Office of Clinical Pharmacology Review

NDA#	For PGTCS: NDA 022254/S-036, NDA 022253/S-046, NDA 022255/S-027 For POS NDA 022254/S-038
EDR location(s)	\\CDSESUB1\evsprod\NDA022254 \\CDSESUB1\evsprod\NDA022253
Submission Date(s)	04/30/2020 (NDA 022254), 01/16/2020 (NDA 022253)
PDUFA Goal Date(s)	02/28/2021 (NDA 022254), 11/16/2020 (NDA 022253)
Submission Type	Prior Approval Efficacy Supplement
Product Name	VIMPAT® (lacosamide)
Dosage Form	50 mg, 100 mg, 150 mg, 200 mg tablets 10 mg/mL oral solution Solution for intravenous infusion (10 mg/mL in 20 mL single-dose vial)
Dosage Regimen	Initial dosage: <50 kg: 1 mg/kg, ≥50 kg: 50 mg Maintenance dosage: 11 to ≤30 kg: 3-6 mg/kg, 30 to ≤50 kg: 2-4 mg/kg, >50 kg: 150-200 mg (monotherapy), 100-200 mg (adjunctive therapy). All doses are BID.
Indication	Treatment of partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) individuals with idiopathic generalized epilepsy (IGE) in 4 years of age and above
Applicant	UCB Biosciences, Inc.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology-II (DN-II)
OCP Reviewer	Adarsh Gandhi, Ph.D. (Clinical Pharmacology)
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GLOSSARY

AED	Anti-epileptic drug
BLQ	Below the limit of quantitation
Css	Concentration at steady state
IGE	Idiopathic generalized epilepsy
IIL	Initiating IV-LCM
IV	intravenous
LCM	Lacosamide
Ng/mL	nanogram per milliliter
µg/mL	microgram per milliliter
OCP	Office of Clinical Pharmacology
OLL	Open label-LCM
PGTCS	Primary generalized tonic-clonic seizures
PK	pharmacokinetics
PMR	Post marketing requirement
pop PK	Population pharmacokinetics
POS	Partial onset seizure
RxL	Prescribed-LCM
TEAE	Treatment emergent adverse event

1. EXECUTIVE SUMMARY

VIMPAT® (lacosamide, LCM) CV (film coated oral tablet approved in 2008 and oral solution approved in 2010) was approved as monotherapy and adjunctive therapy for the treatment of partial-onset seizures (POS) in epilepsy patients ≥4 years of age. The injection for intravenous (IV) LCM use was approved in 2008 for POS patients when oral administration is temporarily not feasible in ≥17 years old adult only.

The applicant is seeking approval for IV LCM as a monotherapy and adjunctive therapy for the treatment of POS and IV and oral LCM as an adjunctive therapy for the treatment of primary generalized tonic-clonic seizures (PGTCS) in subjects (b) (4) 4 years of age and above.

POS:
In NDA 022254/S-038, the applicant conducted study EP0060, a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of IV LCM infusions in 103 pediatric participants ≥1 month to <17 years of age with epilepsy (POS). The proposed dosing regimen for IV monotherapy is the same as that of oral tablet and oral solution (refer to Table 1).

The combined previous adult and pediatric pharmacokinetic (PK) data obtained from study EP0060 were analyzed using the population pharmacokinetic (popPK) approach. The results demonstrated a comparable PK profile of LCM between the IV and oral routes in both pediatrics (≥1 month to <17 years of age) and adults across the different body weight groups. Safety for IV LCM was acceptable where no pediatric study participants reported severe Treatment emergent adverse events (TEAEs) in study EP0060. These support IV LCM as monotherapy and adjunctive therapy for POS and oral dosing can be substituted with IV dosing without further dose-adaptation.

PGTC:
In NDA 022253/S-046, NDA 022254/S-036, NDA 022255/S-027oral LCM was evaluated as an adjunctive therapy for the treatment of primary generalized tonic-clonic seizures (PGTCS) in subjects with idiopathic generalized epilepsy (IGE). Study SP0982 was a phase 3 double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM vs. placebo as adjunctive therapy for PGTCS in study participants ≥4 years of age with IGE currently taking 1 to 3 concomitant antiepileptic drugs (AEDs). This study met the primary objective for efficacy i.e. statistically significant lower risk of developing a second PGTCS, as well as a statistically significant higher rate of seizure freedom in the 24-week treatment period in LCM treated IGE subjects compared to placebo. Sparse PK was collected, in which patients receiving LCM dose had comparable concentrations to that in the POS safety study (EP0060). The safety for IV LCM for PGTCS is being borrowed from Study EP0060. These data support the use of both oral and IV LCM for the treatment of PGTCS in subjects (b) (4) 4 years of age and above.

1.1. Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the submitted information contained in NDA 022254/S-038 and NDA 022253/S-046 and finds them acceptable from a clinical

pharmacology perspective. The OCP recommends approval of VIMPAT® injection for infusion as monotherapy and adjunctive therapy for treatment of POS and VIMPAT® oral tablets, oral solution and injection for infusion as adjunctive therapy for treatment of PGTCS in ≥4 years of age.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of safety and/or efficacy	For POS, the efficacy had been demonstrated for the approved oral LCM down to 4 years of age and IV LCM in adult patients. The results of Study EP0060 demonstrated acceptable safety profiles of IV LCM in pediatrics and supportive comparable PK data between the oral and IV LCM formulations across the different body weight groups in pediatric POS patients. These data support approval of IV LCM in pediatric POS patients ≥4 years of age. For PGTC, efficacy (statistically significant lower risk of developing a second PGTCS, as well as a statistically significant higher rate of seizure freedom in the 24-week treatment period) of oral LCM was demonstrated for in subjects with IGE ≥4 years of age in Study SP0982. Safety for the oral and IV formulations of LCM was acceptable (refer to original approval of oral and IV LCM and study EP0060).
General dosing instructions	See Section 1.2, Table 1
Dosing in patient subgroups (intrinsic and extrinsic factors)	For Pediatric patients, see Section 1.2 Table 1
Labeling	Within the PI for NDA 022254 (POS) and NDA 022253 (PGTCS), Sections 2.1 (b) (4) updated to include the oral and IV dosing recommendations for subjects 4 years of age and older.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulations were used in both EP0060 (for POS) and SP0982 (for PGTCS) studies.

1.2. Dosing regimen

Table 1: Recommended Dosage for Adults and Pediatric Patients 4 Years and Older for POS and PGTCS*

Age and Body Weight	Initial Dosage	Titration Regimen	Maintenance Dosage
Adults (17 years and older)	Monotherapy: 100 mg twice daily (200 mg per day) Adjunctive Therapy: 50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	Monotherapy: 150 mg to 200 mg twice daily (300 mg to 400 mg per day) Adjunctive Therapy: 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
	Alternate Initial Dosage: 200 mg single loading dose, followed 12 hours later by 100 mg twice daily		
Pediatric patients weighing 50 kg or more	50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	Monotherapy: 150 mg to 200 mg twice daily (300 mg to 400 mg per day) Adjunctive Therapy: 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 30 kg to less than 50 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day)
Pediatric patients weighing 11 kg to less than 30 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)

* This dosage regimen is approved for oral VIMPAT in ≥4 years and older and for IV VIMPAT in adults for treatment of POS.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of action:
Current experimental data suggest a dual mechanism of action: a) modulation of the slow inactivation of sodium channels, and b) modulation of collapsin-response mediator protein 2-mediated neurotrophic signals. These mechanisms elicit the pharmacodynamic effect of LCM for management of seizures.

Pharmacokinetics:
VIMPAT® is currently approved for treatment of POS in ≥4 years (oral tablet and oral solution) and in ≥17 years (IV injection). Absolute bioavailability of LCM (a BCS class 1 drug) is ~100% indicating an almost complete absorption after oral treatment. The C_{max} of main metabolite, SPM 12809 at steady state occurs between 1.8-4 h (LCM t_{max} = 0.5-4 h). The plasma half-life of the unchanged drug is approximately 13 hours and is not altered by different doses or by multiple dosing.
Based on the results of popPK analysis, LCM PK between the pediatric and adults was comparable for both oral and IV formulations across the different body weights.

In Supplements S-038 and S-046, based on the results of Study EP0060 (for POS) and SP0982 (for PGTCS), the applicant proposed to extend the indication for the use of IV LCM as monotherapy for POS and oral and IV LCM as adjunctive therapy for PGTCS (diagnosed with IGE) in patients ≥4 years of age. The proposed dosing regimens for POS and PGTC, which are the same as the approved ones, are shown in Table 1.

2.2. Post-marketing requirement (PMR) that are addressed in this submission:

The applicant conducted Study EP0060 as part of the PMR fulfillment under two PREA requirements (2774-1 and 3293-2).

PREA PMR 2774-1 (partial fulfillment only): A safety study of replacement of oral dosing with IV dosing administered over 30 to 60 minutes in pediatric patients 1 month to <17 years of age with POS. If safety is acceptable, a replacement study at a faster rate of infusion (15 minutes) must be conducted in this population. Sparse PK samples must be collected to evaluate the PK of LCM and its metabolite using PPK approach in this population.

PREA PMR 3293-2: Deferred pediatric studies under PREA for the treatment of partial-onset seizures in pediatric patients ages 4 years to <17 years.

There is no new PMR required for this submission.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

The efficacy had been demonstrated for the approved oral lacosamide (LCM) ≥4 years of age and IV LCM in adult patients to treat POS. A safety study EP0060 of replacement of oral dosing with IV dosing administered over 30 to 60 minutes in pediatric patients 1 month to <17 years of age with POS was conducted. With ~100% absolute bioavailability, it is expected to have similar exposure of LCM between oral and IV LCM. Sparse PK samples were collected to evaluate and confirm the similarity of PK of LCM and its metabolite using pop PK approach in this population.

3.1. Study EP0060 for POS – PK study

Study EP0060 is 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. The primary objective of this study was to evaluate the safety and tolerability of IV LCM infusion(s) in pediatric study participants ≥1 month to <17 years with epilepsy. An additional objective of this

study was to evaluate the pharmacokinetics (PK) of IVLCM in pediatric study participants with epilepsy.

The following study participants were eligible for enrollment in EP0060:

- Open-label LCM (OLL) study participants: currently receiving oral LCM as adjunctive or monotherapy as participants in an open label long-term study.
- Prescribed-LCM (RxL) study participants: currently receiving prescribed oral LCM from commercial supply (e.g., VIMPAT) as adjunctive or monotherapy.
- Initiating IVLCM (IIL) study participants: not currently receiving LCM and will receive IVLCM as adjunctive treatment in EP0060.

Out of 113 participants screened, 103 participated and completed the study. Specifically, 48 study participants in Cohort 2 (≥1 month to <8 years of age) and 55 study participants in Cohort 1 (≥8 to <17 years of age). There were 12 study participants ≥1 month to <2 years of age, 14 study participants ≥2 to <4 years of age, 22 study participants ≥4 to <8 years of age, 20 study participants ≥8 to <12 years of age, and 35 study participants ≥12 to <17 years of age.

After completion of this study, eligible study participants from the RxL and IIL groups had the option to continue open-label LCM treatment in study SP848.

For OLL and RxL study participants, the daily dose of IV LCM was equivalent to the study participant's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). For IIL study participants, the IV LCM dose was 1mg/kg bid (study participants weighing <50kg) or 50mg bid (study participants weighing ≥50kg).

For the first IV LCM infusion (Day 1): PK samples were taken pre-dose for OLL and RxL study participants (within 1 hour prior to IV LCM infusion) and post dose for all study participants (within 1 to 4 hours after end of IV LCM infusion). If the study participant had more than 1 IV LCM infusion, it was optional to also collect plasma samples for the final IV LCM infusion (Day 2 to 5/Early Termination).

Plasma concentrations of LCM and SPM 12809 (main active metabolite) after IV administration of LCM on Visit 2/Day 1 by age cohort and weight group are presented in Table 1 and Table 2, respectively. For each cohort and each weight group, the LCM and SPM 12809 plasma concentrations (GeoMean, mean, and median values) measured +1 to +4 hours after the end of IV administration of LCM on Visit 2/Day 1 were lower and showed higher variability (GeoCV) than the pre-dose LCM and SPM 12809 values, respectively (Table 1 and Table 2).

Table 1: Plasma concentrations of LCM and SPM 12809 after IV administration of LCM on Visit 2/Day 1 by age cohort (PK-per protocol set)

Parameter Statistic	Predose LCM (-59 to -3 minutes before start of iv LCM infusion)		Postdose LCM (+1 to +4 hours after end of iv LCM infusion)		Predose SPM 12809 (-59 to -3 minutes before start of iv LCM infusion)		Postdose SPM 12809 (+1 to +4 hours after end of iv LCM infusion)	
	Cohort 2 ≥1 mo to <8 yrs N=6	Cohort 1 ≥8 yrs to <17 yrs N=22	Cohort 2 ≥1 mo to <8 yrs N=48	Cohort 1 ≥8 yrs to <17 yrs N=53	Cohort 2 ≥1 mo to <8 yrs N=6	Cohort 1 ≥8 yrs to <17 yrs N=22	Cohort 2 ≥1 mo to <8 yrs N=47	Cohort 1 ≥8 yrs to <17 yrs N=53
Plasma concentrations (ng/mL)								
GeoMean	3282.677	4840.185	1256.523	1704.022	998.158	977.054	117.715	124.285
GeoCV (%)	32.6	75.0	340.0	1087.6	49.1	77.7	276.0	841.7
Mean (SD)	3415.0 (989.4)	5776.2 (3490.3)	2361.0 (2461.1)	4699.2 (5320.4)	1073.67 (369.23)	1208.50 (811.66)	307.78 (478.07)	542.11 (776.18)
Median (min, max)	3670.0 (2000, 4700)	5500.0 (567, 17500)	1415.0 (2.5, 10300)	1680.0 (2.5, 26500)	1135.00 (402, 1520)	975.00 (219, 3290)	106.00 (2.5, 1700)	90.40 (2.5, 3380)

GeoCV=geometric coefficient of variation; GeoMean=geometric mean; iv=intravenous; LCM=lacosamide; max=maximum; LLOQ=lower limit of quantification; min=minimum; mo=month; PK-PSS=Pharmacokinetic-Per Protocol Set; SD=standard deviation; yrs=years
Note: Means, SDs, and CVs were only calculated if at least 2/3 of the concentrations were quantified at the respective time point.
Note: Values below the limit of quantification were replaced by a value of LLOQ/2 in calculations of means, SDs, and CVs.

Source: SP0060 Study report, ep0060-bodytext.pdf, page 113 of 119

Table 2: Plasma concentrations of LCM and SPM 12809 after IV administration of LCM on Visit 2/Day 1 by weight group (PK-per protocol set)

Parameter Statistic	Predose LCM (-59 to -3 minutes before start of iv LCM infusion)			Postdose LCM (+1 to +4 hours after end of iv LCM infusion)			Predose SPM 12809 (-59 to -3 minutes before start of iv LCM infusion)			Postdose SPM 12809 (+1 to +4 hours after end of iv LCM infusion)		
	0 to <30kg weight group N=9	≥30 to <50kg weight group N=7	≥50kg weight group N=12	0 to <30kg weight group N=60	≥30 to <50kg weight group N=16	≥50kg weight group N=25	0 to <30kg weight group N=9	≥30 to <50kg weight group N=7	≥50kg weight group N=12	0 to <30kg weight group N=59	≥30 to <50kg weight group N=16	≥50kg weight group N=25
Plasma concentrations (ng/mL)												
GeoMean	4515.806	5054.078	4094.351	1213.314	3069.034	1472.036	953.782	1133.305	922.207	109.646	179.167	119.359
GeoCV (%)	69.8	46.4	85.7	465.3	122.0	2877.2	45.2	82.6	87.0	333.3	538.2	1285.1
Mean (SD)	5571.1 (4718.0)	5498.6 (2509.3)	4911.4 (2494.0)	2766.5 (4039.2)	4731.9 (4586.0)	4827.4 (4638.8)	1023.11 (348.78)	1391.43 (952.95)	1173.42 (833.68)	306.05 (467.55)	672.89 (957.16)	574.96 (774.93)
Median (min, max)	3940.0 (2000, 17500)	5470.0 (2770, 10300)	4885.0 (567, 9430)	1460.0 (2.5, 26500)	1965.0 (1060, 16000)	1670.0 (2.5, 13700)	1090.00 (402, 1520)	1330.00 (332, 3290)	875.00 (219, 2850)	106.00 (2.5, 1700)	87.20 (22.7, 3380)	45.60 (2.5, 2670)

GeoCV=geometric coefficient of variation; GeoMean=geometric mean; iv=intravenous; LCM=lacosamide; max=maximum; LLOQ=lower limit of quantification; min=minimum; PK-PSS=Pharmacokinetic-Per Protocol Set; SD=standard deviation
Note: Means, SDs, and CVs were only calculated if at least 2/3 of the concentrations were quantified at the respective time point.
Note: Values below the limit of quantification were replaced by a value of LLOQ/2 in calculations of means, SDs, and CVs.

Source: SP0060 Study report, ep0060-bodytext.pdf, page 114 of 119

For this study in NDA 022254, a consult request to the Office of Scientific Inspections and Surveillance (OSIS) for clinical and bioanalytical site inspections was not sent as study EP0060 was an open-label safety study.

Reviewer's comments:

The higher variabilities in post-dose LCM plasma concentrations may be because of (a) the different number of subjects analyzed compared to the pre-dose subjects and (b) the different sample collection times (+1 to +4 h post-dose) due to the protocol deviations.

The reviewer conducted independent analysis to explain these findings. Out of 101 subjects, there were 30 protocol deviations in PK sample collection times. Specifically, 29 subjects had their PK samples collected before the +1 h post-dose time (maximum deviation was -49 min) and 1 subject had PK samples collected after the +4 h post-dose time (deviation of +607 minutes).

Our analysis (see Table 3) further revealed that there were a total of 16 subjects which had values as BLQ (below the limit of quantification) in which the applicant reported as 2.5 ng/mL (LLOQ (5.0 ng/mL) / 2). Out of these 16 subjects, there were 10 in the pre-dose group and 6 in the post-dose group. Out of these 6 post-dose subjects with BLQ values, 5 subjects had protocol deviations listed as "procedural noncompliance" such as PK samples were not collected within +1 to +4 h post-dose window (3 subjects), enrolled subject was not dosed LCM at approximately 12-hour (+/- 2 hours) intervals (1 subject) and the enrolled subject's final visit was not performed within 1 day after the final IV infusion (1 subject). Refer to ep0060-listing-pro-dev.pdf for additional information.

As body weight was a significant covariate for dosing recommendations, our analysis focused on presenting LCM concentration data by different body weight categories after removing the subjects which had values as BLQ (see Table 3). As seen in Table 3, LCM concentration overlapped between pre-dose and post-dose groups for all 3 body weight categories and higher variability in 0 to <30 kg post-dose category could be driven by the subject with 50.80 ng/mL LCM plasma concentration.

Table 3: Plasma concentrations of LCM after IV administration of LCM by weight group (PK-per protocol set)

Body weight	PK Sampling time	Lacosamide				
		N	Mean	Std	Min	Max
0 to <30kg	PREDOSE	11	4631.09	4711.12	149.00	17500.00
	POSTDOSE	58	2909.19	4057.65	50.80	26500.00
30 to <50kg	PREDOSE	7	5498.57	2509.35	2770.00	10300.00
	POSTDOSE	16	4731.88	4585.95	1060.00	16000.00
>= 50kg	PREDOSE	12	4911.42	2494.02	567.00	9430.00
	POSTDOSE	22	5485.36	4562.22	897.00	13700.00

Source: Reviewer's analysis using SAS 9.4.

Reviewer's comments: Although there is an initial drop in LCM concentration shown in Figure 1, by removing six subjects which were BLQs (due to protocol deviations such as procedural non-compliance), LCM concentration largely overlapped between pre-dose and post-dose groups for all 3 body weight categories (Table 3).

3.2. Applicant's popPK analysis for study EP0060

The Applicant utilized the pediatric population PK model described in report CL0447-Part II, the PK data from study SP0982 (in subjects ≥4 years of age diagnosed with PGTCS-IGE) as well as prior modeling data from CL0447-Part I (including adult PK data from CL0261) for generating the simulated adult and pediatric exposures to inform pediatric dose selection. The final PK model comprised of above data along with data from study EP0060. In the pediatric model, age, weight, coadministration with valproic acid or enzyme inducers (mainly carbamazepine) were covariates on the clearance of LCM. The adult and pediatric models are briefly described below.

A one-compartment model with first-order absorption (and zero-order IV input) was the initial structural model, in line with the original modeling reports. The random effect model describing

inter-individual variability (IIV) was revisited. The model was extended with IV dosing into the central compartment, allowing the estimation of bioavailability. No covariates were incorporated aside from weight using allometric scaling with potentially estimated exponents.

Covariate PK model development

Body weight (at baseline) was included *a priori* in the base model according to allometric theory on CL and volume. Initially, fixed exponents were used according to allometric theory (θ=0.75 for CL and Q, θ=1 for Vc and Vp), and scaled to the standard body weight of 70 kg. Model development additionally included assessment of improvement by estimating the allometric exponents. No further covariates were assessed.

The population estimates from the final population PK model were used to simulate C_{ss} values for all records in the Nhanes database with the following dosing schedule, as implemented in SP0982:

- 6 mg/kg bid for weight <30 kg
- 4 mg/kg bid for weight ≥30 kg and weight <50 kg
- 200 mg bid for weight ≥50 kg

The results for adults were used to derive the median and 90% of the predicted C_{ss} concentrations. These results were graphically compared for oral and IV dosing with the median and 90% of the concentrations for children, by body weight and age classes.

The final model parameter estimates are shown in the table below.

Table 4: NONMEM parameter estimates for the final population PK model (run107)

Parameter	Estimate (95% CI)	IIV	Shrinkage*
CL (L/hr)	1.86 (1.62/2.11)	26.0%	27.9%
Vc (L)	47.0 (41.2/52.8)	46.3%	53.8%
Ka (1/hr)	1.78 (1.45/2.10)	67.7%	75.8%
F (fraction)	0.899 (0.721/0.968)	112.8%	47.7%
Allometric scaling CL	0.532 (0.497/0.566)		
Allometric scaling Vc	1.00 Fixed		
Proportional RUV (fraction)	0.205 (0.192/0.217)		13.0%
Additive RUV (ug/mL)	0.339 (0.222/0.456)		13.0%

*CL: clearance, Vc: central volume, Ka: absorption constant, F: bioavailability, RUV: residual unexplained variability, IIV: inter-individual variability. *Shrinkage calculated using the standard deviation.*

Source: CL0447-Part III pop PK study report, cl0447-lacosamide-pk-report-part-iii-ep0060-190924.pdf, page 25 of 82

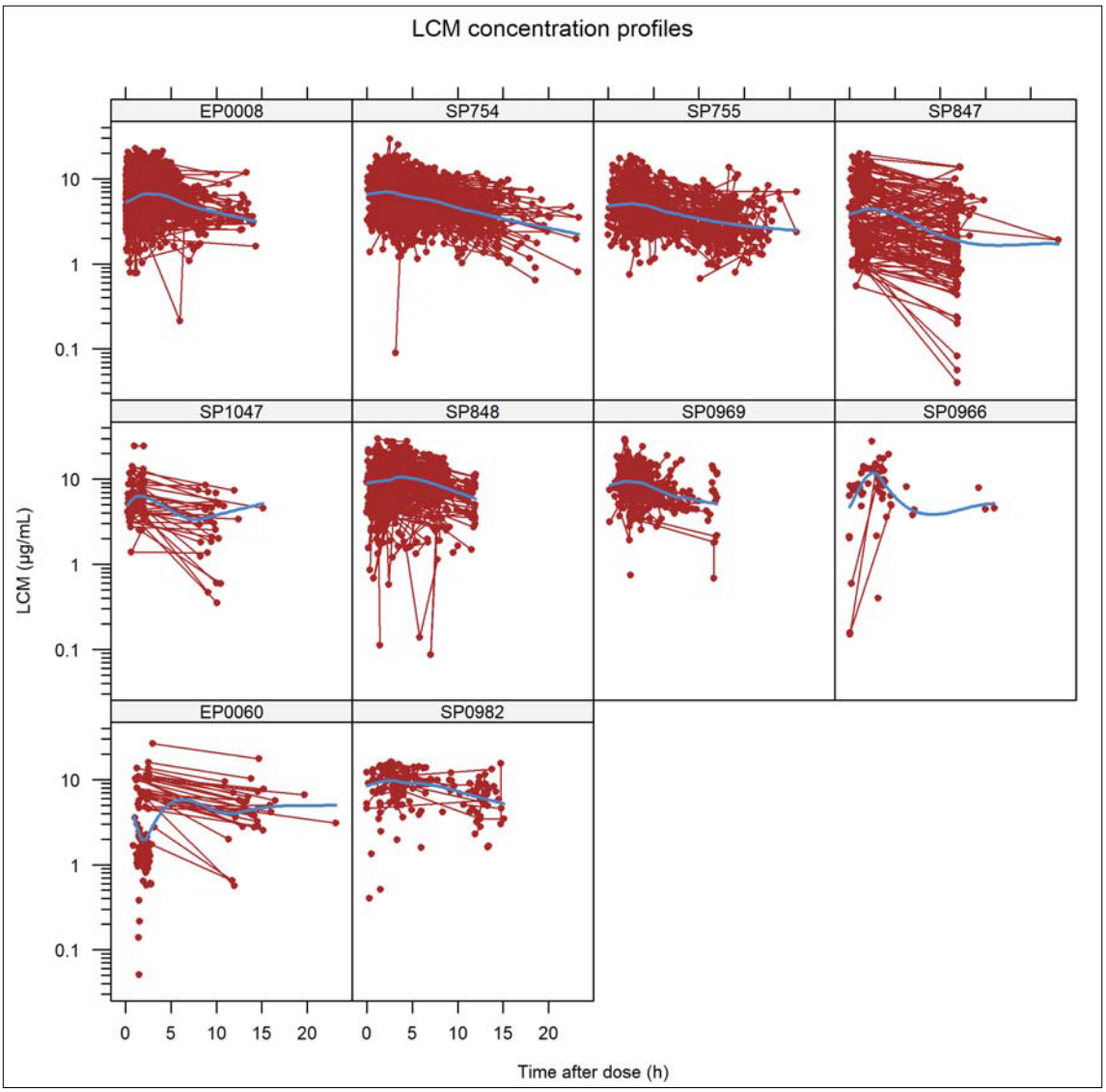
The resulting equations incorporating the effect of weight are:

$$CL_i = 1.86 \cdot e^{\eta_{CL,i} + 0.532 * log\left(WT_i/70\right)}$$

$$Vc_i = 47.0 * e^{\eta_{V1,i} + 1.00 * log\left(WT_i/70\right)}$$

The plots shown in Figure 1 below suggest and support a one-compartment model with first order absorption for LCM in epilepsy patients.

Figure 1: Overlaid LCM concentration profiles by time after dose on logarithmic scale stratified by study



Red lines and dots: individual curves and observations, blue lines: loess smooths though the data

Source: CL0447-Part III pop PK study report, cl0447-lacosamide-pk-report-part-iii-ep0060-190924.pdf, page 22 of 82

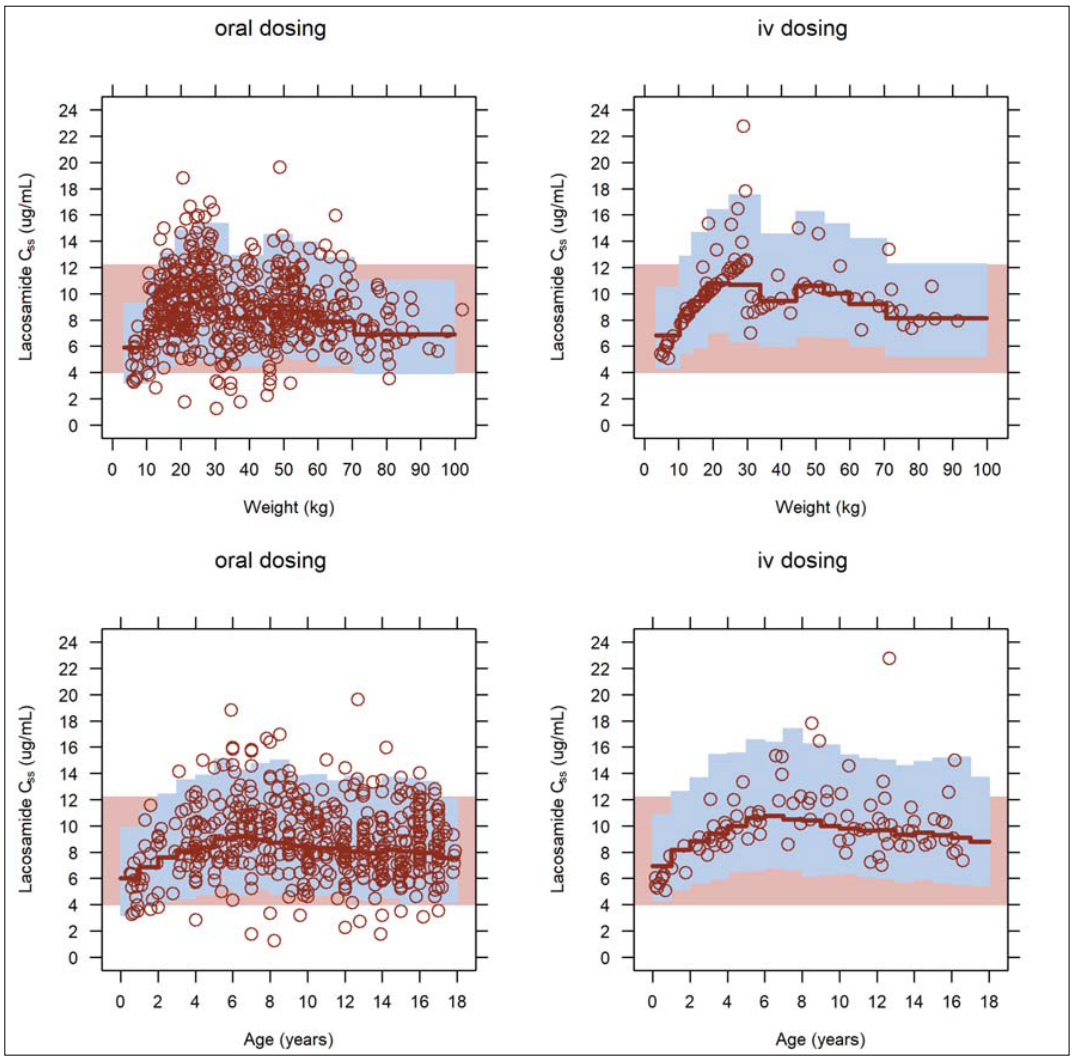
Simulations

Simulations were performed to assess if predicted LCM pediatric steady state concentrations over 24 hours (C_{ss}) fall within the range of adult values, and if these values are comparable between oral and IV dosing in children for the same dosing regimen.

In the graphs, the pink shaded area depicts 90% of the simulated adult C_{ss} values receiving 200 mg LCM bid after oral dosing in all panels, and the red line and blue shaded area depict the median and 90% of the simulated pediatric C_{ss} values for oral dosing (left) and IV dosing (right). The red circles indicate the predicted C_{ss} values for the pediatric individuals in all studies for oral dosing (left) and IV dosing in EP0060 (right).

The oral dosing scheme positioned the model-predicted pediatric C_{ss} values (blue area) in the adult range (pink area) for most body weights; IV dosing resulted in slightly higher exposures due to the bioavailability of 89.9% (Figure 2).

Figure 2: Predicted LCM C_{ss} for a 6 mg/kg bid dose for weight <30kg, a 4 mg/kg bid dose for ≥30 to <50 kg, and a 200 mg bid dose for ≥50 kg vs. age (bottom row) and weight (top row) for children, using the final LCM population PK model.



Css: average steady state concentration. Red line and blue area: median and 90% of simulated LCM C_{ss} values for study participants <18 years sampled from the Nhanes database for oral dosing (left column) and IV dosing (right column). Red circles: individual predicted LCM C_{ss} values. Pink area: 90% of simulated LCM C_{ss} values for adult study participants after oral dosing in all graph panels.

Source: CL0447-Part III pop PK study report, cl0447-lacosamide-pk-report-part-iii-ep0060-190924.pdf, page 36 of 82

Based on the simulation presented in Figure 2, bioavailability was estimated at 89.9% indicating a close correspondence in exposure between oral and IV dosed study participants, and simulations of the proposed dosing schedule of:

- 6 mg/kg bid for weight <30 kg
- 4 mg/kg bid for weight ≥30 kg and weight <50 kg
- 200 mg bid for weight ≥50 kg

resulted in pediatric exposures in line with adult exposures. Due to the slightly lower than 100% bioavailability, predicted exposures were slightly higher in the IV dosed study participants than in the oral-dosed study participants.

Sponsor's conclusions: These results suggest that the proposed dosing schedule of 6 mg/kg bid for weight <30 kg, 4 mg/kg bid for weight ≥30 kg and weight <50 kg, and 200 mg bid for weight ≥50 kg, results in uniform exposures across the investigated age and weight ranges, and oral dosing can be replaced with IV dosing without further dose-adaptation.

Reviewer's comments: The efficacy had been demonstrated for the approved oral LCM down to 4 years of age and IV LCM in adult patients. The results of study EP0060 demonstrated acceptable safety profiles of IV LCM in pediatrics. It also provided supportive comparable PK data between the oral and IV LCM formulations across the different body weight groups in pediatric POS patients. Although there is an initial drop in LCM concentration shown in Figure 1, by removing six subjects which were BLQs (due to protocol deviations such as procedural non-compliance), LCM concentration largely overlapped between pre-dose and post-dose groups for all 3 body weight categories (Table 3). In addition, the pop PK model concluded that individual predictions for pediatric study participants (red circles) were mostly contained within the model-predicted range (blue area), illustrating the adequacy of the individual model predictions (Figure 2). All the above evidences support approval of IV LCM in pediatric POS patients ≥4 years of age. Oral LCM dosing can be replaced with IV dosing without further dose-adaptation.

3.3. Study SP0982 for PGTCS

A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy. Oral LCM doses in study SP0982 for PGTCS were the same as those in study EP0060 for POS (see Table 1 for specific dosage regimen information).

The primary study objective was to demonstrate the efficacy of oral LCM vs. placebo as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures (PGTCS) in study participants with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant antiepileptic drugs (AEDs) independent of the number of prior failed AEDs.
The secondary study objective was to assess the safety and tolerability of LCM in study participants with IGE with uncontrolled PGTCS.

The efficacy of VIMPAT® as adjunctive therapy in patients 4 years of age and older with IGE experiencing PGTCS was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center study (Study 5). The study consisted of a 12 week historical baseline period, a 4 week prospective baseline period and a 24-week treatment period (which included a 6-week titration period and an 18- week maintenance period). Eligible patients on a stable dose of 1 or 3 antiepileptic drugs experiencing at least 3 documented PGTC seizures during the 16-week combined baseline period were randomized 1 to 1 to receive VIMPAT or placebo (VIMPAT n=121, placebo n=121). Approximately 20% of the enrolled subjects were pediatrics.

The primary efficacy variable (time to the second PGTCS) and key secondary efficacy variable (seizure freedom for PGTCS) during the 24-week treatment period were analyzed using a gatekeeping strategy. Based on the sponsor's result, data from SP0982 demonstrate that treatment with LCM, compared with placebo, resulted in a statistically significant lower risk of developing a second PGTCS, as well as a statistically significant higher rate of seizure freedom in the 24-week treatment period, which measures the proportion of study participants with no PGTCS reported in the seizure diary during the study.

All subgroup analyses (age at enrollment, development, racial group, gender, region, baseline PGTCS frequency, number of concomitant AEDs at study entry) were directionally consistent with the primary analysis and had hazard ratios that favored LCM over placebo, indicating a reduced risk of developing a second PGTCS during the treatment period for the LCM group compared with placebo. One exception was for the Western/Central Europe subgroup; the survival estimates for the Western/Central Europe subgroup were roughly equivalent.

Safety: The overall safety for oral LCM was acceptable with majority of the treatment emergent adverse events (TEAEs) as mild-to-moderate in intensity. The safety for IV LCM for POS (study EP0060) is referenced for PGTCS.

Sparse PK was collected, in which all except three patients on placebo had LCM concentrations as BLQ whereas patients receiving LCM dose had comparable concentrations to the POS study (EP0060). For 2 of these study participants, LCM concentrations were measured at <3 µg/mL. For the remaining study participant, LCM concentration was 10.58 µg/mL at week 24. In LCM

treated patients, the LCM plasma concentrations were similar to the ones observed after IV dosing in the POS study (study EP0060, Figure 1).

For this study in NDA 022253, although a consult request to inspect the three clinical sites was sent on 02/28/2020, imposed travel restrictions due to COVID-19 global pandemic could not allow the OSIS to conduct these inspections (DARRTS 08/26/2020).

Please refer to the Clinical review (by Dr. Emily Freilich) for a detailed interpretation of this efficacy study.

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