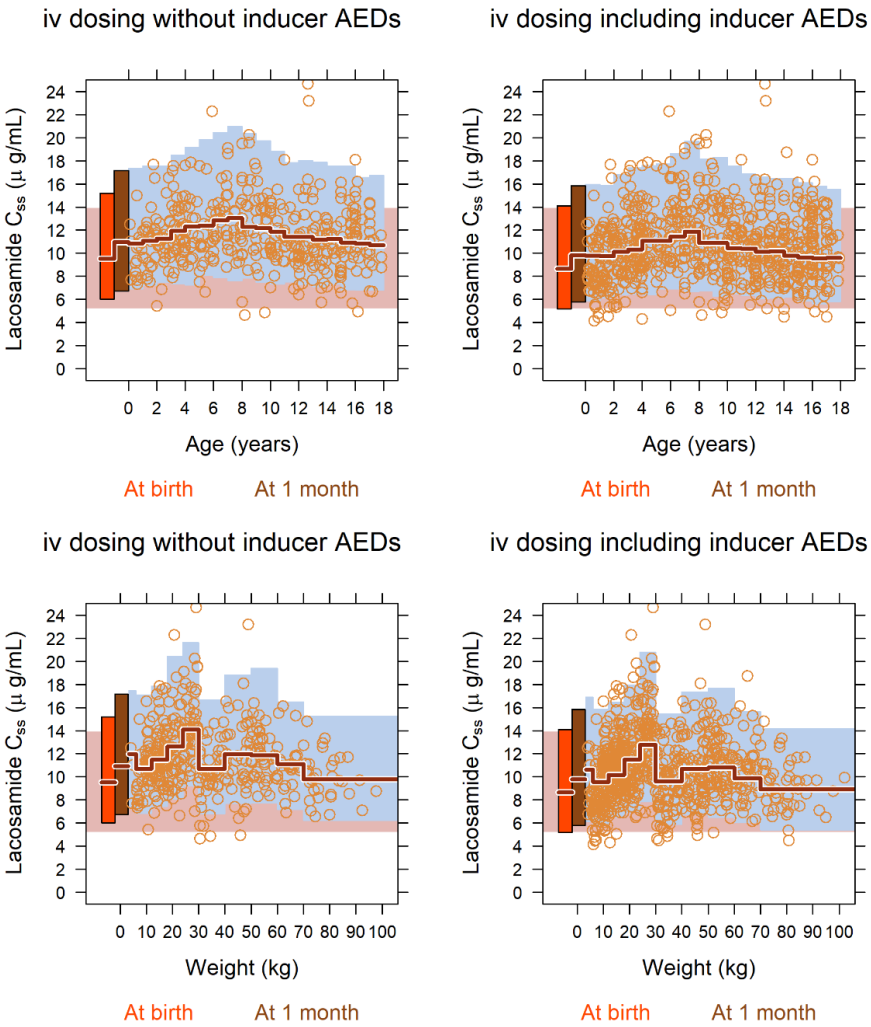


Figure 8 Predicted LCM steady state concentrations after iv administration. Note: Bars at the left of the graphs indicate predictions at birth and at 1month. Red line and blue area: median and 90% of simulated LCM Css values for study participants <18 years sampled from the Nhanes database. Orange circles: individual predicted paediatric LCM Css values.

Summary of LCM PK profile in paediatric patients ≥1 month to <4 years of age

Absorption

No specific studies have been performed to evaluate the absorption of LCM in study participants ≥1month to <4years of age who have epilepsy with POS. The observations in SP0967 that nearly all plasma concentrations were in the expected range indicate that extent of absorption of orally administered LCM in this age group was consistent with adult data.

In the popPK analysis, bioavailability was estimated at 84.7% (95% CI: 70.7%/92.7%) indicating a close correspondence in exposure between oral and intravenously dosed study participants.

Distribution

The estimate of Vc in the updated PK model was 45.4 L (normalised to a 70 kg person). This is consistent with the previously determined volume of distribution of LCM of between approximately 40 and 60L.

Metabolism

No specific studies have been performed to evaluate the metabolism of LCM in study participants ≥1month to <4years of age who have epilepsy with POS. PopPK analysis showed that co-administration with hepatic enzyme inducing anti-epileptic drugs (CBZ, PHT, PB, and/or primidone) resulted in a 22.2% decrease in exposure.

Excretion

The estimate of plasma clearance in CL0447-Part IV was 1.74 L/h (normalised to a 70 kg person). Due to maturation of the elimination processes, clearance increases with age with 50% of the maximum value reached at 0.709 years post-conceptional age. The typical plasma clearance was estimated to be 0.22 L/h, 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 3.5 kg, 10 kg, 20 kg, 30 kg and 50 kg, respectively.

Influence of intrinsic factors

Age and gender

A maturation function for CL could be defined i.e. a relation between post-conceptional age and CL. This maturation results in a lower clearance in the youngest patients than expected based on weight alone. No effect of gender was detected.

Race

According to the popPK analysis influence on CL was detected for Japanese nationality (13.8% increase in exposure) and Chinese nationality (17.8% increase in exposure). This is consistent with previous results. No dose adjustment is considered necessary based on race.

Body weight

The results of popPK analysis indicated that the PK of LCM is associated with body weight in an allometric fashion with an estimated exponent on CL of 0.467 and a fixed exponent on Vc of 1.

Renal impairment

In the popPK analysis, the eGFR using the Schwartz bedside equation was not found to significantly influence CL of LCM, but SP0967 did not include any study participant with severe renal impairment.

Hepatic impairment

The effect of hepatic impairment was not evaluated in study participants with epilepsy ≥1 month to <4 years of age.

2.4.3. PK/PD modelling

No PK/PD modelling data have been provided in this submission.

2.4.4. Discussion on clinical pharmacology

Study SP0967

The starting dose was 4 mg/kg/day (2 mg/kg bid) with titration increments of 2 mg up to a maximum dose of 12 mg/kg/day. Sparse PK data was collected in study SP0967 with two PK samples per patients at day 17 and 27, respectively. Due to the sparseness of data, descriptive PK should be interpreted with caution. Nonetheless, plasma concentrations from 106 patients at day 27 indicate that the plasma concentration increase with increasing dose, as expected. It is also apparent that across all age groups, close to 50% of patients did not reach maximum dose in the titration phase.

PopPK analysis

A pooled popPK analysis including 1655 epilepsy patients over the age range 1 month to 71 years. The pooled analysis approach is supported, although the MAH was asked to provide one summary table on number of patients ≥1 month to <4 years including a description of the demography and dose history in the target age group. In the response to questions, the MAH provided information that in the age group 2-4 years, 96 patients were included in the popPK analysis. The mean weight, height, and body mass index were 13.8 kg [min 7.0 kg, max 22.8 kg], 81.0 cm, and 15.3 kg/m^2, respectively. The median overall duration of LCM exposure was 41 days (range: 1 to 722 days). The median of the minimum dose at time of PK sampling was 5.00 mg/kg (range: 0.8 to 6.0 mg/kg), and the median of the maximum dose at time of PK sampling was 5.00mg/kg (range: 1.0 to 6.0 mg/kg).

Adequate model development and evaluation tools have been used. The popPK model for LCM have evolved over time and previous versions of the model were assessed by CHMP. In the present analysis important elements for the target population such as allometric scaling and a maturation function have investigated and included. The maturation function used is based on PCA (PCA is calculated by starting with the chronological age and subtracting the number of weeks of prematurity from that age), however no age correction seems to have been made which is accepted since presumably no premature babies were included in the studies. Baseline body weight was used as a covariate, although time-varying body weight could be of relevance in a paediatric population. When time-varying body weight was tested in the popPK model, the estimated CL remained largely the same. Thus, the constant body weight covariate is accepted.

Although model evaluation indicates an adequate model fit to data, to be able to fully assess the model predictions for children ≥1 month to <4 years of age the MAH was asked to provide VPCs for this age group, stratified on several age groups and in addition by different weight groups. Graphs with adequate stratifications have been provided, however slight modification to the graphs was requested to fully assess the model performance. The requested graphs were provided in response to questions and the model performance is acceptable. However, the MAH argues that the estimated bioavailability (84%) is an artefact (further discussed under IV dosing), thus the actual values of all parameter estimates are questioned and should be interpreted with caution. Nevertheless, the final PK model describe the data well and the predicted exposures (C_{ss}) are considered adequate.

Simulations to support dose selection

The following dosing schedules (maximum dose) were found to best match the adult exposure:

- 7.5 mg/kg bid (oral) or 5 mg/kg tid (iv) for weight <6 kg
- 6 mg/kg bid (oral) dose for ≥6 kg and weight <30kg
- 4 mg/kg bid (oral) dose for ≥30 kg and weight <50 kg
- 200 mg bid (oral) dose for weight ≥50 kg

However, the 7.5 mg/kg bid and 5 mg/kg tid (iv) dosing regimen is higher than the maximum dose (6 mg/kg bid) in study SP0947. Exposure predictions (i.e. simulations) for the dosing regimen used in study SP0947 could not be found. Therefore, to support the proposed posology, the MAH provided exposure simulations for both the dosing regimen used in study SP0976 and the proposed dosing regimen, including the dose level 5 mg/kg ≥20 kg and weight <30kg. For patients <6 kg, comparisons of exposures above and below the reference exposure interval were provided for both 7.5 mg/kg bid and 6 mg/kg bid, respectively.

All adult reference exposure intervals are representing the adult exposure reference interval given monotherapy oral 200 mg bid which is not considered representative for adjunctive therapy as well as iv administration. In addition, it is noted that different adult reference exposure ranges were used in the application for POS patients 4 to 16 years (EMEA/H/C/000863/II/0065/G). Thus, it is difficult to evaluate

the adequacy of the proposed posology in new paediatric population. When an extrapolation approach based on PK matching is employed, it is of essence that adequate exposure matching is made and that the target exposure range (i.e. adult reference range) is clearly reported. In general, when extrapolating efficacy it is important to compare the paediatric exposure to the adult exposure range where efficacy has been established. The MAH has clarified that the reference exposure interval is based on simulations from the pooled adult and paediatric data (popPK analysis - report CL0447), given 200 mg bid adjunctive therapy to adult patients. These simulations result in a reference interval for Cav of 5.27-13.78 µg/mL, while a reference interval of 4.51 – 11.7 µg /L was used in the previous extension of indication for 4-16 year old patients. As it is not acceptable that different adult exposure intervals are used for patients 4-16 year-olds and 1 month to 4 years and as it is not clear whether the 7.5 mg/kg dose in patients <6 kg is justified given if the comparison is made to the 4.51 – 11.7 µg /L interval, the MAH was asked to provide updated exposure comparisons to the previously used interval (4.51 – 11.7 µg /L). The MAH provided exposure comparisons with the previously used interval, and as expected the predicted paediatric exposure exceed the old reference interval. It is acknowledged that the final popPK model is based on paediatric and adult data, and the estimated clearance in this model is lower (1.76 vs 1.92) leading to a higher exposure for all age groups. It is further reassuring that the reference interval for the adult monotherapy setting was approximately 9 – 19 µg /L (EMEA/H/C/000863/II/0065/G) which is overlapping with the present paediatric exposures. The CHMP agrees that the final model describes adult and paediatric data well and is acceptable for the purpose of exposure matching, however it would have been valuable to have a reference interval that is based on the adult data where efficacy has been established.

In the previous extension of indication to 4-16 years, an increased C_{max},iv of 9-21% compared to C_{max},oral was accepted. Whereas the AUC remained fairly similar between iv and oral administration (assumption of 100% oral bioavailability), the present popPK analysis and subsequent simulations suggest that the oral bioavailability is 84% and thus the total concentration (C_{ss}) is considerably higher with iv compared to oral administration in the paediatric population. The MAH was asked to discuss the discrepancy in bioavailability between the two paediatric extensions of indication. It argued that the estimated oral bioavailability of 84% is an artefact and that the previously established 100% bioavailability based on clinical pharmacology studies is more accurate. This is agreed, and it is also noted that the estimated oral bioavailability is informed by only 28 patients with very sparse data (study EP0060) which give very limited information.

Since the model predictions are reasonable despite the miss-specified bioavailability estimate, other estimates in the model have compensated for the miss-specification and thus all parameter estimates, in particular CL, should be interpreted with caution. In conclusion, the predicted exposures after IV administration are not reliable and can thus not be used to support IV dosing. Nonetheless, given the same reasoning as used in the age group 4-16 years, under the assumption of 100% oral bioavailability, the comparison between oral and IV exposure indicate a slightly higher Cmax with IV administration but similar AUC. In addition, the study EP0060 where IV treatment was used has been reviewed in a P46 procedure (EMEA/H/C/000863 P46 037) and no safety concerns were identified.

PK in target population

No major deviations from previous knowledge of LCM PK profile were detected in the age group ≥1 month to <4 years. The detection of a maturation function for CL indicates that not only body weight can explain differences in CL in the youngest patients. The estimated maturation showed that 50% of adult CL is reached at 0.709 years. The typical plasma clearance was estimated to be 0.22 L/h, 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 3.5 kg, 10 kg, 20 kg, 30 kg and 50 kg, respectively.

2.4.5. Conclusions on clinical pharmacology

The PK of LCM in the age group ≥1 month to <4 years of age has been investigated in a pooled popPK analysis. No unexpected differences in PK from older children and adults were detected.

The dose regimens in POS patients ≥1 month to <4 years are supported by simulations from the popPK analysis with the aim to match adult reference exposure levels. Although there are discrepancies between reference intervals in different applications, it is agreed that the proposed dosing recommendation in paediatric patients match the exposure of the adult patients sufficiently well. It is noted that, due the extrapolation of efficacy under 2 years of age not supported (see section Benefit Risk assessment and discussion below), the dose recommendation for patients <6 kg is not relevant.

2.5. Clinical efficacy

Background

The Guideline on clinical investigation of medicinal products in treatment of epileptic disorders states that efficacy trial results of adults with focal epilepsy can be extrapolated to children and adolescents provided that the PK/PD relationship in adults is established and that the dose regime proposed in children and adolescents results in similar exposure levels as in adults in all age categories. However, the same guideline also emphasizes that efficacy cannot be extrapolated in the very young children due to the uncertainty of impact of the developing brain on the disease and response. Once efficacy has been shown in the older paediatric population, short term assessment of response by using video electroencephalogram (EEG) monitoring may be sufficient (CHMP/EWP/566/98 Rev.3).

In 2011, the MAH sought advice from the EMA to discuss clinical development to support indication of LCM for monotherapy of POS with or without secondary generalization in patients with epilepsy down to 1 month. It was concluded that it was not possible to extrapolate to the youngest group aged ≥1 month to <2 years group merely from PK and literature; at least short-term pivotal data was required. The conclusion was based on differences and possible changes in receptor function and affinity due to maturation (EMA/CHMP/SAWP/528383/2011).

The MAH has discussed the extrapolation of adult data to paediatric population in association with another antiepileptic compound brivaracetam (EMEA 000332-PIP01-08-M06), and in that context it was agreed that the treatment of POS with or without secondary generalization in paediatric participants down to 2 years of age with epilepsy can be based on extrapolation of adult efficacy data and would be supported by PK data from paediatric participants and by relevant sufficient safety data.

Subsequently, it has been put forth by paediatric epileptologists and researchers, during the Epilepsy Foundation Research Roundtable for Epilepsy in May 2020 with European Medicines Agency and FDA representatives in attendance, that the underlying pathophysiology of POS, seizure characteristics and symptoms, EEG features, disease progression, and treatment response are similar in patients ≥1 month to <2 years to those in older, as demonstrated by the data shared at the occasion. This view would support the possibility that no separate efficacy studies (which would be very difficult to accomplish) would be needed for these young children as efficacy can be extrapolated in children ≥1 month to <2 years of age. In these circumstances, evidence of safety would need to be independently established in the infant age group and could not be extrapolated.

2.5.1. Main studies

Study SP0967: A phase 3 multicentre, 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

Study participants

The patients 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)

Specific rules were applied for withdrawal from the study on the basis of epileptic state, AEs, need for medication or compliance issues, as well as signs of potential drug-induced liver injury.

Treatments

The double-blind randomization in a 1:1 ratio was done at visit 3 after completion of end-of-baseline video-EEG and ascertainment of met selection criteria, with age stratification into four categories (≥1 month to <6 months; ≥6 months to <1 year; ≥1 year to <2 years; ≥2 years to <4 years). The study medication was LCM as oral solution (10mg/mL) and matching placebo oral solution twice a day (with approximately 12-hour intervals). The medication dosing according to weight was defined specifically for the titration, tapering, or transition periods, depending on whether the patient entered later on the open label extension study.

Objectives

The primary objective was to evaluate the efficacy of LCM administered concomitantly with 1 to 3 AEDs in patients ≥1 month to <4 years of age with epilepsy who currently have uncontrolled 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 PK of LCM in children ≥1 month to <4 years of age.

Outcomes/endpoints

The efficacy variables were based on video-EEGs (up to 72 hours). POS frequency was based on electrographic seizures for infants ≥1 month 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):

- 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):

- 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

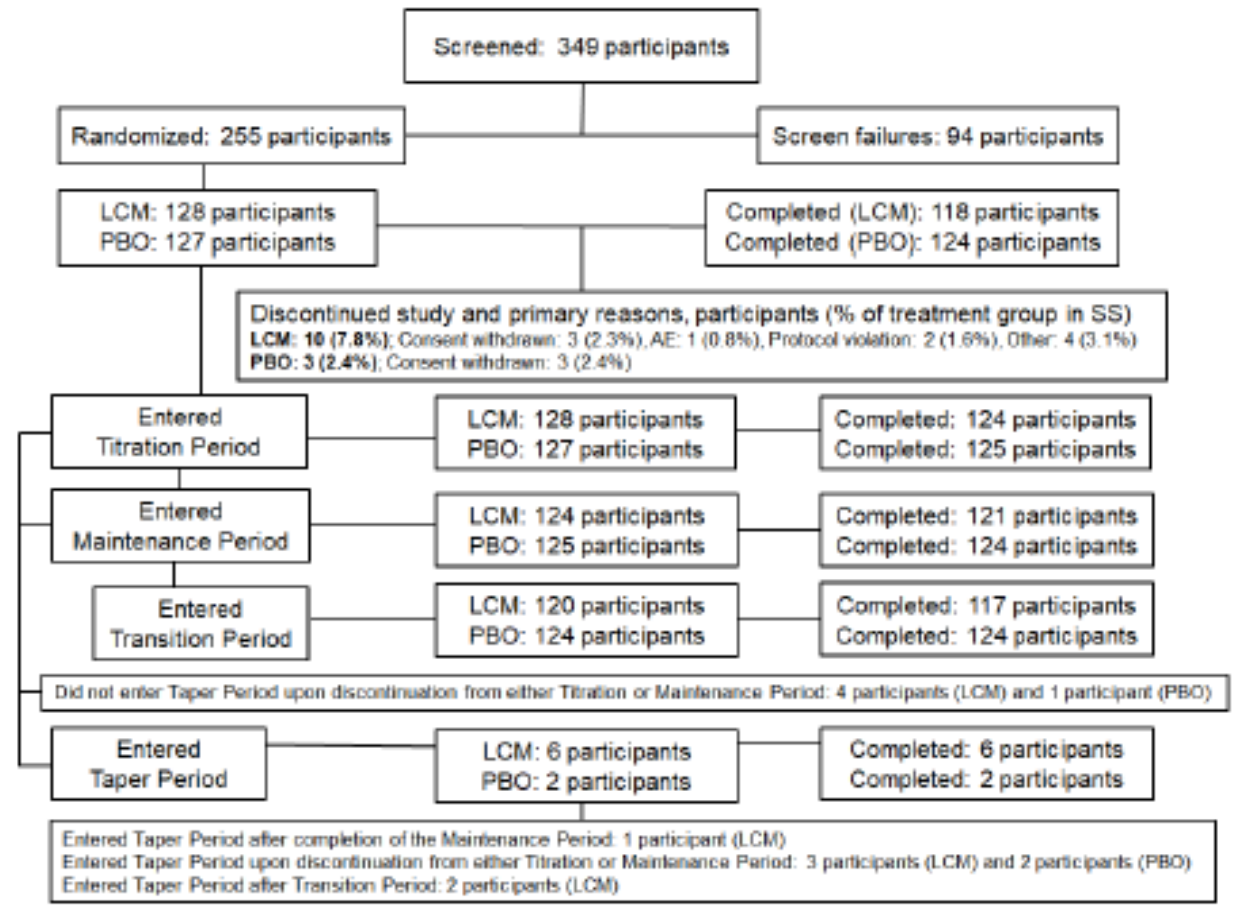
- proportion of patients who experienced a ≥25% to <50%, 50% to 75%, or >75% reduction in ADF of electrographic POS from the end-of-baseline period video-EEG to the end-of-maintenance period video-EEG
- proportion of patients who experienced no change in ADF of electrographic POS (between <25% reduction 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

Sample size

The planned number of patients to be enrolled was 244 (122 per treatment arm). Overall, 255 patients were randomized: 128 to LCM and 127 to placebo, and all took at least 1 dose of study medication.

Results

Participant flow



AE=adverse event; LCM=lacosamide; PBO=placebo; SS=Safety Set

Baseline data

Table 9: 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)

Table 10: Baseline seizure characteristics (SS)

Variable Statistic	PBO N=127	LCM N=128	All study participants N=255
History of withdrawal seizures, n (%)	10 (7.9)	11 (8.6)	21 (8.2)
History of status epilepticus, n (%)	12 (9.4)	7 (5.5)	19 (7.5)
Epilepsy duration (years), n [a]	127	128	255
Mean (SD)	1.446 (1.003)	1.248 (0.916)	1.347 (0.964)
Median (min, max)	1.340 (0.06, 3.69)	1.005 (0.05, 3.86)	1.110 (0.05, 3.86)
Age at diagnosis (years), n	127	128	255
Mean (SD)	0.762 (0.792)	0.886 (0.946)	0.824 (0.873)
Median (min, max)	0.454 (0.00, 3.33)	0.426 (0.00, 3.52)	0.438 (0.00, 3.52)

LCM=lacosamide; max=maximum; Min=minimum; PBO=placebo; SD=standard deviation; SS=Safety Set
Note: Percentages were based on the number of study participants in the SS.
[a] Relative to date of informed consent.

Table 11: Number of 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 12: Concomitant AEDs used by ≥3% 0f patients in treatment groups (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.

Statistical methods

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 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 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.

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 analysed using analysis of covariance (ANCOVA) with terms for treatment, age stratification categories, and centre (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 $100\times(1-\exp[LSM_{LCM}-LSM_{placebo}])$. The treatment estimates (LSMs and 95% 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.

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.

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%.

Table 13: 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

Table 14: 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

Table 15: Summary of proportional responders by age group (FAS)

	≥1 month to <6 months		≥6 months to <1 year		≥1 year to <2 years		≥2 years to <4 years	
Statistic	PBO N=8	LCM N=8	PBO N=13	LCM N=18	PBO N=38	LCM N=36	PBO N=68	LCM N=66
n [a]	8	7	12	16	35	32	65	61
Responder, n (%)	2 (25.0)	4 (57.1)	3 (25.0)	4 (25.0)	14 (40.0)	14 (43.8)	26 (40.0)	26 (42.6)
Nonresponder, n (%)	6 (75.0)	3 (42.9)	9 (75.0)	12 (75.0)	21 (60.0)	18 (56.3)	39 (60.0)	35 (57.4)

ADF=average daily frequency; EEG=electroencephalogram; EOB=End-of-Baseline; EOM=End-of-Maintenance; FAS=Full Analysis Set; LCM=lacosamide; PBO=placebo; POS=partial-onset seizure(s)
Note: Percentages were based on the number of study participants in the FAS with response data.
Note: A responder was a study participant experiencing a ≥50% reduction in ADF of electrographic POS recorded on the EOM Period video-EEG compared to EOB Period video-EEG; otherwise a study participant was a nonresponder.
Note: Study participants with 0 seizures at EOB Period were considered nonresponders.
[a] The analysis consisted of all study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

<u>Study EP0034</u>: a Phase 3, multicentre, open-label, long-term extension study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric study participants (≥1 month to ≤17 years of age) with POS

EP0034 is an ongoing, long-term safety and efficacy open-label extension study for study participants who have completed SP0967 or SP0969.

A total of 517 patients had been enrolled, including 195 patients <4 years of age (all from SP0967) and 322 participants ≥4 years of age (all from SP0969). The main efficacy variable used for the interim analysis was based on seizure diary data. EP0034 efficacy data for which baseline data are required, such as seizure diary data, are only available for participants ≥4 years of age (entering from SP0969), since no baseline seizure diary was collected in SP0967.

Overall, the percentage of seizure-free days and the proportion of all patients achieving seizure-free status generally increased over time. The majority of patients entering from SP0969 (all ≥4 years of age) were 50% responders from the ≤3 month time interval onward in the study (range: 50.2% to 69.3%). The proportion of 50% responders and 75% responders from Baseline to the Treatment Period was 50.2% and 31.8% respectively. For patients entering from SP0969, a reduction in seizure frequency per 28 days was also observed during the Treatment Period. Results of the Clinical and Caregiver Global Impression of Change scales and, to a lesser extent, the Pediatric Quality of Life Inventory indicate that patients improved over the course of the study.

The Clinical and Caregiver Global Impressions of Change results support that the majority of study participants improved over the course of the study. In the target population of ≥1 month to <4 years, the proportion of study participants considered by the investigator to have improved generally increased over the course of the study (range: 85.4% to 95.0%) and considered by the participants' caregiver to have improved generally increased over the course of the study (range: 89.2% to 95.0%).

The Pediatric Quality of Life Inventory results showed small positive mean changes in the majority of the subscale scores and the total score from Baseline to Last Visit, suggesting improvement, and small negative mean changes in scores for the Physical components, suggesting worsening. However, these changes were associated with large variability across time points.

Study SP848: a Phase 2, open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children (≥1 month to ≤18 years of age) with epilepsy

SP848 is an ongoing, long term safety and efficacy open-label extension study for paediatric patients with POS from SP847, participants with epileptic syndromes associated with generalized seizures from SP0966, patients ≥1 month to <18 years of age with epilepsy who were administered iv LCM from EP0060, and from patients who had enrolled directly without previous participation in a LCM clinical study (patients from SP0966 were excluded from the interim analysis since they do not provide data on POS in support of this application.

A total of 323 patients started in the study and were treated with LCM, including 37 participants ≥1 month to <4 years of age.

Overall and across age groups, reduction in seizure frequency per 28 days was observed during the Treatment Period. The majority of study participants were 50% responders after 3 months and for the duration of the study. The overall proportion of 50% responders and 75% responders from Baseline to the Treatment Period was 53.7% and 40.4% respectively. In addition, the proportion of participants with seizure free status for at least 1 of the specified time intervals during the Treatment Period was 44.4%. Comparing across age groups, the highest proportion of 50% responders, 75% responders, and participants achieving seizure free status from Baseline to the Treatment Period were in the ≥1 month to <4 years group compared with the ≥4 to <16 and ≥16 years age groups.

Results of the Clinical and Caregiver Global Impression of Change support that study participants improved over the course of the study. The Pediatric Quality of Life Inventory results support that study participants' health-related quality of life remained stable over the course of the study.

Supportive study

Study SP0969: 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 ≥4 years to <17 years of age with partial onset seizures

SP0969 was a randomized, double-blind, placebo-controlled trial conducted at 114 sites in Europe, North America, Latin America, and the Asia Pacific region. Paediatric patients (≥4–<17 years of age) were eligible if they had a diagnosis of epilepsy with focal (partial onset) seizures, with ≥1 prior EEG and MRI/CT scans consistent with this diagnosis. Additional inclusion criteria were uncontrolled focal seizures after an adequate course of treatment (in the opinion of the investigator) with ≥2 AEDs (concurrently or sequentially); an average of ≥2 focal seizures per 28 days, with no more than 21 days without seizures in the 8-week period before entering the baseline period, and at least 2 focal seizures during the 8-week prospective baseline; and a stable dose regimen of 1 to 3 AEDs for ≥4 weeks before the baseline period and throughout the trial. Exclusion criteria included assignment to LCM in a previous trial, convulsive status epilepticus (within the previous 2 months); Lennox-Gastaut syndrome; primary generalized epilepsy; mixed seizure disorder; exclusively febrile seizures; nocturnal seizures only; or epilepsy secondary to a progressive cerebral or neurodegenerative disease.

The enrolled patients (n=343) were randomized (1:1) to adjunctive LCM/placebo. Of the patients, 306 (LCM 152 of 171 [88.9%]; placebo 154 of 172 [89.5%]) completed treatment. From baseline to maintenance, percent reduction in focal seizure frequency per 28 days for LCM (n = 170) vs placebo (n = 168) was 31.7% (p = 0.0003). During maintenance, median percent reduction in focal seizure frequency per 28 days was 51.7% for LCM and 21.7% for placebo. Fifty percent responder rates (≥50% reduction) were 52.9% and 33.3% (OR 2.17, p = 0.0006).

It is noted that the final clinical study report SP0969 was initially submitted and reviewed by the CHMP in the procedure Vimpat EMA/H/C/863/P46 028 (CHMP outcome in November 2017). The relevant findings of the study were thereafter summarised and reflected in the Product Information in the variation EMEA/H/C/000863/II/0070/G (CHMP adoption in July 2018). Adjunctive LCM was efficacious in reducing seizure frequency and was generally well tolerated in children and adolescents ≥4 years to <17 years of age (Farkas et al, 2019). The efficacy data confirmed the extrapolation approach used for the previous extension of indication in the treatment of POS in pediatric patients ≥4 to <16 years of age.

The populations in SP0967 and SP0969 showed high similarity in terms of pathophysiology, concomitant medical conditions and use of prior/concomitant AEDs. Differences were in the baseline duration, treatment duration of LCM, and efficacy endpoint measures. Exposure to LCM treatment was much longer in SP0969 than SP0967 (Maintenance Period of 10 weeks in SP0969 vs 1 week in SP0967). The efficacy endpoint in SP0969 was the change from Baseline in seizure frequency per 28 days, which was measured over 10 weeks of treatment, allowing longer time for the clinical effect to evolve. In SP0967, the primary efficacy variable was measured over a much shorter time based on 72 hours of continuous recording video-EEGs (with every attempt to obtain at least 48 hours of interpretable recording) 27 days after the Baseline Period, allowing the clinical effect a shorter time to evolve.

Table 16: Comparison of SP0967 and SP0969 populations

Population characteristics	SP0967	SP0969
Age	≥1 month to <4 years	≥4 years to <17 years
Number of concomitant AEDs	1 to 3	1 to 3
1 concomitant AED	74/235 (29.0%)	59/343 (17.2%)
2 concomitant AEDs	109/255 (42.7%)	160/343 (46.6%)
≥3 concomitant AEDs	70/255 (27.5%)	124/343 (36.2%)
Missing	2/255 (0.8%)	0
Most frequent AEDs		
Valproate	128/255 (50.2%)	166/343 (48.4%)
Levetiracetam	114/255 (44.7%)	142/343 (41.4%)
Carbamazepine	41/255 (16.1%)	89/343 (25.9%)
Topiramate	55/255 (21.6%)	82/343 (23.9%)
Dosing[a]	8 to 12mg/kg/day	<30kg: 8 to 12mg/kg/day ≥30kg to <50kg: 6 to 8mg/kg/day ≥50kg: 300 to 400mg/day
Treatment duration until primary endpoint	27 days	16 weeks
Efficacy endpoint	Average daily frequency of POS from 72-hour video-EEG (min 48 hours of interpretable recording)	Seizure frequency per 28 days from 10-week Maintenance Period

AED=antiepileptic drug; EEG=electroencephalogram; min=minimum; POS=partial-onset seizure

[a] Of note, both studies followed the dosing recommendations that approximate 200mg twice a day dosing in adults (since all participants in SP0967 were ≥6kg to <30kg)

2.5.2. Discussion on clinical efficacy

Study SP0967, a phase 3 multicentre, double-blind, randomized, placebo-controlled, parallel-group study was 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 POS and currently uncontrolled seizures. Efficacy was the primary objective of assessment, and the efficacy variables were based on video-EEG recordings, which is recommended by the EMA guideline as a complementary assessment (2018) and even as sufficient short-term assessment of response in the very young patients (2010). The video-EEG recordings were evaluated locally by the investigator, sub-investigator, or qualified designated reader, as well as centrally.

The treatment groups may be considered sufficiently balanced as for their epilepsy and the seizure types, as well as demography and the general morbidity and the concomitant medications. The results unequivocally indicate no increase in efficacy for the outcome variables in LCM users, and the results were consistently supported by all sensitivity analyses. The *post hoc* analyses of the interpretation of video-EEG data as well as the number and classification of seizures revealed a very low level of agreement between the local and central readers, which seriously undermined the conclusions that can be made. Nevertheless, as the bottom line, the results do not provide data in support of increased efficacy when LCM is used concomitantly with 1-3 AEDs in paediatric patients ≥1 month to <4 years of age with currently uncontrolled partial-onset epilepsy.

It is also notable that the number of patients in the very young age groups is limited, with 15 patients in the age group >1 month to ≤6 months, and 28 patients in the age group >6 months to<1 year. This is important especially considering the fundamental question on the similarity of pathophysiology of POS regardless of age, particularly concerning the youngest age group.

2.5.3. Conclusions on the clinical efficacy

The efficacy results provided by the randomized controlled trial SP0967 and the open label extension studies do not provide data in favour of superior efficacy of LCM in paediatric patients of the age group ≥1 month to <4 years. Consequently, the CHMP is of the view that the extension of indication cannot be based on clinical efficacy data.

2.6. Clinical safety

Introduction

The safety overview is based on clinical studies SP0967 with initially 255 patients, EP0034 with 517 patients (195 patients in the relevant age group), SP847 SP848 with 324 enrolled patients (37 in the relevant age group), EP0060 with 103 patients (48 patients in the age group ≥1 month to <8 years of age), and Pool SPX-1 (comprising of patients from SP846, SP848, and EP0060) including 847 patients (258 in the relevant age group with ages ≥1 month to <4 years of age). In addition to these studies, reference is made to a retrospective register study EP0147 examining the safety and tolerability of iv. LCM loading dose in neonates (<30 days) and in paediatric patients ≥30 days to <17 years of age.
The safety observations are focused on the similarity of the safety profile with adults and older children as well as absence of unexpected safety concerns in the safety database, and rationale of the study EP0147 was to study the safety of loading dose as recorded in off-label paediatric use.

The study SP847 was a multicentre, open-label, dose-titration study investigating LCM oral solution (syrup) (2mg/kg/day to up to 12mg/kg/day) as adjunctive therapy in paediatric patients ≥1 month to ≤17

years of age with uncontrolled POS, with the objectives to evaluate the safety, tolerability, and PK of LCM when added to a stable dose regimen of 1 to 3 concomitant AEDs as well as to obtain preliminary efficacy data on seizure frequency. Plasma concentrations of LCM and its major metabolite SPM 12809 were determined for characterization of steady-state PK of LCM and SPM 12809 using popPK methods.

There were 3 periods in the study (Screening Period, Treatment Period, and End-of-Study Period) with a maximum duration of treatment of up to approximately 13 weeks. Patients in SP847 had the option to enrol in the long-term, open-label study (SP848). Five patient age cohorts with uncontrolled POS on a stable dose regimen of at least 1 but no more than 3 AEDs were enrolled. They were to be on each LCM dose for at least 5 days before the dose was titrated up to the next dose. After at least 3 days on the maximum recommended dose or the maximum tolerated dose, blood samples were collected for PK analysis. Patients who withdrew from the study prior to completion of the Treatment Period completed an Early Termination Visit where blood samples were collected for the maximum tolerated dose achieved by the patient.

Patient exposure

Table 17: exposure to study medication by age groups in the study SP0967.

	≥1 month to <6 months		≥6 months to <1 year		≥1 year to <2 years		≥2 years to <4 years	
Maintenance Period Statistic	**PBO N=8**	**LCM N=8**	**PBO N=13**	**LCM N=18**	**PBO N=38**	**LCM N=36**	**PBO N=68**	**LCM N=66**
Study medication duration (days)								
n	8	8	12	17	37	34	68	65
Mean (SD)	7.5 (1.2)	7.0 (1.3)	6.8 (1.3)	6.9 (1.6)	7.0 (1.8)	7.6 (2.6)	7.4 (1.8)	7.8 (2.7)
Median (min, max)	7.5 (6, 9)	7.0 (4, 8)	7.0 (5, 9)	7.0 (3, 10)	7.0 (3, 12)	7.0 (5, 21)	7.0 (3, 12)	7.0 (4, 19)
Median total daily dose (mg/kg/day)								
n	8	8	12	17	37	34	68	64
Mean (SD)	11.3 (1.0)	10.6 (1.4)	10.7 (1.3)	10.9 (1.2)	10.8 (1.4)	11.1 (1.3)	10.9 (1.4)	10.6 (1.7)
Median (min, max)	12.0 (10, 12)	10.5 (8, 12)	10.0 (8, 12)	12.0 (8, 12)	12.0 (8, 12)	12.0 (8, 13)	12.0 (8, 12)	12.0 (4, 12)

LCM=lacosamide; max=maximum; min=minimum; PBO=placebo; SD=standard deviation; SS=Safety Set
Note: A study participant's study medication duration = (date of last dose-date of first dose) + 1.

Table 18: Exposure to study medication by age groups in the study SP848.

	≥1 month to <4 years N=37		All study participants N=323	
LCM exposure	**n (%)**	**Total participant-years exposed**	**n (%)**	**Total participant-years exposed**
>0 months	37 (100)	48.5	323 (100)	503.5
>6 months	37 (100)	48.5	283 (87.6)	495.5
>12 months	31 (83.8)	44.0	252 (78.0)	474.4
>18 months	11 (29.7)	20.4	188 (58.2)	401.4
>24 months	8 (21.6)	15.2	126 (39.0)	299.1

LCM=lacosamide; SS=Safety Set
Note: Duration of LCM exposure (days) was calculated as the date of final dose of LCM minus the date of the first dose of LCM plus 1 day.
Note: A month was defined as 28 days.
Note: Participant-years of exposure was defined as the total LCM exposure in days divided by 365.25.
Note: Percentages were based on the number of study participants in the SS.

	≥1 month to <4 years		All study participants	
	Number of study participants N= 195 n (%)	Total participant-years exposed	Number of study participants N=517 n (%)	Total participant-years exposed
>0 months	195 (100)	207.8	517 (100)	716.7
>6 months	140 (71.8)	195.2	421 (81.4)	693.8
>12 months	100 (51.3)	166.1	362 (70.0)	651.6
>18 months	73 (37.4)	134.9	323 (62.5)	607.1
>24 months	52 (26.7)	99.6	260 (50.3)	497.5

LCM=lacosamide; SS=Safety Set
Note: Duration of LCM exposure (days) is calculated as the date of last dose of LCM minus the date of the first dose of LCM plus 1 day.
Note: Participant-years of exposure is defined as the total LCM exposure in days divided by 365.25.
Note: Percentages are based on the number of study participants in the SS.
Note: A month is defined as 28 days.

Table 20: Exposure to study medication by age groups in the study EP0060.

	OLL and RxL 15 to 30 minutes		OLL and RxL 30 to 60 minutes		IIL 15 to 30 minutes		IIL 30 to 60 minutes		Overall		
Parameter	Cohort 2 ≥1 mo to <8 yrs N=1	Cohort 1 ≥8 yrs to <17 yrs N=7	Cohort 2 ≥1 mo to <8 yrs N=5	Cohort 1 ≥8 yrs to <17 yrs N=16	Cohort 2 ≥1 mo to <8 yrs N=7	Cohort 1 ≥8 yrs to <17 yrs N=7	Cohort 2 ≥1 mo to <8 yrs N=35	Cohort 1 ≥8 yrs to <17 yrs N=25	Cohort 2 ≥1 mo to <8 yrs N=48	Cohort 1 ≥8 yrs to <17 yrs N=55	All Study participants N=103
Intravenous LCM exposure duration (days)											
Mean (SD)	1.00 --	1.00 (0.00)	1.00 (0.00)	1.06 (0.25)	1.00 (0.00)	1.00 (0.00)	1.14 (0.36)	1.52 (1.33)	1.10 (0.31)	1.25 (0.93)	1.18 (0.71)
Median (min, max)	1.00 (1.0, 1.0)	1.00 (1.0, 1.0)	1.00 (1.0, 1.0)	1.00 (1.0, 2.0)	1.00 (1.0, 1.0)	1.00 (1.0, 1.0)	1.00 (1.0, 2.0)	1.00 (1.0, 5.0)	1.00 (1.0, 2.0)	1.00 (1.0, 5.0)	1.00 (1.0, 5.0)

IIL=initiating intravenous lacosamide; iv=intravenous; LCM=lacosamide; max=maximum; min=minimum; mo=month; OLL=open-label lacosamide; RxL=prescription lacosamide; SD=standard deviation; SS-iv=Safety Set-intravenous; yrs=years
Note: Percentages were based on the number of study participants in the SS-iv.

Table 21: Exposure to LCM by age groups in the pool SPX-1.

	≥1 month to <4 years		All study participants	
	Number of study participants	Participant-years of exposure	Number of study participants	Participant-years of exposure
LCM exposure	N=258 n (%)	Total	N=847 n (%)	Total
>0 months	258 (100)	284.7	847 (100)	1225.4
>3 months	224 (86.8)	280.8	770 (90.9)	1215.6
>6 months	193 (74.8)	270.3	706 (83.4)	1194.3
>9 months	177 (68.6)	261.4	665 (78.5)	1171.4
>12 months	144 (55.8)	234.4	615 (72.6)	1130.7
>15 months	126 (48.8)	216.1	567 (66.9)	1082.0
>18 months	94 (36.4)	176.2	511 (60.3)	1012.1
>21 months	84 (32.6)	161.4	470 (55.5)	950.2
>24 months	69 (26.7)	134.5	393 (46.4)	812.9
≥1 calendar year	136 (52.7)	226.7	596 (70.4)	1112.4
≥2 calendar years	6 (2.3)	14.0	64 (7.6)	185.0

LCM=lacosamide
Note: Overall exposure as of cutoff date 06 Mar 2020.
Note: Participant-year is defined as the total LCM exposure in days divided by 365.25.
Note: A month is defined as 28 days; a calendar year is defined as 365 days.
Note: Percentages are based on the number of study participants exposed to LCM for any amount of time.

Table 22: Exposure to LCM, maximum daily dose, and modal daily dose for participants with ≥1 calendar year of exposure in the pool SPX-1.

Parameter	≥1 month to <4 years	All study participants
Statistic	Nsub=136	Nsub=596
Duration of exposure (days)		
n	136	596
Mean (SD)	608.8 (133.8)	681.7 (188.7)
Median	673.0	691.0
Min, max	368, 1223	365, 1520
Maximum daily dose (mg/kg/day)		
n	136	596
Mean (SD)	10.53 (1.73)	9.20 (2.59)
Median	10.00	10.00
Min, max	4.0, 12.0	2.0, 17.6
Modal daily dose (mg/kg/day)		
n	136	596
Mean (SD)	10.29 (1.92)	8.39 (2.68)
Median	10.00	8.60
Min, max	3.0, 12.0	1.7, 16.8

LCM=lacosamide; max=maximum; Min=minimum; SD=standard deviation
Note: Duration of exposure (days) is calculated as the date of last dose of LCM minus the date of the first dose of LCM plus 1 day.

Adverse events

≥1month to <4 years of age

Table 23: Overview of the incidence of TEAEs for the study SP0967 (SS)

Category	Overall study	
	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

AE=adverse event; LCM=lacosamide; PBO=placebo; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n is the number of study participants reporting at least one TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Drug-related TEAEs are determined as per the Investigator.
Note: Percentages are based on the number of study participants in the Safety Set.

Table 24: Overview of the incidence of TEAEs for the study EP0060 (SS-iv)

Category	OLL and RxL 15 to 30 minutes		OLL and RxL 30 to 60 minutes		IIL 15 to 30 minutes		IIL 30 to 60 minutes		Overall		
	Cohort 2 ≥1 mo to <8 yrs N=1 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=5 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=16 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=7 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=35 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=25 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=48 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=55 n (%) [#]	All Study participants N=103 n (%) [#]
Any TEAEs	0	1 (14.3) [2]	0	1 (6.3) [1]	1 (14.3) [1]	0	2 (5.7) [3]	0	3 (6.3) [4]	2 (3.6) [3]	5 (4.9) [7]
Serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Nonserious TEAEs	0	1 (14.3) [2]	0	1 (6.3) [1]	1 (14.3) [1]	0	2 (5.7) [3]	0	3 (6.3) [4]	2 (3.6) [3]	5 (4.9) [7]
Study participant discontinuation due to TEAEs	0	0	0	0	0	0	0	0	0	0	0
Permanent withdrawal of study medication due to TEAEs	0	0	0	0	0	0	0	0	0	0	0
Drug-related TEAEs	0	0	0	0	0	0	0	0	0	0	0
Drug-related serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	0	0	0	0	0	0	0
All deaths (AEs leading to death)	0	0	0	0	0	0	0	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	0	0	0

Table 25: Overview of the incidence of TEAEs for the Pool SPX-1

Category	≥1 month to <4 years N=258 n (%) [#]	All study participants N=847 n (%) [#]
Any TEAEs	183 (70.9) [1313]	677 (79.9) [5287]
Serious TEAEs	62 (24.0) [143]	177 (20.9) [420]
Study participant discontinuations due to TEAEs	10 (3.9) [10]	46 (5.4) [59]
Drug-related TEAEs	44 (17.1) [99]	276 (32.6) [891]
Severe TEAEs	26 (10.1) [38]	83 (9.8) [144]
All deaths	4 (1.6) [4]	6 (0.7) [8]
Deaths (TEAEs leading to death)	3 (1.2) [3]	5 (0.6) [7]

TEAE=treatment-emergent adverse event
Note: n is the number of study participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Drug-related TEAEs are determined as per the Investigator.
Note: Study participant discontinuations due to TEAEs refers to the last study in which a study participant participated.
Note: Percentages are based on the number of study participants in Pool SPX-1.

Adverse events

≥1month to <4 years of age

Table 23: Overview of the incidence of TEAEs for the study SP0967 (SS)

Category	Overall study	
	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

AE=adverse event; LCM=lacosamide; PBO=placebo; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n is the number of study participants reporting at least one TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Drug-related TEAEs are determined as per the Investigator.
Note: Percentages are based on the number of study participants in the Safety Set.

Table 24: Overview of the incidence of TEAEs for the study EP0060 (SS-iv)

Category	OLL and RxL 15 to 30 minutes		OLL and RxL 30 to 60 minutes		IIL 15 to 30 minutes		IIL 30 to 60 minutes		Overall		
	Cohort 2 ≥1 mo to <8 yrs N=1 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=5 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=16 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=7 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=35 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=25 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=48 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=55 n (%) [#]	All Study participants N=103 n (%) [#]
Any TEAEs	0	1 (14.3) [2]	0	1 (6.3) [1]	1 (14.3) [1]	0	2 (5.7) [3]	0	3 (6.3) [4]	2 (3.6) [3]	5 (4.9) [7]
Serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Nonserious TEAEs	0	1 (14.3) [2]	0	1 (6.3) [1]	1 (14.3) [1]	0	2 (5.7) [3]	0	3 (6.3) [4]	2 (3.6) [3]	5 (4.9) [7]
Study participant discontinuation due to TEAEs	0	0	0	0	0	0	0	0	0	0	0
Permanent withdrawal of study medication due to TEAEs	0	0	0	0	0	0	0	0	0	0	0
Drug-related TEAEs	0	0	0	0	0	0	0	0	0	0	0
Drug-related serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	0	0	0	0	0	0	0
All deaths (AEs leading to death)	0	0	0	0	0	0	0	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	0	0	0

Table 25: Overview of the incidence of TEAEs for the Pool SPX-1

Category	≥1 month to <4 years N=258 n (%) [#]	All study participants N=847 n (%) [#]
Any TEAEs	183 (70.9) [1313]	677 (79.9) [5287]
Serious TEAEs	62 (24.0) [143]	177 (20.9) [420]
Study participant discontinuations due to TEAEs	10 (3.9) [10]	46 (5.4) [59]
Drug-related TEAEs	44 (17.1) [99]	276 (32.6) [891]
Severe TEAEs	26 (10.1) [38]	83 (9.8) [144]
All deaths	4 (1.6) [4]	6 (0.7) [8]
Deaths (TEAEs leading to death)	3 (1.2) [3]	5 (0.6) [7]

TEAE=treatment-emergent adverse event
Note: n is the number of study participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Drug-related TEAEs are determined as per the Investigator.
Note: Study participant discontinuations due to TEAEs refers to the last study in which a study participant participated.
Note: Percentages are based on the number of study participants in Pool SPX-1.

Serious adverse event/deaths/other significant events

Deaths

There were no reported deaths among treated patients in studies SP0967 and EP0060. Across all age groups (Pool SPX-1) by the clinical cut-off date, a total of 6 patients (0.7%) had died; of these, 5 deaths (0.6%) were due to TEAEs, and 1 death was posttreatment. No deaths were considered related to LCM by the investigator. Four deaths occurred in patients in the age group >1 month to <4 years of age, 3 of the 4 deaths occurred during treatment with LCM.

- A patient died from status epilepticus, cardiac arrest, and dyspnoea. The patient entered EP0034 and was receiving a dose of LCM 7.1mg/kg/day. The patient died after 444 days on LCM in EP0034. The patient awoke with a high fever and subsequently experienced epileptic seizures. The patient, cyanotic and in status epilepticus, developed asystole despite treatment, and resuscitation attempts were unsuccessful. Relevant medical history included intraventricular haemorrhage, hydrocephalus, ventricular drainage, sleep disorder, and muscle hypotonia. Other relevant concomitant medications included VPA, oxcarbazepine, nitrazepam, amoxicillin/clavulanate, epinephrine, and aminophenazone.
- A patient died from pneumonia aspiration after 70 days on LCM during participation in EP0034, having been hospitalized with a serious treatment emergent adverse events (TEAE) of sepsis. Other TEAEs reported were diarrhoea and convulsion. During the fatal pneumonia aspiration event, the patient received PB, clobazam, diazepam, CBZ, valproate sodium, PHT, domperidone, amikacin, ceftriaxone, cefepime, ceftazidime, clindamycin, gentamicin, meropenem, vancomycin, oseltamivir, furosemide, dipyrone, morphine, paracetamol, beclomethasone dipropionate/salbutamol, ipratropium, salbutamol, hydrocortisone, and prednisolone. Relevant medical history included a prior aspiration pneumonia, salivary hypersecretion, and malnutrition.
- A patient died from respiratory failure after 422 days on LCM during participation in EP0034, after treatment in intensive care. The concomitant AED medications were valproate sodium and levetiracetam.

- A patient died from influenzal pneumonia 712 days after starting treatment with LCM during participation in EP0034, having been hospitalized for 11 days. The concomitant medications at the time of the fatal event were valproate magnesium, VPA, lamotrigine, topiramate, and montelukast.

SAEs

- SP0967: Overall, the incidence of serious TEAEs was similar between the LCM and placebo groups. In each treatment group, 4 patients (3.1%) experienced a total of 9 serious TEAEs, 4 of which occurred in the LCM group and 5 in the placebo group. In the LCM group, serious TEAEs were reported for vomiting (2 patients) and convulsion (2 patients). Serious TEAEs reported in the placebo group included pyrexia, upper respiratory infection, urinary tract infection, thermal burn, and respiratory failure (1 patient).
- EP0060: no serious TEAEs were reported.
- Pool SPX-1: by the cut-off date, a total of 172 study patients (20.3%) experienced 395 treatment-emergent serious adverse events (SAEs) which included 61 patients (23.6%) in the age group ≥1 month to 4 years of age that experienced 138 treatment-emergent SAEs. The incidences and types of serious TEAEs were similar between the total patients and those ≥1 month to <4 years of age.

  Overall, the most frequently reported serious TEAEs in patients ≥1 month to <4 years of age were convulsion (11 patients, 4.3%), status epilepticus (7 patients, 2.7%], pneumonia (10 patients, 3.9%), and epilepsy (3 patients, 1.2%). Four serious TEAEs in patients ≥1 month to <4 years of age were related to study medication: status epilepticus, abnormal liver function test, hypophagia, and epilepsy (1 patient each). All related SAEs were resolved at the time of the clinical cut-off date. Drug-related SAEs that led to patient discontinuation were status epilepticus and liver function test abnormal.

  For the subset of study participants ≥1 month to <4 years of age who were exposed to LCM for ≥1 calendar year, the most frequently reported serious TEAEs were pneumonia (8 patients, 5.9%), and convulsion and status epilepticus (5 patients, 3.7%, each)

TEAEs leading to discontinuation

- SP0967: two patients, both in LCM group, experienced a TEAE leasing to discontinuation
  - idiopathic generalized epilepsy in a patient during the maintenance period (Day 26) at the onset of dose 10 mg/kg/day. AE was considered mild, resolved after 39 days.
  - sinus bradycardia occurring in a patient during the maintenance period day 29) at the onset of dose 6 mg/kg/day. AE was considered mild in severity.
- EP0060: no TEAEs leading to discontinuation were reported.
- Pool SPX-1: A total of 46 patients (5.4%) experienced a total of 59 TEAEs leading to discontinuation in the last study in which they participated. Among them, a total of 10 patients (3.9%) had a total of 10 TEAEs leading to discontinuation in the ≥1 month to <4 years age group. The most frequently reported TEAEs leading to discontinuation in study participants ≥1 month to <4 years of age were convulsion and status epilepticus (2 participants each). Dizziness leading to discontinuation was not observed in study participants ≥1 month to <4 years of age.

  Related TEAEs leading to discontinuation in patients <4 years of age were convulsion (2 study patients), rash, somnolence, status epilepticus, and sinus bradycardia (1 patient each). All related TEAEs leading to discontinuation were resolved at the time of clinical cut-off date with the exception of convulsion and sinus bradycardia (1 patient), and all were considered nonserious, apart from status epilepticus.

The majority of patients ≥1 month to <4 years of age had the event within 3 months of starting the study (7 patients).

TEAEs of special interest

Growth, neurodevelopment, behaviour and endocrinology-related

- SP0967: in LCM group, aggression was experienced by two patients in the ≥1 month to <4 years age group. Both occurred during the titration period at onset of dose 6 mg/kg/day, were considered mild in intensity, and both were considered related to study drug. Neither resolved.

  Developmental delay was reported in a patient at onset of dose 8 mg/kg/day during the titration period. The TEAE was considered mild in severity and not related to study drug.

  No patients were reported as having suicidal ideation, behaviour, or attempts.

- EP0060: no TEAEs related to this area were reported.

- Pool SPX-1: by the clinical cut-off, 4 patients (1.6%) experienced 4 TEAEs of aggression. They were considered mild or moderate in intensity, and not related to study drug. One patient (0.4%) had a psychotic disorder that was considered mild and not related to study medication.

Cardiological TEAEs

- SP0967: no clinically relevant changes were observed in mean or median ECG findings that were considered related to LCM. Sinus bradycardia was reported in 1 patient during treatment and one in the transition period.

- SP848: similar small mean changes across each age group for Bazett-corrected QT interval (QTcB), PR duration, and QRS duration were detected, and they were not considered clinically relevant. There was no evidence of QT, QTcB, or QTcF prolongation following treatment with LCM. Fifteen TEAEs related to 12 lead ECG findings were reported by 10 study participants, but none of these in the age group ≥1 month to <4 years: 4 instances of first-degree AV block in 3 patients (0.6%), 3 with QT prolongation (0.6%). The TEAEs were considered mild or moderate in intensity and not serious but possibly related to study medication.

- EP0060: similar small mean changes between baseline and final visit for PR interval, QRS duration, QTcF and QTcB, which were not considered clinically relevant. No ECG-related TEAEs were reported.

- EP0034: similar small mean changes between baseline and final visit for PR interval, QRS duration, QTcF and QTcB, which were not considered clinically relevant. One patient in the group <4 years of age had a TEAE of Brugada syndrome reported on day 98 on LCM dose 10 mg/kg/day. It was considered mild in intensity and not related to study drug.

- Pool SPX-1: Seven patients (2.7%) ≥1 month to <4 years of age experienced 9 events of status epilepticus; all were treatment-emergent SAEs, either moderate or severe in intensity, and resolved. The events were considered to be not related to study medication in 6 patients and related in 1 patient. TEAEs of epilepsy occurred in 6 patients (2.3%) ≥1 month to <4 years of age, and they were considered serious for 3 patients (1.2%), no events led to discontinuation, no events were considered related to study medication, and with the exception of 1 participant, all were resolved or resolving at the time of the clinical cut-off date. TEAEs of partial seizures with secondary generalization occurred in 1 patient ≥1 month to <4 years of age. The event was not serious, led to discontinuation, was not considered related to study medication, and was not resolved at the time of the clinical cut-off date. TEAEs of complex partial seizures and partial seizures occurred in

4 patients ≥1 month to <4 years of age each (1.6%). The AEs of complex partial seizures and partial seizures were considered serious for 1 patient (0.4%) and 4 patients (1.6%), respectively; no events led to discontinuation. Overall, TEAEs of simple partial seizures occurred in 2 patients (0.8%) ≥1 month to <4 years of age. The TEAEs of simple partial seizures were not serious, did not lead to discontinuation, were not considered related to study medication, and were not recovered/resolved at the time of the clinical cut-off date.

Laboratory findings

Overall, no consistent or clinically relevant changes from Baseline after onset of treatment were observed in mean haematology or clinical chemistry values across studies (SP0967, SP848, EP0034, EP0060). The incidence of TEAEs related to abnormal haematology or clinical chemistry values was low. None were serious or led to discontinuation.

Safety of the loading dose for initiation of treatment

The **study EP0147** was a retrospective cohort study with the objective to assess the paediatric safety profile of clinically administered intravenous LCM, comparing higher-than-recommended to the recommended dosage in paediatric patients including neonatal cases as a group. The study utilized an electronic healthcare record data from a paediatric learning health system data network (PEDSnet) to estimate the incidence of a number of selected medical events of interest (for 8 of System Organ Classes [SOC] and 3 of Standardized Medical Dictionary for Regulatory Activities Queries[SMQ]) in paediatric patients after treatment with higher than recommended iv. LCM doses, compared to paediatric patients treated with the recommended initial or maintenance iv. LCM dose. The baseline period was at least 3 months before the qualifying treatment episode (for patients less than 3 months of age, the time since birth was considered), and the follow-up period was a maximum of 37 days from the index date. The episode of care concluded on discharge from the acute care (home, post-acute care, another hospital), 37 days after the index event, or at death. The end date was the last day of the follow-up period. In case of multiple episodes of care, only the first one was included in the analysis. Total of 686 cases aged ≥1 month to <17 years were identified, with 471 patients in the recommended-dose cohort and 215 patients in the higher-loading-dose cohort, as well as 28 neonatal patients, with 16 in the recommended-dose and 12 in the higher-loading-dose cohorts.

The majority of neonatal patients weighed <4 kg (19 patients, 67.9%). The dominant weight categories among the older patients were 4-10 kg in patients 30≥days to <1 year, 10-20 kg in patients from 1 to <4 years, 20-30 kg in patients from 4 to <12 years, and ≥50 kg in patients from 12 to <17 years of age.

The crude incidence rates of AEs did not differ between recommended-dose (RD) and higher-loading-dose cohorts (LD): among patients aged ≥1 month to <17 years, it was in RD cohort 64.44 per 1000 person days (95% CI: 55.88-73.95) and in the LD cohort 50.00 per 1000 person days (95% CI: 39.82-61.98). In the neonates, the incidence rate of AEs in the RD cohort was 36.04 per 1000 person days (95% CI: 15.56-71.01) and in the LD cohort 8.85 per 1000 person days (95% CI: 1.07-31.97).

There were no differences in the crude incidence rates by AE diagnostic categories apart from a two-fold incidence of rash in the LD cohort compared with the RD cohort (adjusted incidence rate ratio 2.11; 95% CI: 1.02, 4.38). In addition, the death rates were similar and fairly high due to the critically ill patient population and not attributed to LCM. It is noted that 7 cases with pancreatitis were recorded in the RD group. This was discussed in the procedure EMEA/H/C/000863 P46 040, no conclusion regarding a causal relationship could be made and it was agreed that a cumulative review will be presented the next Periodic Safety Update Reports (PSUR).

Post marketing experience

During the period from 29 Aug 2008 to 29 Feb 2020, a total of 428 cases (77 serious and 351 nonserious) were identified from the UCB Global Safety database in patients ≥1 month to <4 years of age.

A review of all cases did not reveal concerns specific to the use of LCM in patients ≥1 month to <4 years of age compared with the known safety profile of LCM in patients ≥4 years to <17 years of age. The review considered fatal cases (including sudden unexpected death in epilepsy) and cases reported with AEs related to topics of interest such as cardiac conduction and ECG-related events; syncope and loss of consciousness; suicidality-related events; hepatotoxicity-related events; dizziness and ataxia; worsening of seizures or emergence of new seizures type; lack of efficacy; multiorgan hypersensitivity and drug reaction with eosinophilia and systemic symptoms (DRESS); severe cutaneous adverse reactions; fall and injuries; drug abuse; and potential long-term effect on growth, neurodevelopment, and puberty.

A review of other medically important events (pancreatitis, renal failure and renal impairment, drug interaction and food interaction, and blood and lymphatic system disorders) also did not identify any new safety concerns related to the use of LCM in patients ≥1 month to <4 years of age. No particular pattern was identified in specific epilepsy syndromes.

A cumulative review of relevant publications describing the use of LCM in patients ≥1 month to <4 years of age did not identify a new safety concern.

In conclusion, the cumulative post-marketing LCM analysis indicates that the safety profile in patients ≥1 month to <4 years of age is consistent with the known safety profile of LCM.

2.6.1. Discussion on clinical safety

The safety data provided satisfies the following Guideline requirements: the safety profile in children aged ≥1 month to <4 years should be compared to the safety in the older paediatric age group of ≥4 to <16 years and the safety database in paediatric patients should include at least 100 children exposed for at least 12 months. On the whole, the observations do not appear significantly different between the youngest age group ≥1 month to 4 years and older children and the existing fluctuations may be explained by heterogeneity between the studies as well as the populations. The spectrum of TEAEs by organ systems is largely as expected and consistent with the known safety profile of LCM.

The TEAEs of specific interest including those concerning cognitive development, growth and maturation were not overrepresented in the any group in the safety database. These safety concerns are nevertheless of specific significance in the youngest and the least mature paediatric patient.

The safety data have not given rise to unforeseen safety concerns. The 7 cases with pancreatitis in the retrospective register-based data of the study EP0147 have been noted and, as agreed in the procedure EMEA/H/C/000863 P46 040, no conclusion regarding a causal relationship could be made and it was agreed that a cumulative review will be presented the next PSUR.

Interim clinical study reports for EP0034 and SP848 were prepared using a clinical cut-off date of 06 Jul 2020. The number of study participants aged ≥1 month to <4 years in the 2 ongoing long-term safety extension studies, SP848 and EP0034, were 38 and 225, respectively. The MAH has provided data for the requested age subgroups (≥1 to <6 months, ≥6 months to <1 year, ≥1 to <2 years, and ≥2 to <4 years). The number of subjects were limited in the two youngest age subgroups; ≥1 to <6 months (N=9), ≥6 months to <1 year (N=30). There was no new safety finding in the age group ≥1 month to <4 years

2.6.2. Conclusions on clinical safety

The CHMP agrees that the available safety data are sufficient to support the present extension of the indication for monotherapy and adjunctive therapy in the treatment of POS.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The WSA submitted/was requested to submit an updated RMP with this application.

The PRAC considered that the risk management plan version 16.2 is acceptable.

The CHMP endorsed the PRAC position and endorsed the RMP version 16.2 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Cardiac adverse events that may be potentially associated with PR interval prolongation or sodium channel modulation
Important potential risks	None
Missing information	Pregnant or lactating women Impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study **status**	**Summary of objectives**	**Safety concerns addressed**	Milestones	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				

Ongoing and planned additional pharmacovigilance activities

Study **status**	**Summary of objectives**	**Safety concerns addressed**	Milestones	**Due dates**
Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy Ongoing	To collect data on pregnancy	Missing information on use of lacosamide (LCM) in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in Periodic Safety Update Reports (PSURs).
Participation in and sponsorship of North American Antiepileptic Drug Pregnancy Registry Ongoing	To collect data on pregnancy	Missing information on use of LCM in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in PSURs.
SP848 Open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children with epilepsy Ongoing	To document the long-term safety, tolerability, and pharmacokinetics of LCM in study participants from 1 month to less than 18 years with epilepsy	Missing information on impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population	Final study report submission	Dec 2021
EP0034 Open-label, multicenter, long-term extension study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric subjects with epilepsy with partial-onset seizures (POS). Ongoing	To document the long-term safety, tolerability, effects on behavior, cognition, and quality of life in study participants from 1 month to less than 18 years with POS	Missing information on impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population.	Final study report submission	Oct 2022

Ongoing and planned additional pharmacovigilance activities

Study **status**	**Summary of objectives**	**Safety concerns addressed**	Milestones	**Due dates**
EP0012 Open-label, multicenter extension study to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy (IGE). Ongoing	To document the long-term safety, tolerability, and efficacy of LCM in study participants 4 years and older with IGE	Missing information on impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population.	Final study report submission	Aug 2024
EP0158 A remote follow-up development assessment study of neonates who participated in SP0968 (LCM or active comparator treating repeated electroencephalographic neonatal seizures) Protocol approved	To collect data regarding the long-term neurocognitive development outcomes of children	Missing information on impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population	Study planned finish	Q2/Q3 2025

LCM=lacosamide; IGE=idiopathic generalized epilepsy; POS=partial-onset seizure; PSUR=periodic safety update report

Risk minimisation measures

Summary of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiac adverse events that may be potentially associated with PR interval prolongation or sodium channel modulation	Routine risk minimization measures: Summary of Product Characteristics (SmPC) Section 4.2 (Posology and method of administration – intravenous formulation), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction), SmPC Section 4.8 (Undesirable effects), SmPC Section 5.3 (Preclinical safety data) Available by prescription only Additional risk minimization measures: None	Routine pharmacovigilance (PhV) activities beyond adverse reactions reporting and signal detections: specific cardiac follow-up query. Additional PhV activities: None
Pregnant or lactating women	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy and lactation), SmPC Section 5.3 (Preclinical safety data) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: participation in and sponsorship of pregnancy registries (European and International Registry of Antiepileptic Drugs and North American Antiepileptic Drug Pregnancy Registry)
Impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population	Routine risk minimization measures: No additional wording in SmPC Available by prescription only. Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities (according to the actual study protocols): ongoing pediatric studies with a follow-up of up to 2 years in SP848/EP0034. Study EP0012 includes pediatric patients who are followed for up to 5 years. Study EP0158 is a planned study which will collect data regarding the long-term neurocognitive development outcomes in neonates who participate in the parent study (SP0968) for up to 2 years

PhV=pharmacovigilance; SmPC=summary of product characteristics

2.8. Update of the Product information

As a consequence of this group of variations, including the extension of indication variation, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.3 and 6.5 of the SmPC have been updated. The labelling and the Package Leaflet have been updated accordingly.

Changes were also made to the PI to implement editorial updates and bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

2.8.1. User consultation

For Vimpat, the WSA has submitted a full user test for the syrup and a bridging report for the film-coated tablets and the solution for infusion.

The results of the user consultation with target patient groups on the package leaflet show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The bridging report has also been found acceptable.

For Lacosamide UCB, as the product information is identical/strongly similar to Vimpat (except for product specific details e.g. product name), no bridging statement was submitted. This was found acceptable.

2.9. Additional Expert Consultation

During the assessment procedure, the CHMP convened an ad hoc expert group (AHEG) in order to discuss a number of questions including the extrapolation of efficacy data in POS from the adults to the younger (1 month-2 year) paediatric population, the extrapolation of efficacy in isolated POS to POS with coexisting seizure types, the validity of the study SP0967 results and impact of the study outcome on the extrapolation discussion and the appropriateness of EEG-video recordings as primary endpoint.

The details of the questions and the summary of the expert group discussion is detailed hereafter:

GENERAL

1. **Is it possible to extrapolate efficacy data in partial onset seizures (POS) from adults to children aged ≥1 month to <2 years based on similar drug exposure only, considering the immaturity of the developing brain, potentially different pathophysiology, and different clinical presentation (POS together with other seizure types) in this age group?**

Whether efficacy can be established based solely on extrapolation (without data from trial) was not considered a straightforward question and the opinion of the experts was clearly split.

- Some experts agreed that extrapolation is possible for this age group based on the arguments presented by the Applicant. Some experts acknowledged that presentation of the seizure is not a relevant aspect related to efficacy. Additionally, it was noted that both drugs are anti-seizures and not anti-epileptogenic drugs and, in this regard, pathophysiology of seizures is considered to be similar in children from 1 month to 2 years and in children from 2 to 4 years. An expert noted that one exception could be West syndrome. Another expert commented that waiting for a perfect study may delay the access for the drug and that extrapolation could be a pragmatic approach provided we are reassured on the safety profile.
- Other experts agreed that extrapolation is possible but based on scientific theoretical grounds that are considered of a rather low scientific level by these experts. Therefore, they must be considered only as supportive arguments in addition to data from trials, which are definitely needed. One expert noted that, paradoxically, extrapolation could be easier for situations without studies (e.g. Brivaracetam) than for situations for which we have studies showing negative results (Lacosamide). Another expert did not

believe that extrapolation was possible because even if the physiopathological manifestations are considered to be similar, impact on the brain may be different, due to a different brain developmental status. For this expert, this argument is also applicable for refusing extrapolation from 2-4 years, an argument shared to some extend also by another member. A couple of experts noted that posology (exposure drug) could be a relevant aspect because PK profile could be different in small children which may impact safety (e.g. metabolism may be slower exposing children to higher doses). It was clarified by the Rapporteurs to the experts that this aspect has been considered in the assessment and that extrapolation is considered under comparable exposure levels.

The two patients´ representatives were convinced that pathophysiology could be similar but still they have concerns specially regarding to the impact on neurodevelopmental status, and thus still consider that well-designed clinical trials are needed. One of the patient's representatives was also concerned about the lack of effect in contrast with potential risk of adverse events, especially on children with severe epileptic syndromes.

2. Can efficacy in isolated POS be extrapolated to efficacy in POS with coexisting seizure types, which is an epileptic syndrome more often present in the younger age group?

Similarly, experts were split as there were some experts who would not agree on extrapolation approach as a sole strategy to get confirmatory evidence on efficacy. Taken this into consideration, experts also express the following views:
While there is a risk of aggregation of other seizures with certain drugs, overall experts do not think that the existence of other seizure does modifies the response of brivaracetam or lacosamide on seizures. However, it was noted that when there are global and focal seizures in children aged 1 month to 2 years, it is possible that these patients, most likely without a diagnosis, suffer from an epileptic encephalopathy and likely a refractory epilepsy. As per regards of refractory epilepsy, it was noted that except for the auto-limitated seizures, young children may become refractory quite soon and several changes in the medication is needed. The prevalence of refractory epilepsy is about the same in both groups (up to 30% as reported by one of the patients representative). Therefore, it was agreed that the need for new drugs is the same in the two age groups.
A couple of experts noted that currently prescription is not based on precision medicine (specific to the syndrome) and therefore, the risk of prescribing an ineffective drug already sin the clinical practice and having another drug could be helpful for the management of seizures in these patients.

VIMPAT/LACOSAMIDE

3. In the placebo-controlled SP0967 study in children ≥1 month to <4 years of age with POS, the efficacy of lacosamide was not demonstrated. Please discuss the validity of the study results, possible explanations of the failure to show efficacy, and the impact of the study outcome on the extrapolation discussion.

Experts fully agreed that the study was poorly designed. First, study population likely included refractory patients with severe seizures - it was noted that there were difficulties in the recruitment- suggesting a potential selection bias. Second, another relevant concern was the large inter-rate variability in the interpretation of video-EEG that could be linked with several reasons including the severity of the seizures (ictal but also inter-ictal activity that makes the diagnosis of an individual seizure more difficult), the fact that EEG-video is not routinely used in the clinical practice and provided training of investigators before study onset was considered insufficient, the too short timeframe of EEG-video recording (48h), taking into consideration the well-known periodicity of epileptic seizures (patients have good and bad periods regardless the medication). One expert noted that design should have included just a single central reading. Third, some experts considered that the video-EGG was not included in the design in an appropriate way (see detail sin answer to Q5). They expressed the view that EGG-video is useful to validate seizures that are difficult to identify clinically (e.g. small children) but should not be used as the primary efficacy endpoint, which should better rely on a clinical outcome based on diaries. Finally, the design should have taken into consideration the type of seizure at entry. Based on the duration of the seizures, the duration of video-EGG recording could have been tailored to better capture the seizures.
As per regards to the impact on the extrapolation discussion, the group was also split. Among experts prone to accept extrapolation approach, some declared that , the negative results impact their view, while some declared that their conviction was not modified, as the poor quality of the study make them to consider it as inconclusive, so that it could not be used to make a decision. Finally, experts already disapproving the

extrapolation approach, considered the study failure as an additional argument for the need of adequately designed trials. One patient representative was doubtful and negative results clearly impacted the perspective of the other patient representative.

4. **Please discuss the appropriateness of EEG-video recordings as primary endpoint and the implications of the study outcome with regards to the claim of the applicant that lacosamide may be considered efficacious in children ≥1 month to <4 years of age with POS.**

Experts agreed that video-EEG could be integrated in a study but there was a consensus that the primary endpoint should not rely solely on EEG-video recording. Some experts insisted again that EGG-video recording could be better useful to validate seizures that are difficult to identify clinically (e.g. neonates) or in in situations with many of seizures (e.g. >100). An expert noted that video-EGG recording could be also proposed as a primary endpoint for drugs targeting specific syndromes such as West Syndrome.
One expert mentioned that a recent article proposed a better protocol for using EEG-video as outcome in clinical trial (Auvin et al., 2019,'Novel study design to assess the efficacy and tolerability of antiseizure medications for focal-onset seizures in infants and young children: A consensus document from the regulatory task force and the pediatric commission of the International Leaugue against Epilepsy (ILAE), in collaboration with the Pediatric Epilepsy Research Consortium (PERC)' published in Epilepsia Open in 2019;4:537–543). For most experts, regarding focal onset seizures, frequency of seizures based on diaries remains the best approach for primary endpoint and seizures should be pre-specified in the protocol. Additionally, it was insisted that diaries capture clinical manifestations closer to the real world.
Patient's representatives agree with the experts on this aspect. Additionally, the patient´s burden of EEG-video recording is substantial as reported by one patient´s representative.

2.10. Benefit-Risk Balance

2.11. Therapeutic Context

2.11.1. Disease or condition

Partial-onset epilepsies are more common (approximately 57%), and generalized epilepsies constitute roughly one third, and in one-tenth of epilepsies the classification remains uncertain. Partial epilepsy is associated with a local abnormality affecting a neuronal network within one hemisphere. Focal or partial seizures are traditionally classified according to the patient's level of awareness and the first most prominent motor or nonmotor features of the seizure. The level of awareness leads to three classes: simple partial (awareness not impaired), complex partial (awareness impaired), or partial seizures evolving to secondarily generalized seizures (tonic-clonic, tonic, or clonic, myoclonic). The etiologies fall into six defined categories: structural, genetic, infectious, metabolic, immune, or unknown.

The incidence peaks in the first year of life and has been estimated to be within the range of 56.8-318 per 100 000. Later in the childhood the incidence rate declines, but another peak is late in life. At any rate, epilepsy in childhood is a highly significant and highly variable form of neurological morbidity with many risks including a higher risk of death and neuropsychiatric disorders. The clinical presentation of POS may be subjective, objective, or both; convulsive or nonconvulsive; brief or prolonged; inconspicuous or dramatic and bizarre. The subjective and/or objective symptoms observed in POS depend on the functional organization at the site of ictal origin and/or sites of propagation. Thus, symptoms may be motor, sensory, mental, emotional, cognitive, or linguistic (alone or in various combinations).

2.11.2. Available therapies and unmet medical need

Pharmacological antiepileptic therapy is needed for the majority of patients. The range of available medicines has widened considerably during the last decades, and the newer AEDs provide different spectra, mechanisms of action and PK properties. Treatment is commonly started with monotherapy, and it may be

necessary to try alternatives if the therapy response appears insufficient, or resort to adjunctive therapies. Despite the various AED options, roughly one third of patients do not achieve an adequate seizure control. There is therefore a need for more effective and better tolerated AEDs.

2.11.3. Main clinical studies

2.12. Favourable effects

Extrapolation of adult efficacy to paediatric patient on the basis of previous PK data has been applied previously to the age group ≥4 years to older, supported by weight-based dosing adaptations. In this application, the extrapolation concept is applied further in attempt to extrapolate efficacy data from adults and older paediatric patients to the younger in the age group ≥1 month to <4 years. Apart from the PK model for LCM, the application refers to efficacy data from three studies, of which one is a completed randomized controlled trial intended as pivotal and two ongoing open-label studies, and a supportive randomized controlled study in paediatric patients aged ≥4 years to < 17 years.

Study SP0967 is the completed Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in study participants with epilepsy ≥1 month to <4 years of age with uncontrolled POS. It enrolled 255 patients, of which 242 completed the study. Most patients were ≥2 to <4 years (134, 52.5%), less than fifth were <1 year (47, 18.5%). partial-onset seizure frequency for infants aged ≥1month to ≤6months was based on electrographic seizures only, whereas POS frequency for children aged >6months to <4years was based on electrographic seizures with an accompanying clinical correlate. No separate clinical seizure data were collected in the study, which is understandable given the short duration (7 days) of the blinded maintenance period part of the study.

The primary efficacy variable of ≥50% responder rate compared to baseline was 41.4% for LCM, 37.5% for placebo, or the mean change in daily frequency of electrographic POS 7.14 in LCM vs. 7.83 in placebo groups (p=0.69). The difference of change was not considered clinically meaningful and is not statistically significant.

Study EP0034 is an open-label extension to the study SP0967 (as well as SP9069) an ongoing Phase 3, multicenter, open-label, long-term study to investigate the efficacy and safety of LCM as adjunctive therapy in paediatric study participants (≥1 month to ≤17 years of age) with POS. This study lacks a control arm. Of the 517 patients, 195 are <4 years of age. The interim efficacy data is diary-based, so comparison is not available for the ages <4 years.

Study SP848 is an ongoing Phase 2, open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children (≥1 month to ≤18 years of age) with epilepsy, including 37 patients ≥1 month to <4 years of age. This study also lacks a control arm. The overall proportion of 50% and 75% responders from baseline to treatment were 53.7% and 40.4%, and the highest proportion of responders were in the youngest group of patients ≥1 month to <4 years of age compared to older groups.

Study SP0969 provides supportive evidence: A Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluating the efficacy and safety of LCM as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled POS. LCM group experienced a 31.72% reduction in seizure frequency, and a statistically significantly higher rate of patients experiencing a ≥50% reduction in POS (primary endpoint) was 52.9% vs. 33.3%.

2.13. Uncertainties and limitations about favourable effects

The pivotal study SP0967 failed to show an increase in efficacy when LCM was used concomitantly with 1-3 antiepileptic drugs in paediatric patients ≥1 month to <4 years of age with currently uncontrolled POS. Therefore, the efficacy of LCM is extrapolated from the adult population to the paediatric population between 2-4 years old based on presumed similar pathophysiology and PK/PD relationship. This, however, gives rise to some uncertainties regarding the precise metrics of efficacy. Extrapolation of efficacy in adjunctive therapy of POS as established in adults is proposed by the MAH, with support of clinical pharmacology data. Similar exposure as in adults and dose recommendations are supported with popPK modelling and simulation. However, in order to allow for an extrapolation based on only a PK bridge (similar exposure), the AHEG did not consider that the pathophysiology in patients <2 years of age is sufficiently similar to that of adults.

With regards to differences in disease between children younger than 2 years of age and adults, it is unclear whether efficacy in isolated POS, as more commonly seen in adults, may be extrapolated to efficacy in POS with coexisting seizure types, which is an epileptic syndrome more often present in the younger age group.

Regarding the EEG-video recordings, the *post hoc* analyses revealed a methodological issue with a very low agreement between the local and central reader interpretations, dramatically lowering the inter-rater reliability of the interpretation of seizure counts and types and identified as a potential underlying cause for the inability to directly demonstrate clinical efficacy. The appropriateness of EEG-video recordings as primary endpoint and the implications of the study outcome with regards to the claim that LCM may be considered efficacious in children ≥1 month to <2 years was discussed at the AHEG.

The AHEG considered the study poorly designed and that EEG-video was not an appropriate primary endpoint. In addition, the experts were not able to disregard the study outcome when considering extrapolation of efficacy to this age group. In summary, while the assay sensitivity of the trial is uncertain, the failure to show an effect results in uncertainties about the extent of benefit, particularly in the younger paediatric population.

The proposed weight-based dose adaptations are based on simulations from popPK model and subsequent exposure matching between adult and paediatric exposure levels. Despite the limitations of the final PK model, the proposed dosing regimen results in similar exposure levels in paediatric patients and adults.

2.14. Unfavourable effects

According to the EMA guideline, the normative size for a safety database should be greater than 100 patients with at least one calendar year of follow-up data.

The pre-requisite size of the safety database is reasonably fulfilled. The collected safety data within the study SP0967 is within expected frame with respect to rates of SAE and TEAE incidences and similar in LCM and placebo groups. The most commonly reported TEAEs in the LCM group were consistent with the known safety profile of the drug in adults and children >4 years of age, and no unforeseen safety concerns were raised. Safety data available in paediatric patients younger than 2 years of age is however limited.

The numbers of TEAEs with specific interest in this paediatric group (growth, neurodevelopment, behaviour and endocrinology-related; cardiological; epileptic phenomena) did not give rise to new concerns.

The study EP0147 was a retrospective cohort study which used electronic health record data to study the safety of LCM loading doses in paediatric patients, comparing treatment with higher than recommended dosage to treatment with recommended dosage. Of the total of 714 eligible patients, 686 patients were aged ≥1 month to <17 years, and 28 patients were aged <30 days. The crude incidences of TEAEs did not differ between the groups apart from rash, which had a two-fold incidence in the loading dose group

compared with the recommended dose group. There were 7 deaths reported, 2 of these in the loading dose group, and the deaths were not deemed associated with LCM. A finding of 7 cases of pancreatitis was noted previously (procedure P46 040) and no conclusion regarding a causal relationship between LCM treatment and pancreatitis could be made.

2.15. Uncertainties and limitations about unfavourable effects

The safety of the loading dose seems reasonable in light of the retrospective data collected within the study EP0147, but the nature of the study sets limits to drawing firm conclusions from the data. The high mortality rate reflects the critically ill patient group and was not associated with LCM. However, it is noted that the number of patients was lower in the loading-dose group (31.3%), and the number of patients was very low in the neonate group, precluding firm conclusions.

The safety profile seems acceptable in the data provided, but there is remaining uncertainty concerning the long-term effects, especially concerning neurocognitive development, growth and maturation, which are crucial especially in the youngest and least mature patients. The interim data from long-term study and post-marketing safety data give some reassurance that there are little negative effects related to neurocognitive development, neuropsychiatric disorders, growth and maturation in children. The risks are also appropriately listed in the RMP as missing information, with agreed risk minimization measures and pharmacovigilance activities.

2.16. Benefit-risk assessment and discussion

2.16.1. Importance of favourable and unfavourable effects

The MAH has performed a double blinded randomised clinical study in children ≥1 month to <4 years of age with uncontrolled POS. This failed to demonstrate the efficacy of LCM.

Nonetheless, the MAH proposes that the efficacy of LCM in adjunctive treatment of POS in children ≥1 month to <4 years of age may be inferred by extrapolation from studies performed in adolescents and adults. Dosing regimens based on body weight have been proposed on the basis of PK modelling.

According to the EMA Epilepsy guideline, extrapolation based on PK bridging is accepted down to 4 years of age. In the scientific advice, discussions have opened up for extrapolation down to 2 years of age, based on the available scientific literature.

In line with the scientific advice, based on available scientific understanding and similarity of disease in the populations, extrapolation of efficacy from adults to children above 2 years of age based on similar exposure is considered acceptable. The safety profile in the proposed paediatric population appears similar to what is observed in adults and is acceptable. Consequently, the CHMP agrees that the B/R risk is positive in the children above 2 years of age.

Due to limitations in the PK/PD model and uncertainties about the similarity of pathophysiology given the lack of maturation of the CNS, the extrapolation of efficacy from adult to paediatrics ≥1 month to <2 years of age is however not supported.

The CHMP convened an AHEG on the 7th of October to discuss whether an extension of indication to children below 2 years of age could be based on the above arguments. The AHEG was split in their views regarding whether an extrapolation of efficacy may be based on similar drug exposure only and there were views that efficacy data from a well-designed study was needed for this age group as well.

The AHEG was also split in their view of the impact of the negative study results of SP0967 on the possibility to base an extension of indication on extrapolation but could not disregard these negative results.

In summary, the discussion held by the AHEG did not provide clear support to the extrapolation of efficacy based similar drug exposure only. In order to impact the CHMP position regarding extrapolation of efficacy from adults to the paediatric population below 2 years of age, there was not sufficient strength and consistency of arguments for the extrapolation whereas substantial uncertainties remain for the younger population.

The proposed dosing recommendations are based on simulated exposure matching between paediatric patients and adult patients. Despite some discrepancies between the exposure reference intervals used in the two paediatric extensions of indication procedures, and some limitations of the final PK model, the proposed dosing recommendation results in similar exposure levels across all weight and age groups.

2.16.2. Balance of benefits and risks

The CHMP agrees that the extrapolated benefit of Vimpat as monotherapy or adjunctive therapy in the treatment of POS with or without secondary generalisation in children from 2 years to 4 years of age is considered established and outweigh the risks.

It is also agreed that the extrapolation of efficacy to children aged ≥1 month to <2 years has not been established. Therefore, the CHMP cannot recommend an extension of the Vimpat POS indication to this younger paediatric population.

2.17. Conclusions

The overall B/R of Vimpat/Lacosamide UCB is for the extension of indication in children from 2 years of age is positive.

3. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.II.f.1.b.2	Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	Type IB	I , IIIA and IIIB

- Extension of indication to include patients from 2 years to 4 years of age for treatment of partial-onset seizures with or without secondary generalisation as monotherapy and adjunctive therapy for Vimpat/Lacosamide USB. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Version 16.2 of the RMP is also agreed.

- Extension of the shelf life of the finished product after the first opening of syrup (supported by real time

data) (B.II.f.1.b.2 - type IB - FINISHED PRODUCT - Stability - Change in the shelf-life or storage conditions of the finished product). As a consequence, section 6.3 of the SmPC (syrup) is updated.

Changes were also made to the PI to implement editorial updates and bring it in line with the latest QRD template.
The labelling and Package Leaflet are updated in accordance.

Amendments to the marketing authorisation

In view of the data submitted with the grouped worksharing procedure, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Vimpat-H-C-WS2049G and Lacosamide UCB-H-C-WS2049G.

Attachments

1. SmPC, Labelling and Package Leaflet of Vimpat as a relevant example with changes highlighted as adopted by the CHMP on 27 January 2022.