Office of Clinical Pharmacology Review

sNDA#	NDA 022253/S-049, NDA 022254/S-039, NDA 022255/S-031 (NDA Efficacy Supplement set)
EDR location(s)	\\CDSESUB1\evsprod\NDA022254 \\CDSESUB1\evsprod\NDA022253
Submission Date(s)	12/15/2020
PDUFA Goal Date(s)	10/15/2021
Submission Type	Prior Approval Efficacy Supplement
Product Name	VIMPAT® (lacosamide)
Approved Dosage Forms	Tablets: 50, 100, 150, 200 mg (NDA 022253) Oral solution: 10 mg/mL (NDA (022255) Solution for intravenous infusion (10 mg/mL in 20 mL single-dose vial) (NDA 022254)
Approved 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
Approved Indication	Monotherapy and adjunctive therapy for treatment of partial onset seizures (POS) and adjunctive therapy for treatment of primary generalized tonic-clonic seizures (PGTCS) individuals with idiopathic generalized epilepsy (IGE) in ≥4 years of age
Proposed Indication	Treatment of POS in ≥1-month to <4 years of age
Applicant	UCB Biosciences, Inc.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology-II (DN-II)
OCP Reviewers	Adarsh Gandhi, Ph.D. (Clinical Pharmacology) Vishnu D. Sharma, Ph.D. (Pharmacometrics)
OCP Team Leaders	Atul Bhattaram, Ph.D. (Pharmacometrics) Gopichand Gottipati, Ph.D. (Clinical Pharmacology)

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1. Executive Summary

Lacosamide (VIMPAT®, LCM) is an antiepileptic agent, originally approved, in 2008, as an adjunctive therapy for the treatment of partial-onset seizures (POS) in epilepsy patients ≥ 17 years: film coated oral tablet (NDA 022253), and LCM intravenous (IV) injection (NDA 022254) for short-term use when oral administration is temporarily not feasible. LCM oral solution was approved in 2010 (NDA 022255) as adjunctive therapy for POS patients ≥ 17 years. In 2014, LCM tablet and oral solution, and IV when oral administration is temporarily not feasible, were approved as monotherapy for treatment of POS in ≥ 17 years. In 2017, LCM tablets and oral solution were approved for treatment of POS (i.e., both monotherapy and adjunctive therapy) in 4 to < 17 years, while IV use was limited to adults (≥17 years) because of lack of safety data for IV use in pediatrics. In 2020, tablets, oral solution and IV formulations were approved as an adjunctive therapy for treatment of primary generalized tonic-clonic seizures (PGTCS) in subjects with idiopathic generalized epilepsy (IGE) in subjects ≥ 4 years of age.

The applicant conducted SP0967, a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study, to evaluate efficacy, safety, tolerability and PK of LCM as adjunctive therapy in epilepsy patients ≥1 month to <4 years, and experience uncontrolled POS, in order to fulfill a post-marketing requirement (PREA 3288-1). In this study, LCM doses 8mg/kg/day to 12mg/kg/day (oral solution) were evaluated. The study failed to meet the pre-specified statistical criteria for efficacy, measured as change in average daily frequency of electrographic POS, assessed via a video-electroencephalogram (EEG), the primary clinical efficacy endpoint. The applicant noted that the study failure was likely due to high inter-rater variability and low inter-rater reliability of the interpretation of seizure types and seizure counts of the primary efficacy endpoint. Further, they noted that LCM demonstrated an acceptable safety profile in ≥1 month to <4 years and comparable PK data to those in adults (>17 years).

In November 2020, the Agency advised the applicant on the potential use of full extrapolation approach to support efficacy (Type C Meeting Written Responses, DARRTS dated 11/30/2020). In December 2020, UCB Inc., submitted the current efficacy supplement (NDA 022253/S-049, with cross-reference to NDA 022254/S-039 and NDA 022255/S-031), and proposed to:

1. Extend indication of LCM as adjunctive therapy and monotherapy for POS in patients ≥1 month to < 4 years of age, for all formulations noted above.
2. (b) (4)

3. Increase in-use shelf-life for oral solution to support proposed indication in POS patients ≥ 1 month to < 4 years of age.

The applicant submitted data from study SP0967, along with population PK analysis report (CL0447-Part IV) to support LCM dosing regimen (**Table 1**) in pediatric patients. Briefly, the population PK analyses were based on adult PK data from 4 studies (EP0008, SP754, SP755 and SP0982), and pediatric PK data from 7 studies (SP847, SP1047, SP848, SP0969, SP0966, EP0060, and SP0967) in which LCM was administered orally (as tablets, and oral solution) or intravenously. These studies are summarized in **Table 2**.

The primary objective of this review is to evaluate the appropriateness of the LCM dosing recommendations in pediatric subjects 1 month to < 4 years. (b) (4) However, the clinical review team determined that lack of access to raw datasets from the RWE studies severely limited the review and acceptability of the applicant's proposal. Please refer to clinical and CMC reviews for further details on review topics #2 and #3 noted above respectively.

2. Office of Clinical Pharmacology Recommendations

The Office of Clinical Pharmacology (OCP) review team has reviewed the submitted information contained in NDA 022253/S-0257 (with cross-reference to NDA 022254/S-0226 and NDA 022255/S-0210) and recommends approval of LCM formulations (tablets and solution for oral administration and solution for IV use) as monotherapy and adjunctive therapy for treatment of POS in patients ≥1 month to <4 years.

Currently approved dosing for VIMPAT™ (in black) and proposed (in BLUE) dosing for ≥1 month to <4 years POS patients is shown in **Table 1**.

Given the relatively high absolute bioavailability (~85%), the dose recommendations in **Table 1** are for tablet, oral solution, and solution for IV infusion.

Table 1 LCM Dosing Schedule for Adults and Pediatric Patients ≥1 month for POS

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) **Alternate Initial Dosage:** 200 mg single loading dose, followed 12 hours later by 100 mg twice daily	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 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	(b)(4) mg/kg to (b)(4) mg/kg twice daily (b)(4) mg/kg/day to (b)(4) mg/kg/day)
Pediatric patients weighing 6 kg to less than 11 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)
Pediatric patients weighing less than 6 kg	IV: 0.66 mg/kg three times daily (2 mg/kg/day)	IV: Increase by (b)(4) mg/kg twice daily (b)(4) mg/kg/day) every week	IV: 2.5 mg/kg to 5 mg/kg three times daily (7.5 mg/kg/day to 15 mg/kg/day)
	oral: 1 mg/kg twice daily (2 mg/kg/day)	oral: Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	oral: 3.75 mg/kg to 7.5 mg/kg twice daily (7.5 mg/kg/day to 15 mg/kg/day)

Proposed LCM dosage (in BLUE text) for ≥1 month to <4 Years of age for POS patients

* Approved dosing regimen for oral and IV LCM in ≥4 years for treatment of POS and PGTCS

3. Dosing Recommendations in Pediatric Subjects 1 Month and Older

3.1. Background – General advice for pediatric extrapolation in POS

On November 12, 2015, Division of Neurology 2 (DN2) sent a General Advice Letter to the Applicant indicating that it was acceptable to extrapolate to pediatric patients ≥4 years of age the effectiveness of drugs approved for the treatment of POS in adults. Based on subsequent ongoing discussions within the Clinical team before and during the review of this submission (general advice letter sent to applicant in DARRTS dated 02/26/2021), DN2 has agreed to extend this concept down to 1 month of age.

The following will be required to rely upon extrapolation to support an indication for the treatment of POS:

- An approved indication for the treatment of POS in adults.
- A PK analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric subjects 1 month of age and older compared with older subjects with POS. This analysis will require PK data from both the adult and pediatric (1 month of age and older) populations.
- Long-term open-label safety study(ies) in pediatric subjects 1 month of age and older.

To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. Thus, to support extrapolation, an applicant must provide PK information adequate to demonstrate such similarity, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter metabolism of the drug.

3.2. Clinical development in pediatric patients

This section provides a brief summary of the clinical studies conducted in pediatric subjects. Specifically, study SP0967 was conducted to fulfill a post-marketing requirement PREA 3288-1, while the rest of the trials were conducted and reviewed previously.

Study SP0967 Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group efficacy/safety, tolerability and PK study of oral (solution 10mg/mL) LCM administered concomitantly with 1 to 3 AEDs as adjunctive therapy in study participants ≥1 month to <4 years of age with epilepsy who experience uncontrolled POS. A total of 255 pediatric participants ≥1 month to <4 years of age were enrolled in this study: 16 study participants ≥1 month to <6 months of age, 29 study participants ≥6 months to <1 year of age, 71 study participants ≥1 year to <2 years of age, and 129 study participants ≥2 years to <4 years of age.

Titration occurred over a 20-day period, with LCM dose initiated at 4 mg/kg/day, titrated by 2mg/kg/day every 4 days until the target dose of 8mg/kg/day to 12mg/kg/day) was achieved for the 7-day maintenance period. Blood sampling for LCM concentration determination was performed at visit 5 (Day 17, Titration period) and visit 6 (Day 27, Maintenance period), respectively.

Study SP0982 A Phase 3, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of oral LCM as adjunctive therapy for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE. The subjects received LCM from 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg (oral solution), 6mg/kg/day to 8mg/kg/day for subjects weighing ≥30kg to <50kg (oral solution), 300mg/day to 400 mg/day for subjects weighing ≥50kg (tablets). Out of 242 randomized subjects, 207 study participants (85.5%) were included in the per protocol set, with 104 study participants (86.0%) in the LCM group and 103 study participants (85.1%) in the Placebo group. Four cohorts of subjects were randomized as follows: ≥4 to <12 years [N=17]; ≥12 to 18 years [N=32]; ≥18 to <65 years [N=191]; ≥65 to <85 years [N=2].

Study SP847 A Phase 2, multicenter, open-label study to investigate the safety, tolerability, and PK of LCM oral solution (syrup) (2mg/kg/day to up to 12mg/kg/day) as adjunctive therapy, i.e., added to a stable dose regimen of 1 to 3 concomitant AEDs in pediatric subjects (1 month to 17 years) with partial-onset seizures. Steady-state plasma PK of LCM and its major metabolite SPM 12809 were characterized using population PK. Five cohorts of subjects were enrolled: Cohort 1: ≥5 to ≤11 years [N=7]; Cohort 2: ≥12 to ≤17 years [N=9]; Cohort 3: ≥2 to <5 years [N=8]; Cohort 4: ≥5 to <12 years [N=11]; Cohort 5: ≥1 month to <2 years [N=12].

Study SP1047 A Phase 1, multicenter, open-label study to investigate the PK of oral LCM in pediatric subjects (1 month to 17 years) with epilepsy. SP1047 was a 1-day study conducted to augment the PK data obtained from SP847 through the

collection of sparse PK samples from pediatric subjects who were already on a stable dose of LCM (tablet or oral solution). A total of 32 subjects were enrolled in the study in the following age groups: 10 subjects in ≥1 month to <4 years, 13 subjects in ≥4 to <12 years age, and 9 subjects in ≥12 to ≤17 years. SP1047 was terminated upon completion of SP847. At the time of completion of SP847, 2 of the planned minimum of 8 subjects were enrolled in the ≥1 month to <2 years age category.

Study SP848 A Phase 2, multicenter, long-term, open-label study to determine safety, tolerability, and efficacy of oral LCM as adjunctive therapy in pediatric subjects (1 month to 17 years) with epilepsy, previously enrolled in SP847, SP0966, or enrolled directly into the study. Subjects who enter SP848 from SP847 or SP0966 begin on the LCM dose that they were receiving at the end of the previous pediatric study, and these doses were in the range of 2mg/kg/day to 12mg/kg/day or 100mg/day to 600mg/day.

Study SP0969 A Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric subjects (4 years to <17 years) with POS. Of the 343 subjects randomized, 182 subjects were in the ≥4 to <12 years age group and 161 subjects were in the ≥12 to <17 years age group. Subjects in the LCM arms received 10mg/mL oral solution (syrup), 50mg/100 mg tablets. Lacosamide dosing was based on subject's weight: 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg, 6mg/kg/day to 8mg/kg/day for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for subjects weighing ≥50kg.

Study SP0966 A Phase 2, multicenter, open-label, exploratory study to investigate the safety and efficacy of oral LCM as adjunctive therapy in pediatric subjects (1 month to <18 years) with epilepsy syndromes associated with generalized seizures. The doses studied were 2-12 mg/kg/day (syrup), 100–600 mg/day (tablet) as bid administered oral solution (syrup) or tablets.

3.3. Applicant's Population PK Analysis – Study CL0447 Part IV

The applicant updated the population PK model with pediatric PK data from study SP0967 to support LCM dosing recommendations of pediatric POS patients 1 month to <4 years (CL0447 Part IV). Simulations focused on the correspondence in exposure between adults and children and the potential implication for the dosing schedule, both for monotherapy and add-on therapy as well as oral and IV dosing.

Overall, the applicant utilized PK data from a total of 1655 adult and pediatric patients (1 month and older) with POS from 11 studies: six placebo-controlled studies and five open-label studies in which three formulations (i.e., intravenous, oral solution, or oral tablet) of LCM were administered.

Table 2: Tabular summary of Clinical studies used to build the population PK model (CL0447) part IV

Study number	Type	Number of active study participants/PK samples	Treatment regimen*
EP0008	Adult study participants with uncontrolled partial-onset seizures	363[a]/1903[b]	Placebo, 200, and 400 mg/day as bid administered tablets
SP754	Adult study participants with partial-onset seizures	301[a]/1322[b]	Placebo, 400, and 600 mg/day as bid administered tablets
SP755	Adult study participants with partial-onset seizures	322[a]/1007[b]	Placebo, 200, and 400 mg/day as bid administered tablets
SP0982	Study participants ≥4 years with uncontrolled PGTCS in idiopathic generalized epilepsy	98[b]/159[b]	Placebo, 8-12 mg/kg/day (solution, study participants weighing <30kg), 6-8 mg/kg/day (solution, study participants weighing ≥30 kg and <50kg), 300-400 mg/day (tablet, study participants weighing ≥50 kg) as bid administered oral solution (syrup) or tablets
SP847	Children ≥1 month to 17 years with uncontrolled partial-onset seizures	47[a]/311[b]	2 - 12 mg/kg/day as bid administered oral solution (syrup)
SP1047	Children ≥1 month to 17 years who were prescribed LCM for epilepsy	32[a]/90[b]	15 mg/mL (syrup), 50 – 200 mg (tablet), or 10 mg/mL (solution) administered bid at the clinically prescribed dose
SP848	Children ≥1 month to 17 years with partial-onset seizures and other pediatric epilepsy syndromes	263[a]/933[b]	2-12 mg/kg/day (syrup), 100 – 600 mg/day (tablet) as bid administered oral solution (syrup) or tablets
SP0969	Children ≥4 to 17 years with partial-onset seizures	171[a]/356[b]	6-12 mg/kg/day (syrup), 300 – 400 mg/day (tablet) as bid

			administered oral solution (syrup) or tablets
SP0966	Children ≥1 month to 17 years with epilepsy syndromes associated with generalized (Type II) seizures	55[a]/53[b]	2-12 mg/kg/day (syrup), 100 – 600 mg/day (tablet) as bid administered oral solution (syrup) or tablets
EP0060	Children ≥1 month to 17 years with epilepsy	95[c]/125[c]	If switching from oral to iv: 2-12 mg/kg/day or 100 to 600 mg/day (same as current oral dose) If initiating LCM treatment: 1 mg/kg bid (study participants weighing <50kg) or 50 mg bid (study participants weighing ≥50kg)
SP0967	Children ≥1 month to <4 years with partial-onset seizures, with approximately 50% < 2 years	122[d]/244[d]	Placebo, 8-12 mg/kg/day with up-titration (10 mg/mL solution) starting at 4 mg/kg/day

[a]Source: investigators brochure [8]; [b]numbers in the PK analysis data selection of the NONMEM file for CL0447-Part II [5]. [c]numbers in the PK analysis data selection of the NONMEM file for CL0447-Part III [6]. [d]Planned number of participants and LCM samples. *Doses cited are intended doses that may be adjusted if clinically indicated.

Source for this review: Population PK model report (CL0447), pages 18-19 of 124.

The demographics and relevant covariates of subjects included in the final population PK analysis dataset are summarized in **Table 3** and **Table *4***.

Table 3: Summary of demographics based on final population PK dataset

Covariates*	**Combined data (N=1655)**	**SP0967 (N=122)**
Age (years)	24.26 (0.08, 71)	2.11 (0.08, 3.92)
Bodyweight (Kg)	55.69 (4.1, 187.8)	11.44 (4.1, 23.8)
Sex (Male)	858 (52%)	69 (57%)
EGFR (mL/min)	113 (16.9, 135)	61 (16.9, 135)
Inducer AEDs	796 (48.1%)	66 (54.1%)

*Mean (Min, Max) is provided for continuous variables; total number of subjects and its percentage is shown for categorial variables.

Table 4: Age distribution based on final population PK Analysis Dataset

Age category	**N (number of POS patients)**
≥1 month to <2years	93
≥1 month to <6 months	*12*
≥6 month to <1 year	*33*
≥1 year to <1.5 year	*22*
≥1.5 year to <2 year	*26*
≥2 years to <4 years	101
≥4 years to <12 years	273
≥12 years to <18 years	238
≥18 years	950

Nonlinear mixed effect PK modeling was conducted using NONMEM® software. The previously developed PK model comprised of single compartment, first-order absorption, and first-order elimination was used as initial model. Covariate modeling was done using forward addition ($p < 0.05$) and backward elimination ($p < 0.001$). Covariates including age, weight, sex, race, inducer AED coadministration, valproic acid coadministration, and eGFR were tested. Continuous covariates were centered on a typical value, like the median of the study population, and scaled across 95% of the covariate range to allow estimates that describe fold-change across 95% of the covariate range. Categorical covariates were similarly estimated as additive shift on the logarithmic scale and back-transformed to a fold-change. The final model was evaluated using goodness-of-fit plots, parameter precision, and visual predictive checks.

The final population PK model retained similar structural model noted above. The effect of weight on clearance and volume 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. Maturation in clearance was assessed as a function of post-conceptional age using sigmoidal-Emax maturation function. Effect of region (e.g., China, Japan), and concomitant use of inducer AEDs on clearance were estimated. The parameter estimates of the final population PK model for LCM are shown in **Table 5**.

Table 5: Parameter estimates of applicant's final population PK model

Parameter	Estimate (95% CI)	IIV	Shrinkage*
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 at 50% maturation on CL (years)	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 (ug/mL)	0.340 (0.222/0.459)		12.8%

Source: Applicant's population PK report: CL0447-Part IV, Table 15, Page 124

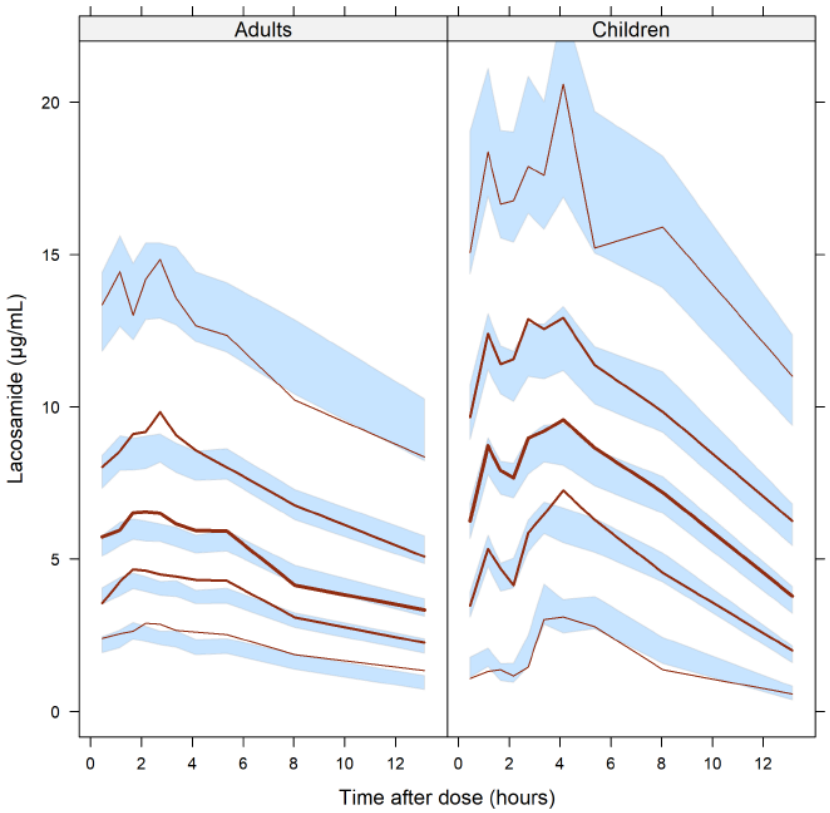
Reviewer's comments

Overall, the sample size of pediatric subjects in > 1 month and < 4 years age from study SP0967 was adequate and the applicant's final population PK model adequately describes the PK of LCM in pediatric patients 1 month and older.

The applicant estimated oral bioavailability of 0.85. The analysis did not reveal any difference between tablet and oral solution formulations. Since lacosamide is primarily cleared by renal excretion, the applicant's inclusion of renal maturation function is acceptable.

The final population PK model was assessed with diagnostics plots including goodness-of-fit and visual predictive checks (**Figure 1**).

Figure 1: Visual Predictive Checks stratified by adults and children. Brown 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 using the final PK model.



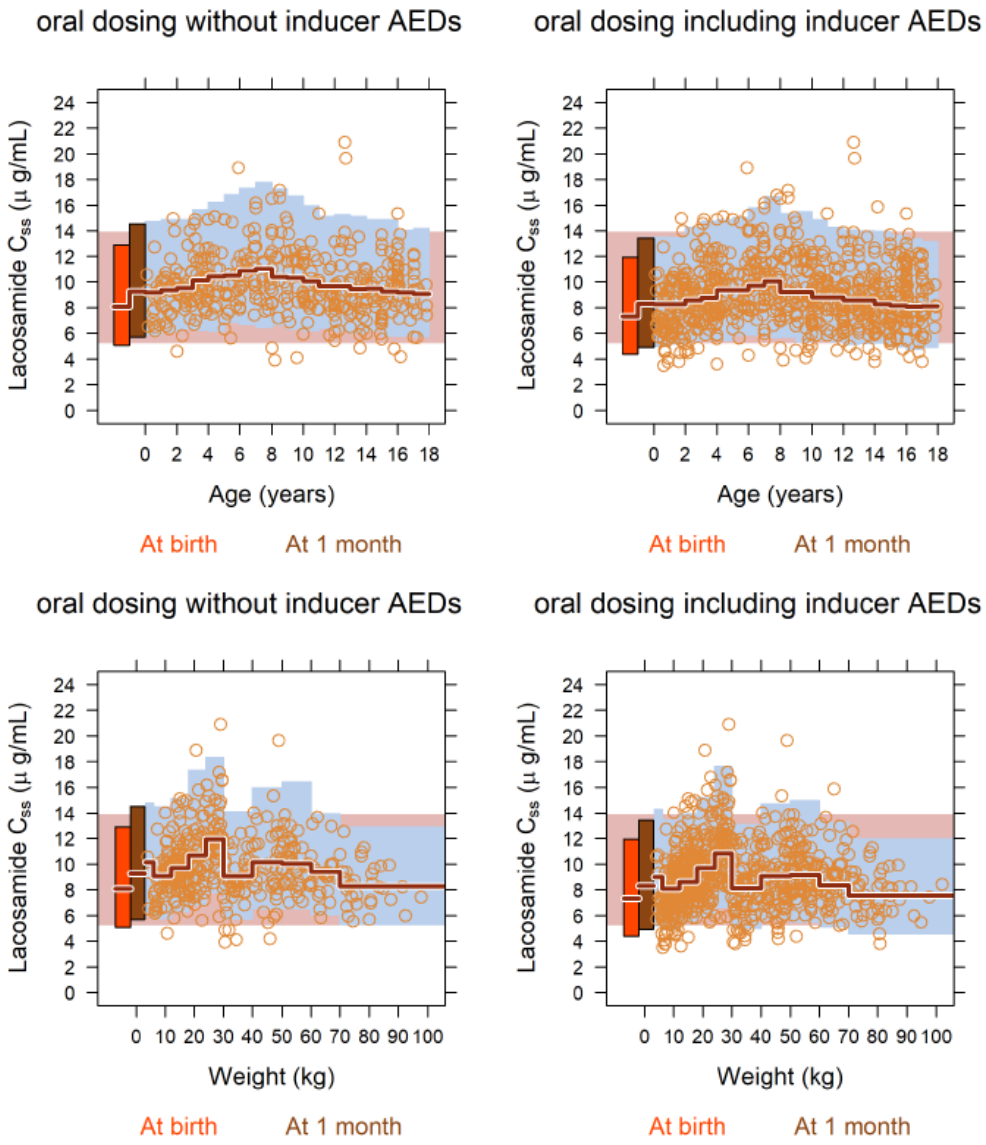
Source: Applicant's population PK report: CL0447-Part IV, Figure 21, Page 50

The VPC plot shows close agreement between the observed and model predicted PK data after 1000 simulations.

Applicant's PK simulations to support pediatric dosing

Simulations were focused on the similarity in exposure between adults and children and the potential implication for the dosing schedule, both for monotherapy and add-on therapy as well as oral and IV dosing. The National Health and Nutrition Examination Survey Dual Energy X-ray Absorptiometry (NHANES DXA) database was used to generate virtual population for PK simulations. The dosing scheme used for these PK simulations were: 7.5 mg/kg bid oral dose or a 5 mg/kg tid IV dose for weight <6 kg, a 6 mg/kg bid oral dose for 6 kg to <30 kg, a 4 mg/kg bid dose for 30 kg to <50 kg, and a 200 mg bid dose for weight ≥ 50 kg. The PK simulations were performed to assess if LCM average steady-state concentrations over 24 hours (Cavg,ss) in pediatric patients are within the range of adult values, and if these values are comparable between oral and IV dosing in children for the same dosing regimen (***Figure 2*** and ***Figure 3***).

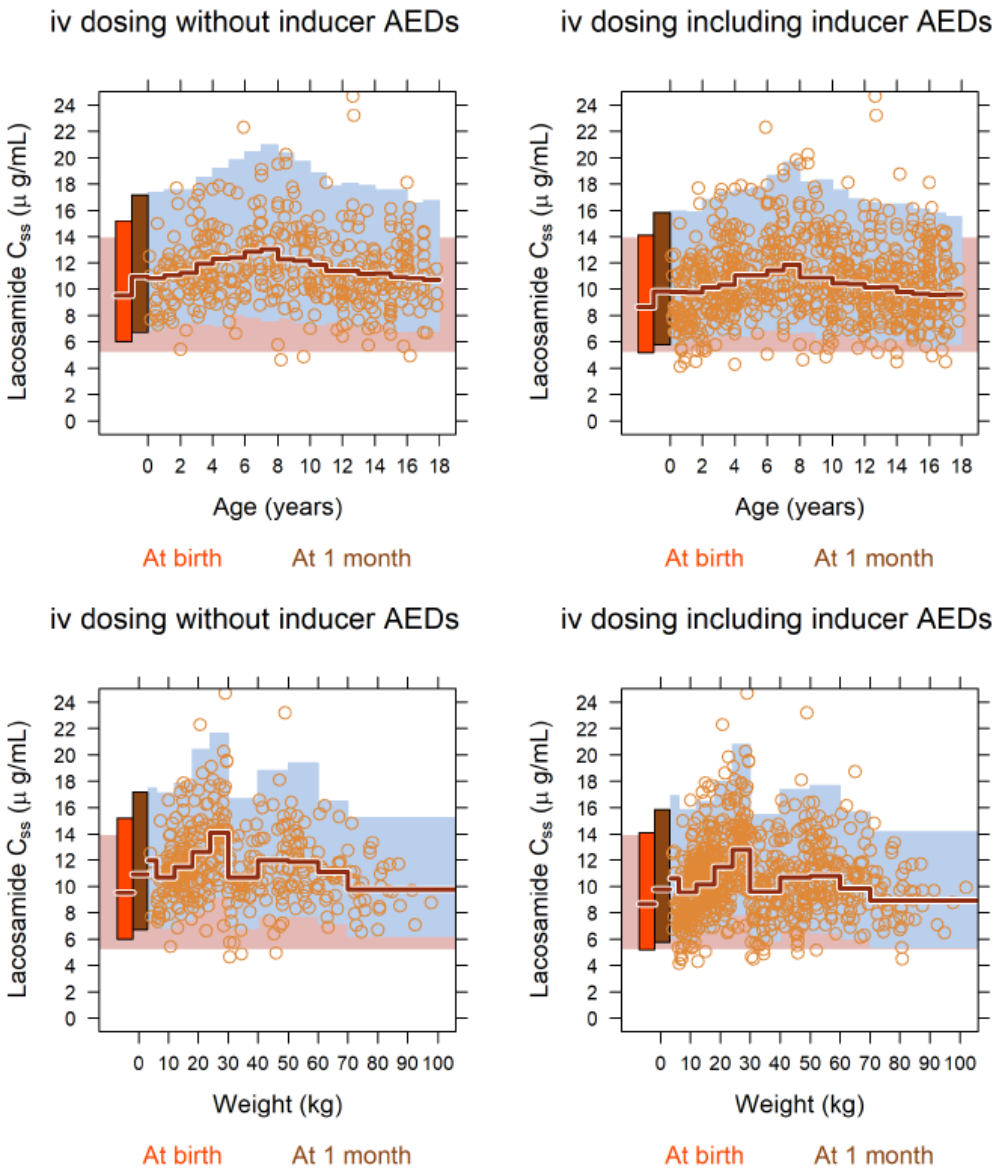
Figure 2: Predicted LCM average steady-state daily concentration after oral dosing (with and without inducer coadministration) across age (0 to 18 years) and weight (0 - 100 kg) ranges after applicant's proposed dosing scheme



Bars at the left of the graphs indicate predictions at birth and at 1 month. Red line and blue area (and bars): median and 90% of simulated average steady-state concentrations for subjects <18 years sampled from the NHANES database. Pink area represents adult concentration range. Orange circles: individual predicted steady-state daily concentrations

Source: Applicant's population PK report: CL0447-Part IV, Figure 25, Page 56

Figure 3: Predicted LCM average steady-state daily concentration after IV dosing administration (with and without inducer coadministration) across age (up to 18 years) and weight (up to 100 kg) after applicant's proposed dosing scheme



Bars at the left of the graphs indicate predictions at birth and at 1 month. Red line and blue area (and bars): median and 90% of simulated average steady-state concentrations for subjects <18 years sampled from the NHANES database. Orange circles: individual predicted LCM Css values.

Source: Applicant's population PK report: CL0447-Part IV, Figure 26, Page 57

***Reviewer Comments**:*

The dosing scheme used by the applicant for conducting PK simulations in adult and pediatric population are acceptable. Overall, the model-predicted Cavg,ss in pediatric patients 1 month and older were in the adult range across all body weights following LCM dosing with oral tablet, solution and IV dosing. The reviewer also conducted independent assessment of the above population PK analysis and is described below.

3.4 Reviewer's Independent Analyses

Final population PK model evaluation

The reviewer was able to run the applicant's final PK model and obtained similar results. Additional model diagnostics were run by the reviewer and are shown in **Figure 4**, **Figure 5**, and **Figure 6**, which suggest that the PK model adequately described the data in pediatric group aged 1 month to 4 years. Individual clearances (normalized based on per kilogram body weight) were also compared across age and weight groups, which showed higher clearance per kilogram for lower body weights and younger age groups and suggested the need of higher dose (mg/kg) in pediatric subjects aged 1 month to 4 year (**Figure 7**).

Figure 4: Goodness-of-fit plots of applicant's population PK model for LCM

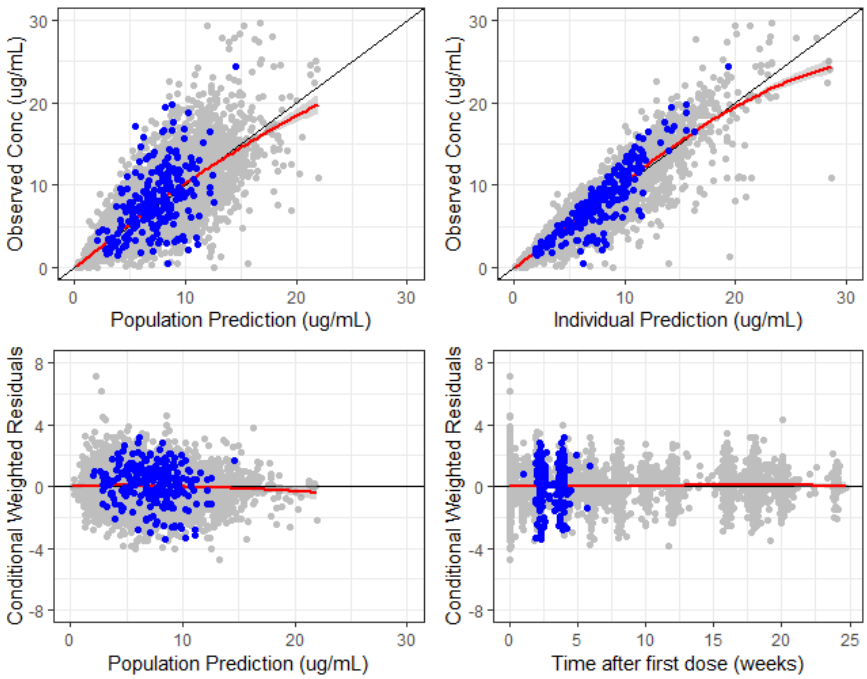


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Figure 5: PK profiles of LCM stratified by age group. Black and blue line represents observed and model-predicted loess smooth lines through data.

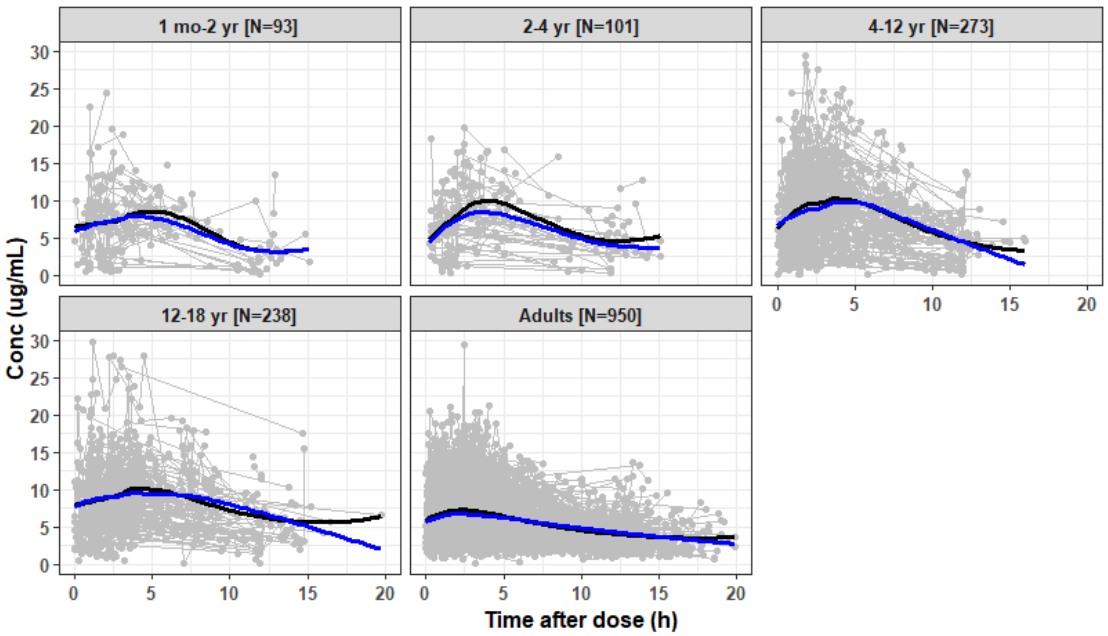

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Figure 6: PK profiles of LCM stratified by age group. Black and blue line represents observed and model-predicted loess smooth lines through data.

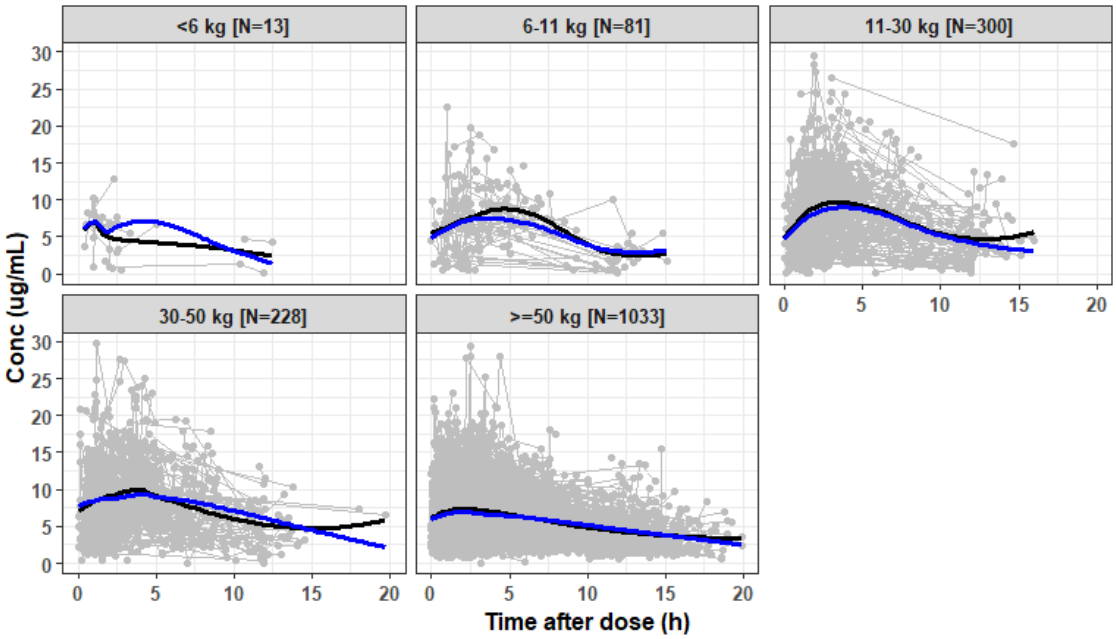

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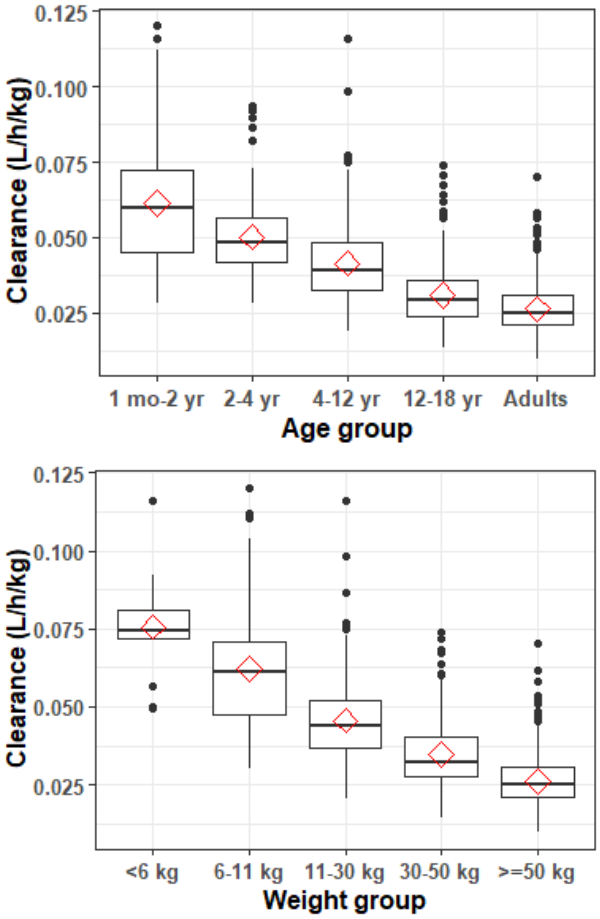
Figure 7: Boxplots of individual clearances (normalized based on per kilogram body weight) were also compared across age and weight groups



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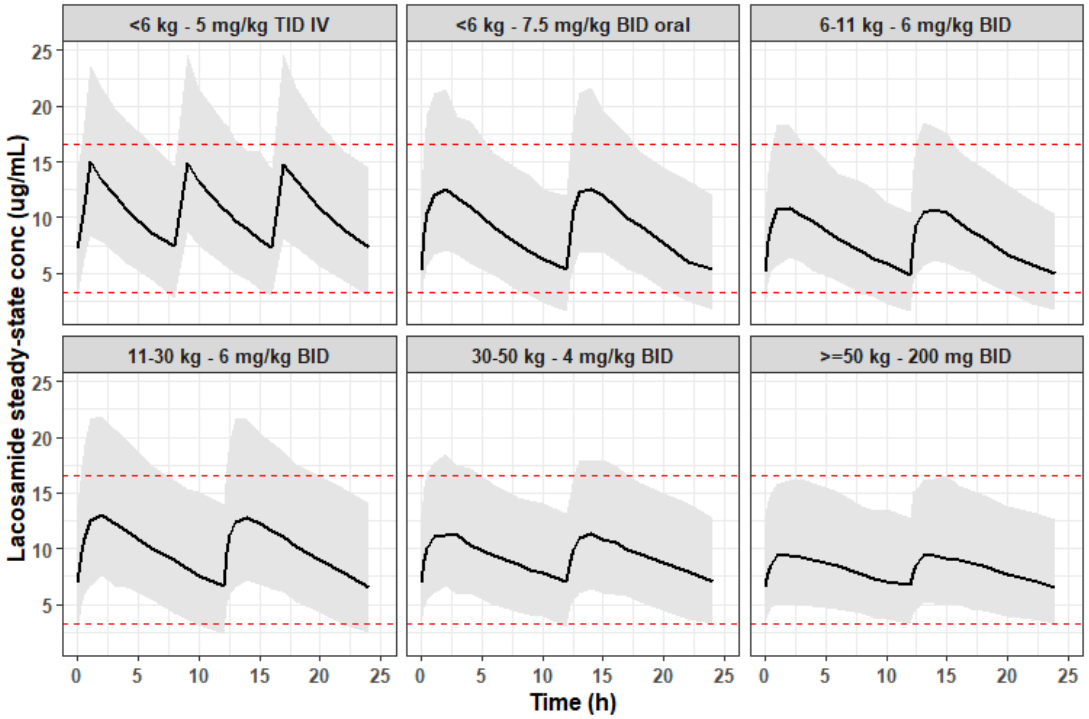
Population PK simulation

Reviewer conducted independent analysis to evaluate the applicant's proposed dosing scheme for pediatric group 1 month to < 4 years using model-based approach. Briefly, PK simulations were performed based on the applicant's final population PK model. The demographic information required for the PK simulation was taken from the available PK dataset of LCM using random sampling with replacement approach. The maintenance dosing scheme used for these PK simulations were: 7.5 mg/kg bid oral dose or a 5 mg/kg tid IV dose for weight <6 kg, a 6 mg/kg bid oral dose for 6 kg to <30 kg, a 4 mg/kg bid dose for 30 kg to <50 kg, and a 200 mg bid dose for weight ≥ 50 kg. The steady-state PK profiles of 50 subjects per weight group in subjects without inducer AEDs were simulated (n=20) to create 1000 PK profiles for each weight groups (**Figure 8**).

Figure 8: Median steady-state PK profiles of LCM after the proposed maximum dose regimen allowed across the weight groups in subjects without inducer AEDs. Grey band and red lines represent 90% prediction intervals in the respective weight groups and adults, respectively.



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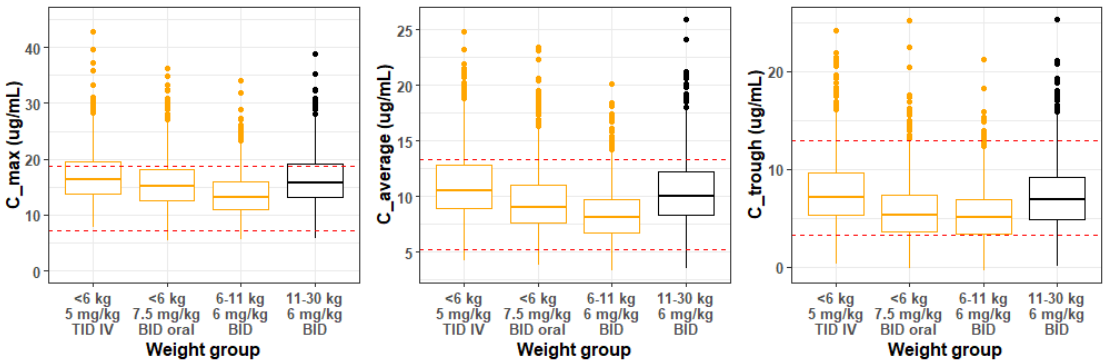
Various PK parameters including steady-state C_{max}, $C_{average}$ and C_{trough} were derived from these PK profiles and evaluated across weights groups and age groups (**Figure 9)**. As shown in **Figure 9A**, middle 50% (range between 25th percentile and 75th percentile) of the PK exposures in pediatric subjects weighing less than 11 kg were within 90% (range between 5th percentile and 95th percentile) of adult exposures. The concentration ranges simulated for pediatric subjects were similar to the adult exposures. In pediatric group <6 kg receiving 5 mg/kg TID IV, the C_{max} was higher than adult group, but similar to the C_{max} obtained in pediatric group 11 - 30 kg at the approved dose of 6 mg/kg BID. The differences in median concentrations between different weight groups were less than 20%. The PK parameters were also evaluated across age groups (**Figure 9B**) which suggested that PK exposures in subject aged 1 month – 4 years at the proposed dose were similar to the exposures achieved in subjects age 4 years and older. These findings will also be applicable for the lower maintenance doses considering linear PK of LCM across these doses. Similarly, these findings will be valid for subjects with

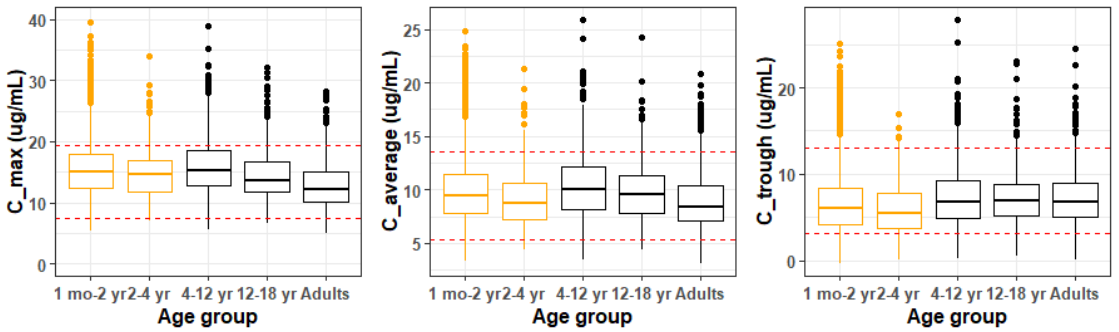
inducer AEDs considering similar impact of inducer AEDs on the PK of LCM across age groups.

Figure 9: Boxplots of steady-state C_{max}, $C_{average}$ and C_{trough} of LCM after the proposed maximum dose regimen allowed across the weight groups (A) and age groups (B).

A.



B.



Red dashed lines represent 90% prediction intervals of the respective adult exposures. Orange and black boxplots represent PK exposures after the proposed and approved dose respectively.

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3.5 Key Conclusions

Consistent with Agency's current policy for extrapolation of efficacy from adults, the Applicant provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar LCM exposures in pediatric subjects 1 months to < 4 years of age to LCM exposure levels demonstrated to be effective in adult subjects with POS (i.e., maintenance dose of 200 mg BID). The applicant's proposed dosing recommendations for maintenance regimen for LCM in patients 1 months to < 4 years of age (weighing < 6 kg) is acceptable.

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/s/

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