Clinical Pharmacology Review

PRODUCT (Generic Name):	Lacosamide
PRODUCT (Brand Name):	VIMPAT ®
sNDA:	022253, 4, 5/SUPPL-039, 30, 22
DOSAGE FORM:	Tablet/injection/oral solution
ROUTE of ADMINISTRATION:	Oral / injection
INDICATION:	Monotherapy or adjunctive therapy in patients 4 years of age and older with partial-onset seizures
SUBMISSION DATE:	01/03/2017
APPLICANT:	UCB Pharma.
OCP REVIEWER:	Dawei Li, Ph.D. (Clinical pharmacology)
	Michael Bewernitz, Ph.D. (Pharmacometrics)
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OCP DIVISION:	DPM/DCP I

1 EXECUTIVE SUMMARY

Vimpat (lacosamide; LCM) is indicated as monotherapy or adjunctive therapy in adult patients with partial-onset seizures. Supplements 39, 30 and 22, efficacy supplements, were submitted for the extension of the LCM indication as monotherapy and adjunctive therapy in the treatment of partial-onset seizures to pediatric patients age 4 years or older with epilepsy using extrapolation. Specifically, the current submissions involve efficacy extrapolation from adult patients to pediatric patients as well as extrapolation from adjunctive therapy to monotherapy.

1) Extrapolating LCM adjunctive therapy from adults to children 4 years of age and older for Partial Onset Seizures (POS): The Applicant provided results of pharmacokinetic (PK) analyses to determine a dosing regimen that would provide similar LCM exposure in pediatric subjects 4 years of age and older to LCM exposure in adult subjects with POS (at levels demonstrated to be effective in adults). Due to concerns of the Applicant's analysis regarding conflicting drug-drug interaction assessments between adults and pediatric patients, the reviewer conducted an independent analysis. To derive pediatric doses to match adult exposure, the reviewer conducted PK simulations in a setting where there is no effect of concomitant medications ("monotherapy scenario"). This approach is based on the well-supported assumption that PK interactions resulting from concomitant medications in pediatric patients 4 years of age and older will be comparable to adults.

Using the monotherapy PK simulation scenario, the reviewer assessed the Applicant's proposed dosing regimens as well as additional potential dosing regimens to inform dose selection for the monotherapy indication and for the adjunctive therapy indication in pediatric POS patients.

2) Extrapolating LCM monotherapy from adjunctive in children for the treatment of POS:
To support use of LCM 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. Although there are some drugs that interact with LCM (i.e., carbamazepine, phenytoin, phenobarbital, or a combination thereof) in the adjunctive setting, none of these interactions are clinically relevant to the extent that they require dose adjustment. In addition, the recommended dose for adults in a monotherapy scenario is similar to the recommended dose for adults in an adjunctive therapy scenario. For this reason, it is reasonable to recommend the same dose in a monotherapy scenario as is recommended for an adjunctive therapy scenario for pediatric patients age ≥ 4 years.

As a result, for monotherapy and adjunctive therapy, OCP proposes a maintenance dose of 3 to 6 mg/kg twice daily, 2 to 4 mg/kg twice daily, and 150 to 200 mg twice daily for pediatric patients weighing 11 kg to < 30 kg, 30 to < 50 kg, and ≥ 50 kg, respectively. Based on the previous labeled doses for adults, 100 mg twice daily can be used in an adjunctive therapy scenario for pediatric patients weighing ≥ 50 kg.

2 RECOMMENDATIONS

The Office of Clinical Pharmacology reviewers have reviewed NDA 022253/4/5 Supplements 039, 30, and 22 for Vimpat (lacosamide). The Applicant's submission is acceptable from the perspective of the Office of Clinical Pharmacology and we recommend approval provided that an agreement is reached between the Applicant and Agency regarding labeling language.

3 BACKGROUND

Lacosamide (LCM) is currently approved as monotherapy and adjunctive therapy of partial onset seizures (POS) in patients 16 years of age and older with epilepsy. For monotherapy in adults, the initial recommended dose is 100 mg twice daily; based on individual patient response and tolerability, the dose can be increased at weekly intervals by 50 mg twice daily, up to a recommended maintenance dose of 150 mg to 200 mg twice daily. For adjunctive therapy in adults, the initial recommended dose is 50 mg twice daily; based on individual patient response and tolerability, dose can be increased at weekly intervals by 50 mg twice daily, up to a recommended maintenance dose of 100 mg to 200 mg twice daily.

In this efficacy supplement, the Applicant proposes to extend the indication for the use of LCM as monotherapy and adjunctive therapy in the treatment of partial onset seizures in patients down to 4 years of age based on extrapolation. OCP's recommended dose regimen is shown in Table 1.

Table 1: LCM Dosage Schedule for Pediatric Patients Aged 4 to 17 Years Old

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	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)

4 GENERAL ADVICE FOR PEDIATRIC EXTRAPOLATION

On November 12, 2015 DNP sent a General Advice Letter to the Applicant indicating that it was acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults and on an analysis of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS.

The following will be required to support an indication for the treatment of POS in subjects 4 years and older that relied upon extrapolation:

• An approved indication for the treatment of POS in adults.

- A pharmacokinetic (PK) analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric subjects 4 years of age and older and in adult subjects with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric subjects 4 years 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 pharmacokinetic information adequate to demonstrate such similarity, taking into consideration possible drug-drug interactions (enzyme inhibition or induction) that may alter the metabolism of the drug.

5 CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

Clinical PK studies conducted in pediatric subjects with epilepsy

SP847: A multicenter, open-label dose-titration study investigating LCM oral solution (1 mg/kg twice daily to up to 6 mg/kg twice daily) as adjunctive therapy in pediatric subjects aged 1 month to 17 years with uncontrolled POS. The objectives of the study were 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.

SP1047: A multicenter, open-label study to investigate the pharmacokinetics of commercial oral LCM as therapy in pediatric subjects aged 1 month to 17 years with epilepsy. SP1047 was designed to augment the PK data obtained from SP847, by collecting sparse samples from pediatric subjects with epilepsy. Patients enrolled were already receiving LCM by prescription and continued their prescribed dose throughout the PK sampling period.

CL0177: Population pharmacokinetic analysis of oral LCM in pediatric studies SP847 and SP1047. This population PK model was developed for pediatric subjects ≥ 1 month to ≤ 17 years of age, to evaluate the influence of demographic factors and concomitant AEDs on pediatric LCM PK parameters, and to estimate pediatric dosing adaptations.

6 RESULTS OF APPLICANT'S POPULATION PK ANALYSIS

The Applicant utilized the pediatric population PK model described in report Cl0177 and the adult population PK model described in report CL0261 for generating the simulated adult and pediatric exposures to inform pediatric dose selection. The adult and pediatric models are briefly described below. A detailed summary of the PK models can be found in the index.

Adult Population PK Model: The following is a summary of the adult population PK model. For details regarding the adult population PK model development, please refer to the appendix.

Applicant utilized data from Phase 3 study EP0008, Phase 3 study SP754, and Phase 3 study SP755 to generate the population PK model representing adult epilepsy patients.

The final model utilized one compartment, first order absorption, and was parameterized in terms of k_a (oral absorption rate constant), V/F (apparent volume of distribution), and Cl/F (apparent clearance). Covariates for clearance include race, categorical use of concomitant enzyme-inducing anticonvulsant drugs (carbamazepine, phenytoin, phenobarbital, or a combination thereof), and weight. Weight was the only covariate for V/F. Weight was related to Cl/F and V/F using allometric scaling based on body weight normalized to 70 kg.

$$CL/F\ (L/h) = 1.92 \cdot (0.827)^{RACE} \cdot (1.34)^{INDUC} \cdot (WT/70)^{0.375} \quad \text{(equation 1)}$$

$$V/F\ (L) = 59.5 \cdot (WT/70)^{0.625} \quad \text{(equation 2)}$$

Source: page 46 of 111, cl0261-pk-report.pdf (sequence 0191)

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

Table 2: PK Parameter Estimates for the Final PK Model in Adults Subjects with Partial Epilepsy

Parameter	*Estimate*	*SE**	*CV (%)*	*95% CI***
Thetas				
CL (L/h)	1.92	0.0301	1.57	1.86 / 1.98
V (L)	59.5	3.19	5.36	53.3 / 65.8
KA (1/h)	1.74	0.222	12.8	1.30 / 2.17
CL_RACEGRP	0.827	0.0179	2.17	0.791 / 0.862
CL_INDUC	1.34	0.0245	1.83	1.29 / 1.38
F1_WTBSL_power	0.375	0.0408	10.9	0.295 / 0.455
Residual error (proportional)	0.160	0.00977	6.11	0.141 / 0.179
Residual error (additive; µg/mL)	0.688	0.0684	9.94	0.554 / 0.822
	Estimate	*SE**	*CV (%)*	*100*sqrt(Omega²)*
Random effects				
Omega² CL	0.0353	0.0135	38.4	18.8%
Omega² V	0.426	0.0518	12.2	65.3%
Omega² F1	0.0201	0.0127	63.5	14.2%

Source: Page 45 of 111, cl0261-pk-report.pdf (sequence 0191)

In the adult model, inducers cause a 34% increase in Cl/F and Asians have 17.3% lower Cl/F compared to non-Asians.

Pediatric Population PK Model: The following is a summary of the pediatric population PK model. For details and discussion regarding pediatric population PK model development, please refer to the appendix.

The Applicant pooled data from Phase 1 study SP847 and Phase 1 study SP1047 to generate the pediatric population PK model.

The Applicant's final model utilized one compartment, first-order oral absorption, and was parameterized in terms of Cl/F, V/F, and k_a. Covariates on Cl/F were categorical use of concomitant enzyme-inducing anticonvulsant drugs (carbamazepine, phenytoin, phenobarbital, or a combination thereof) and weight. Weight was the only covariate for V/F. Weight was related to both Cl/F and V/F using weight-based allometric scaling normalized to 70 kg.

$$CL/F = \exp((\log(\Theta 3) + \Theta 6 * \log(WT/70) + IND * \Theta 7) + ETA1)$$

(equation 3)

$$V/F = \exp((\log(\Theta 4) + \log(WT/70)) + ETA2)$$

(equation 4)

Source: Page 45 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

Table 3: PK Parameter Estimates for the Final PK Model in Pediatric Subjects with Partial Epilepsy

Parameter	Estimate	SE[1] (%CV)	95% CI [2]	IIV[3]	Shrinkage (%)
CL/F[4] (L/h) (θ3)	2.37	6.9%	2.05/ 2.69	32.3%	6.7%
V/F[5] (L) (θ4)	50.6	6.7%	44.0/ 57.3	24.0%	42.4%
Ka (1/h) (θ5)	2.45	19.5%	1.51/ 3.38	55.1%	51.3%
Allometric scaling factor CL/F (θ6)	0.624	8.8%	0.516/ 0.732		
Change in CL with IND co-administration (%) (θ7)	53.5%	21.0%	23.4%/ 76.6%		
Proportional residual error (SD/mean) (θ1)	0.194	12.5%	0.146/ 0.242		
Additive residual error (SD) (θ2)	0.283	38.1%	0.0716/ 0.495		

Source: Page 45 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

[*Reviewer comment: The theta7 estimate is 0.429. When applying the exponential transformation included in the Applicant's pediatric population PK model, the effect of inducers is* $e^{0.429} = 1.535$*, or a 53.5% increase in Cl/F.*]

Applicant's PK Simulations: Applicant performed simulations to inform pediatric dose selection. PK profiles were simulated for virtual pediatric patients using the pediatric PK model. PK parameters were generated for adults based on the sets of demographic and covariate information from actual adult patients whose data were used to build the adult PK model.

Maintenance Dose Target: Applicant utilized the 200 mg twice daily dose in adults as a target for pediatric dosing.

Simulation Methodology: Applicant obtained data on pediatric weight and age distribution from the Nhanes DXA database for 1999-2004 provided by CDC. For pediatric virtual patients, Applicant selected age and weight combinations from subjects in the Nhanes database with a mass < 76 kg (as the maximum body weight in pediatric PK analysis report cl0177 was 75.6 kg) and age < 17 years. Inducer status for the virtual pediatric patients was randomly assigned such that the same proportion of virtual patients were using inducers as pediatric patients included in pediatric PK analyses (report cl0177). The weight values and assigned inducer status were utilized to generate PK parameters which were then used to simulate LCM exposures in the virtual pediatric patients.

[*Reviewer comment: The pediatric and adult simulations incorporated a concomitant inducer proportion comparable to the ratio of patients receiving inducers in the corresponding adult or pediatric patient PK dataset.*

The Applicant's analyses indicate that the inducer effect size in pediatric patients is greater than the inducer effect size in adult patients (53.5% versus 34.4% increase in Cl/F, for pediatric and adult patients, respectively). However, the effect of PK interactions is expected to be comparable between adults and pediatric patients, suggesting that other factors (i.e., sample size, study design, variability) may be affecting the PK interaction estimate in pediatric patients. Please refer to the Reviewer's Analyses in Section 7 for details regarding the impact of PK interactions (inducers such as carbamazepine, phenytoin, phenobarbital, or a combination thereof) on the PK simulations and ultimately on pediatric dose selection.]

The adult population PK model has an additional covariate not present in the pediatric population PK model, "race" that refers to the Chinese/Japanese populations (referred to as "Asian") having 17.3% lower CL (CL_RACEGRP = 0.827 in Table 3) than patients that are not Asian. For this reason, Applicant only used the non-Asian adults from studies SP754 and SP755 for the adult PK simulations. Furthermore, patients assessed in study EP0008 were excluded from adult PK simulations as EP0008 enrolled only Asian patients.

Applicant simulated adult steady-state exposure at the 200 mg twice daily adult dose with the equation AUC_{ss} = Dose / CL where Dose is the total daily dose of 400 mg. The AUC_{ss} was divided by 24 hours to obtain steady-state concentration (C_{avss}) in adults.

Applicant derived the 5th percentile and 95th percentile of C_{avss} for adults to use as a reference range for assessing pediatric dose regimens.

The PK simulations of the dosing regimen Applicant provided in support of the proposed dosing are shown in the figure below.

Figure 1: Predicted Cavss for Children < 17 years by Body Weight (Left Panel) and Age (Right Panel)

Based on these simulations, Applicant proposed a dose regimen as is described in the table below.

Table 4: Applicant's Proposed Monotherapy and Adjunctive Dosage Schedule for Pediatric Patients Aged 4 to 17 Years Old

(b) (4)

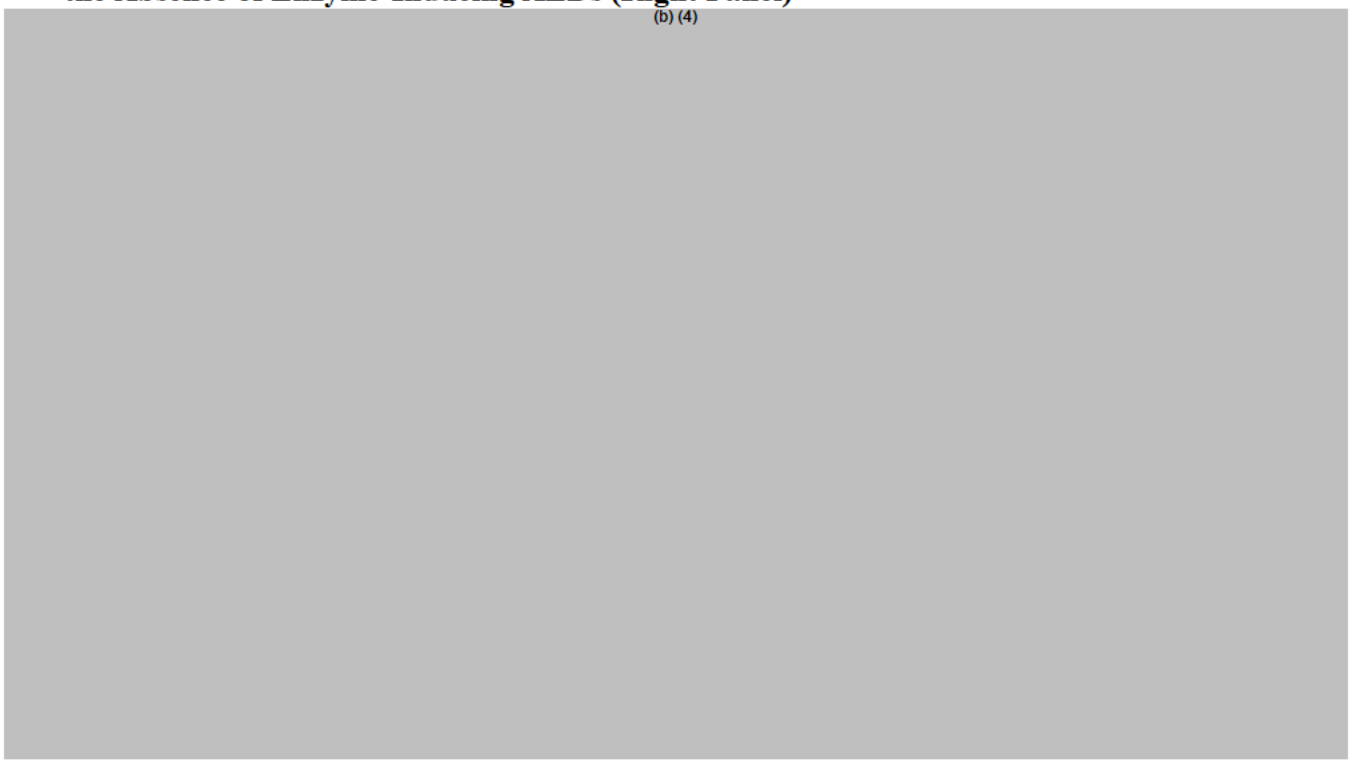
OCP sent an information request on 06/02/2017 stating the following:

> "We are concerned about the potential confounding effect introduced into your pharmacokinetic (PK) simulations by enzyme-inducing anti-epilepsy drug (AED) coadministration. In particular, there appears to be different estimates of the effect of enzyme-inducing AED co-administration in adults versus pediatric patients (e.g. 53.5% CL/F increase for pediatric patients [cl0177-lcm-pediatrics-extension-report.pdf, page 43 of 125] versus 34% CL/F increase for adult patients [cl0261-pk-report.pdf, page 45 of 111]). However, we expect the effect of AEDs to be similar in the two populations and suggest that the apparent difference in your analyses may be due to other factors (i.e., sample size, study design, variability) and does not represent a true difference. The comparison also appears to be confounded by the different frequency of AED coadministration in adult and pediatric patients used in your PK simulations. Overall, it is unclear how these factors related to drug interaction influence your comparison of simulated PK data from adult patients versus pediatric patients.
>
> You should conduct additional PK simulations in order to provide a comparison of adult epilepsy patients and pediatric epilepsy patients where the potential confounding effect of drug interactions is likely reduced (e.g., adult and pediatric patients both without co-administration of enzyme-inducing AEDs).
>
> As an alternative approach, you may consider estimating the drug interaction effect in the combined pediatric/adult dataset, and conducting additional simulations under the assumption of a similar drug interaction between adult patients in pediatric patients. If you opt to follow this alternative approach, we'd also recommend that you designate the proportion of virtual patients receiving concomitant enzyme inducing AEDs to be the same in adult patients as it is in pediatric patients."

The Applicant's response to the information request was received on 06/23/2017 (sequence 0201). Applicant conducted additional PK simulations under a scenario where the effect of concomitant enzyme-inducing AEDs was inactive for both pediatric patients and adult patients. The resulting "monotherapy scenario" PK simulations provided in sequence 0201 as well as the "adjunctive therapy scenario" PK simulations included in the original submission are provided side-by-side for comparison in the figure below.

Figure 2: Predicted C_{avss} for Children < 17 years by Body Weight and Adult Reference Range with Concomitants Enzyme-Inducing AEDs (Left Panel) and in the Absence of Enzyme-Inducing AEDs (Right Panel)

(b) (4)



The Applicant believes that the difference is small between the PK simulated in monotherapy scenario and PK simulated in an adjunctive therapy scenario. For this reason, the Applicant continued to support their original dose proposal of (b) (4)

[*Reviewer comment: Applicant utilized estimates of between subject variability in PK parameters (eta values from NONMEM) in the PK simulations in adults and pediatric patients. The adult population PK model also includes some off-diagonal elements in the covariance matrix. However, the possibility that physiologically-impossible combinations of PK parameters were generated (particularly involving combinations of PK parameters that did not have an off-diagonal covariance value estimated) when including the full covariance matrix in the PK simulations cannot be ruled out.*

In addition, the Applicant only utilized the maximum adult dose of 200 mg twice daily (400 mg/day) for generating the adult reference range. However, the approved dose range for adult monotherapy is 150 to 200 mg twice daily and the approved dose range for adult adjunctive therapy is 100 to 200 mg twice daily.

For these reasons, OCP decided to conduct independent PK simulations in a monotherapy scenario, retaining the original set of covariates from patients in the observed adult and pediatric population, without between subject variability terms, using the population PK models developed for adult and pediatric patients.]

7 REVIEWER'S ANALYSIS

Based on concerns regarding the reliability of drug interaction estimation in pediatric patients, the reviewer conducted independent PK simulations. In addition, Applicant's PK simulations utilized only the maximum approved adult maintenance dose of 200 mg twice daily. The reviewer's PK simulations included the full range of approved adult doses.

The reviewer's simulations were conducted under a monotherapy scenario (inducer drug interaction term inactive). Though the PK simulations were all conducted under a "monotherapy scenario", the reviewer's independent analyses assessed the proposed regimen for monotherapy treatment as well as the proposed regimen for adjunctive therapy treatment. Bioavailability was assumed to be 1 for both pediatric and adult patients as the current approved label, section 12.3, states that bioavailability is approximately 100%. Pediatric PK simulations utilized the tablet formulation and not the oral solution as OCP previously determined that Applicant provided adequate in vitro and in vivo characterization of lacosamide formulations and adequate data to support a biowaiver request for in vivo assessment of commercial lacosamide tablets (50 to 300 mg strengths) and oral lacosamide syrup (15 mg/ml) (please see the clinical pharmacology review of NDA 022253 signed on 04/04/2008 for details). To ensure a consistent covariate distribution in the virtual population compared to the observed population, covariate sets (weight and race combinations) from individual patients from the observed dataset were obtained to create the virtual population for adults. As weight was the only covariate for pediatric patients, then the n=79 weight values from the observed dataset were applied to create the n=79 virtual pediatric patients. Between subject variability terms were set to zero to help avoid occurrences of physiologically impossible combinations of PK parameters. As there is a race effect on PK in adults (17.3% higher Cl/F in Asians compared to non-Asians) and since 2.5% of the pediatric dataset is Asian, Asians were excluded from PK simulations in adults and pediatric patients. The Applicant also excluded Asians from PK simulations.

The approved dose range for adult monotherapy of 150 to 200 mg twice daily and the approved dose range for adult adjunctive therapy of 100 to 200 mg twice daily were used to generate adult reference ranges. Similar to the Applicant, the reviewer applied weight-based dosing to patients weighing < 50 kg and "flat" non-weight-based dosing to pediatric patients weighing ≥ 50 kg. C_{avss} was simulated for pediatric patients as a function of weight and plotted alongside the simulated C_{avss} for adults for comparison.

The initial PK simulations conducted by the reviewer utilized the Applicant's proposed dose regimen for the monotherapy scenario (b) (4) The simulated PK data are presented in the figures below for the Applicant's proposed pediatric monotherapy dosing and proposed pediatric adjunctive therapy dosing.

Figure 3: Simulated C_{avss} in Pediatric Patients Based on Body Weight and Dose Using Applicant's Proposed Dosing Compared with Simulated C_{avss} in Adult Patients at Proposed Adjunctive Therapy Doses Using a Monotherapy Simulation Scenario

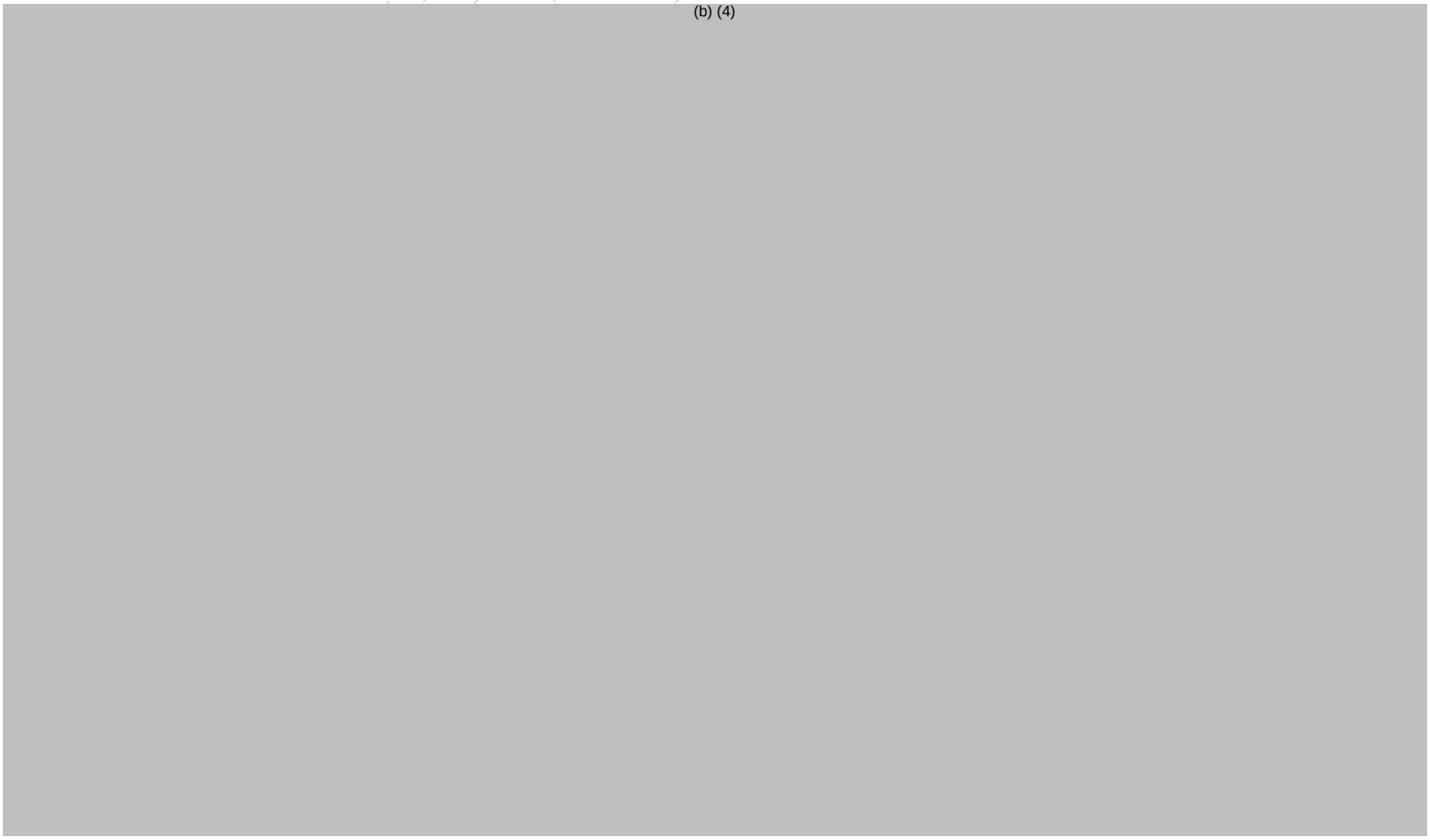


Figure 4: Simulated C_{avss} in Pediatric Patients Based on Body Weight and Dose Using Applicant's Proposed Dosing Compared with Simulated C_{avss} in Adult Patients at Proposed Monotherapy Doses Using a Monotherapy Simulation Scenario

(b) (4)

(b) (4)

OCP conducted additional PK simulations to explore a range of pediatric doses to match the exposure range associated with the range of approved adult doses for both the monotherapy indication as well as the adjunctive therapy indication. The simulated exposures from OCP's final proposed maintenance dose regimens are displayed in the figures below.

Figure 5: Simulated C_{avss} in Pediatric Patients Based on Body Weight and Dose Using OCP's Proposed Dosing Compared with Simulated C_{avss} in Adult Patients at Proposed Adjunctive Therapy Doses Using a Monotherapy Simulation Scenario

(b) (4)

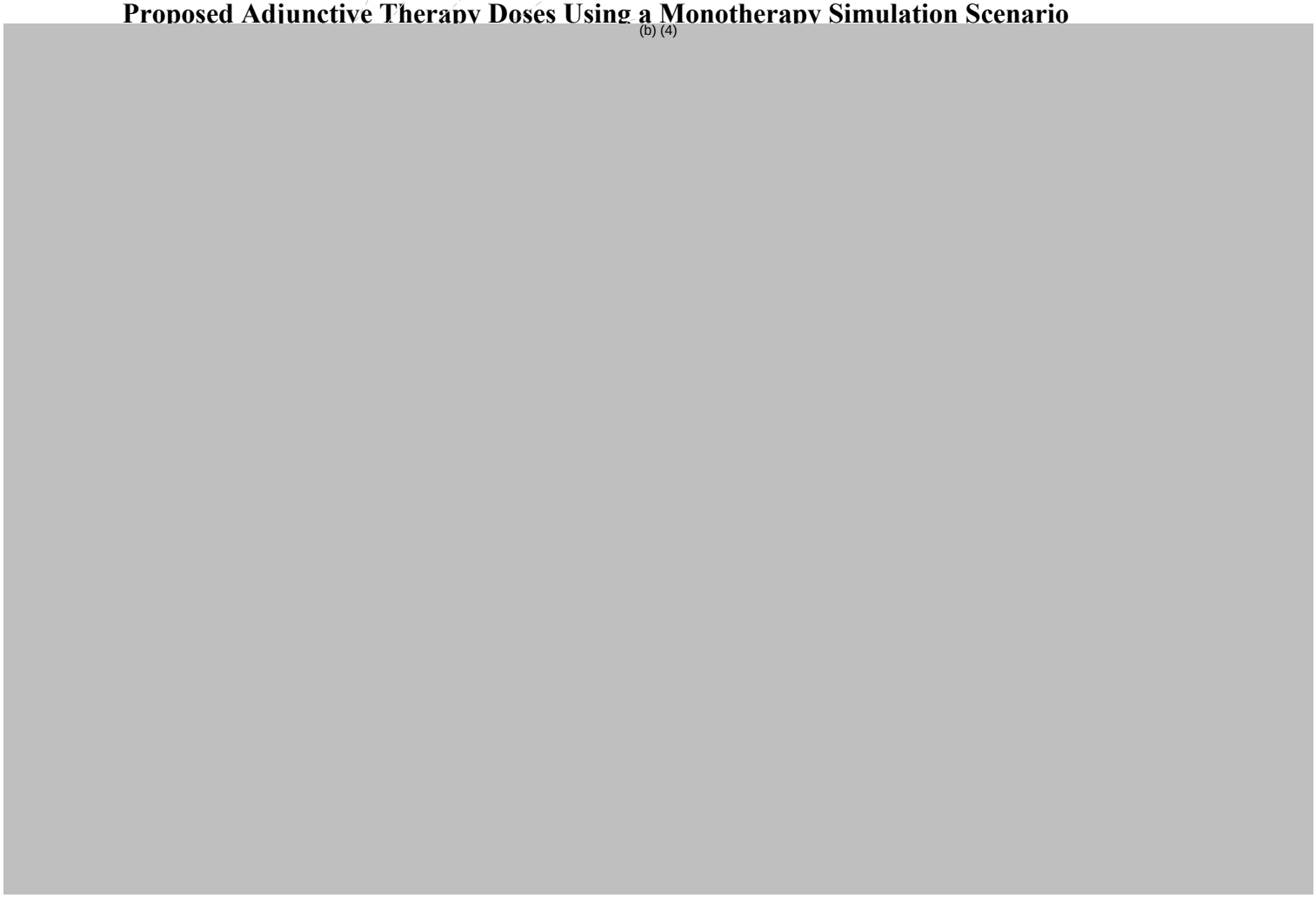
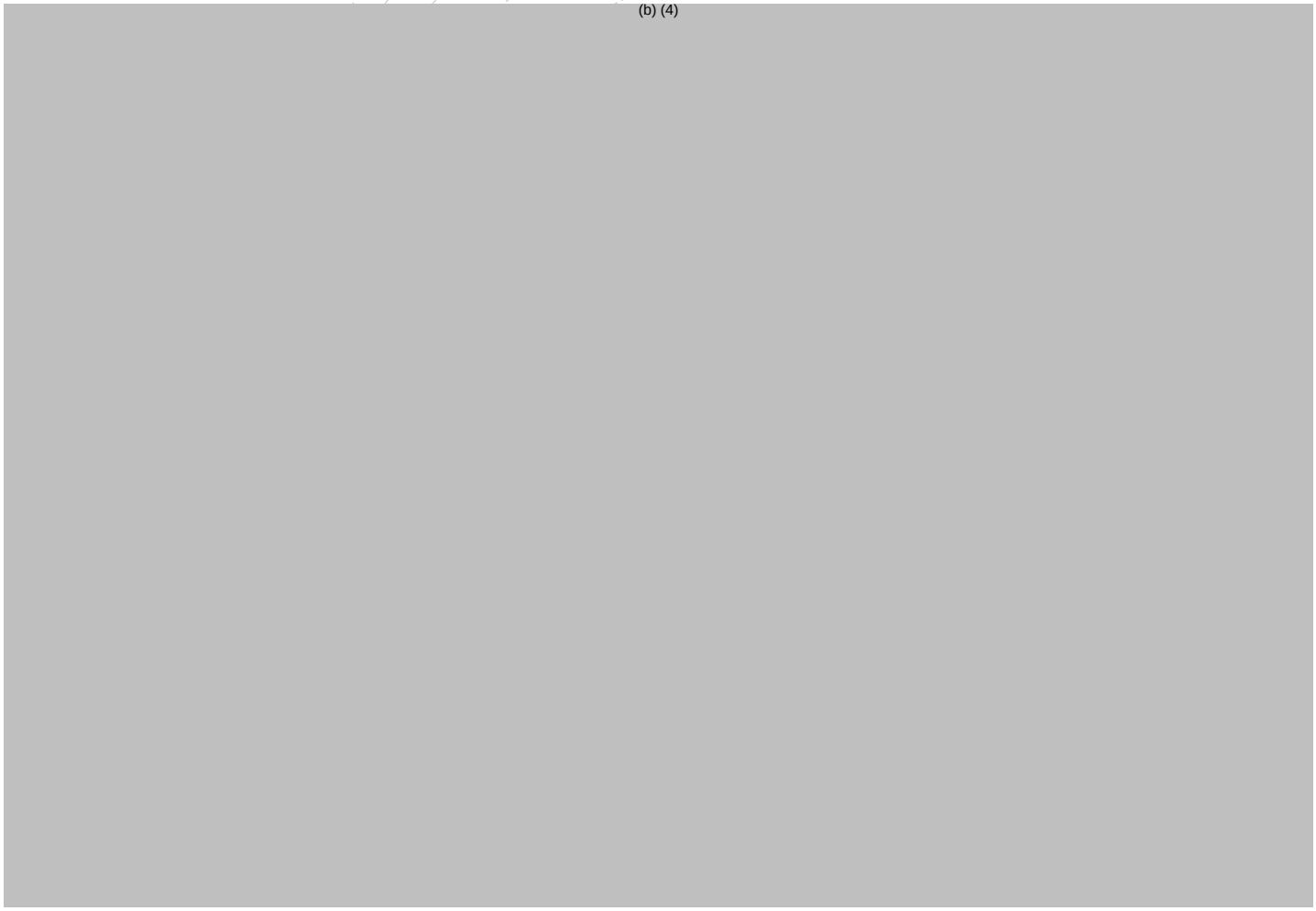


Figure 6: Simulated C_{avss} in Pediatric Patients Based on Body Weight and Dose Using OCP's Proposed Dosing Compared with Simulated C_{avss} in Adult Patients at Proposed <u>Monotherapy</u> Doses Using a Monotherapy Simulation Scenario

(b) (4)



simulations support the use of 3 to 6 mg/kg twice daily, 2 to 4 mg/kg twice daily, and 100 to 200 mg twice daily for pediatric patients weighing < 30 kg, 30 to < 50 kg, and ≥ 50 kg, respectively. Based on the reviewer's simulations regarding monotherapy dosing, the PK simulations support the use of 5 to 6 mg/kg twice daily, 3 to 4 mg/kg twice daily, and 150 to 200 mg twice daily for pediatric patients weighing < 30 kg, 30 to < 50 kg, and ≥ 50 kg, respectively. Following discussions with the clinical team, and to simplify and streamline dosing, **OCP proposes a maintenance dose for both monotherapy and adjunctive therapy of 3 to 6 mg/kg twice daily, 2 to 4 mg/kg twice daily, and 150 to 200 mg twice daily for pediatric patients weighing 11 kg to < 30 kg, 30 to < 50 kg, and ≥ 50 kg, respectively. Based on the previous labeled dosing for adults, pediatric patients weighing ≥ 50 kg, 100 mg twice daily can be used in an adjunctive therapy scenario.**

For patients weighing < 50 kg, Applicant is proposing to use the same titration regimen in the label as was used in the clinical study SP847 (initiation at 1 mg/kg twice daily, increased by 2 mg/kg each day). For patients weighing ≥ 50 kg, Applicant is proposing a lower initiation (50 mg twice daily) and titration schedule (increased by 50 mg twice daily) than was administered to the n=2 subjects weighing ≥ 50 kg in study SP847 (initiation at 1 mg/kg twice daily, increased by 2 mg/kg each day in SP847). After discussion with the Clinical team, OCP and clinical agree **that the proposed initiation dose and dose regimen are acceptable**.

Key label edits: The Applicant's proposed label was edited to include the updated maintenance dose for monotherapy and adjunctive therapy as proposed by OCP.

Michael Bewernitz, Ph.D.

Reviewer, Division of Pharmacometrics (DPM)

Dawei Li, Ph.D.

Reviewer, Division of Clinical Pharmacology 1 (DCP1)

Kevin Krudys, Ph.D.

Team Leader, DPM

Concurrence:

Angela Men, M.D., Ph.D._____

Team Leader, DCP1

cc: HFD-120 NDA# 022253/s-039

HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Dawei Li

Appendix A:

Pediatric Population PK Model Review

The Applicant developed a population PK model to characterize the pharmacokinetics of LCM in pediatric patients with epilepsy, to assess the relationship between LCM exposure and demographics or other covariates, and to conduct PK simulation for informing dose selection in pediatric patients.

Summary of PK Data: Applicant collected 402 concentration measurements from n=79 pediatric patients for use in PK analyses.

Trials: Applicant incorporated PK data from pediatric patients age 0.5 to 17.0 years (n=47) in study SP847 and from pediatric patients age 0.6 to 17.3 years (n=32) in study SP1047. The following table provides key details for these two studies.

Table 5: Clinical Studies from Which PK Data Were Sourced for Population PK Analyses

Study number (country) (Module 5 location)	Study objective(s)	Study design	Number of subjects entered/completed (M/F)	Mean age and age range	Route of administration /dosing regimen	Duration of LCM study treatment
SP847 (US, Mexico, and Belgium) (Module 5.3.5.2)	To evaluate the safety, tolerability, and PK of LCM when added to 1 to 3 concomitant AEDs in pediatric subjects aged 1 month to 17 years with a diagnosis of uncontrolled partial-onset seizures To obtain preliminary efficacy data on seizure frequency	Open-label, uncontrolled, multicenter	57/47 (23M/24F) Cohort 1: (n=7) ≥5 to ≤11 years Cohort 2: (n=9) ≥12 to ≤17 years Cohort 3: (n=8) ≥2 to <5 years Cohort 4: (n=11) ≥5 to <12 years Cohort 5: (n=12) ≥1 month to <2 years	7.03 years (0.5 to 17.0 years)	Oral/LCM oral solution (2mg/kg/day to up to 12mg/kg/day)	Up to 13 weeks
SP1047 (US) (Module 5.3.5.2)	To evaluate the PK of LCM in pediatric subjects with epilepsy, aged 1 month to 17 years	Open-label, uncontrolled, multicenter	34/32 (14M/18F) ≥1 month to <4 years age group (n=10) ≥4 to <12 years age group (n=13) ≥12 to ≤17 years age group (n=9)	8.93 years (0.6 to 17.3 years)	Oral/ commercially available LCM tablets (50mg, 100mg, 150mg, or 200mg), oral solution (10mg/mL) at the dose prescribed[a]	1 day[b]

AED=antiepileptic drug; F=female; LCM=lacosamide; M=male; PK=pharmacokinetics

[a] LCM doses in the Safety Set (N=32) ranged from 1.3 to 5.2 mg/kg/day (SP1047, Module 5.3.5.2, Listing 5.5.1)

[b] LCM study exposure was 1 day; however, subjects were to have been prescribed LCM treatment for at least 7 days before enrollment into SP1047.

Source: Page 10 of 22, sum-clin-pharm-us-peds-4yrs.pdf (sequence 0191)

Dosing: In Study SP847, all patients initiated at 1 mg/kg twice daily and had dose increase by 1 mg/kg/day each day. Cohort 1 titrated up to 4 mg/kg twice daily and Cohorts 2 to 5 titrated up to 6 mg/kg twice daily. Once titration was complete, patients received daily LCM treatment for up to 13 weeks.

Pediatric Population PK Model

The structural model was a one-compartment model with first-order absorption. PK parameters included Cl/F, V/F, and k_a.(absorption constant for the tablet).

Allometric Scaling: weight-based allometric scaling normalized to 70 kg was applied to both Cl/F and V/F.

Inter-individual Variability: exponential

Residual Variability: additive and proportional

Final Model: Cl/F and V/F were expressed using the following equations

$$CL/F = \exp((\log(\Theta 3) + \Theta 6 * \log(WT/70) + IND * \Theta 7) + ETA1)$$

(equation 5)

$$V/F = \exp((\log(\Theta 4) + \log(WT/70)) + ETA2)$$

(equation 6)

Source: Page 45 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

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

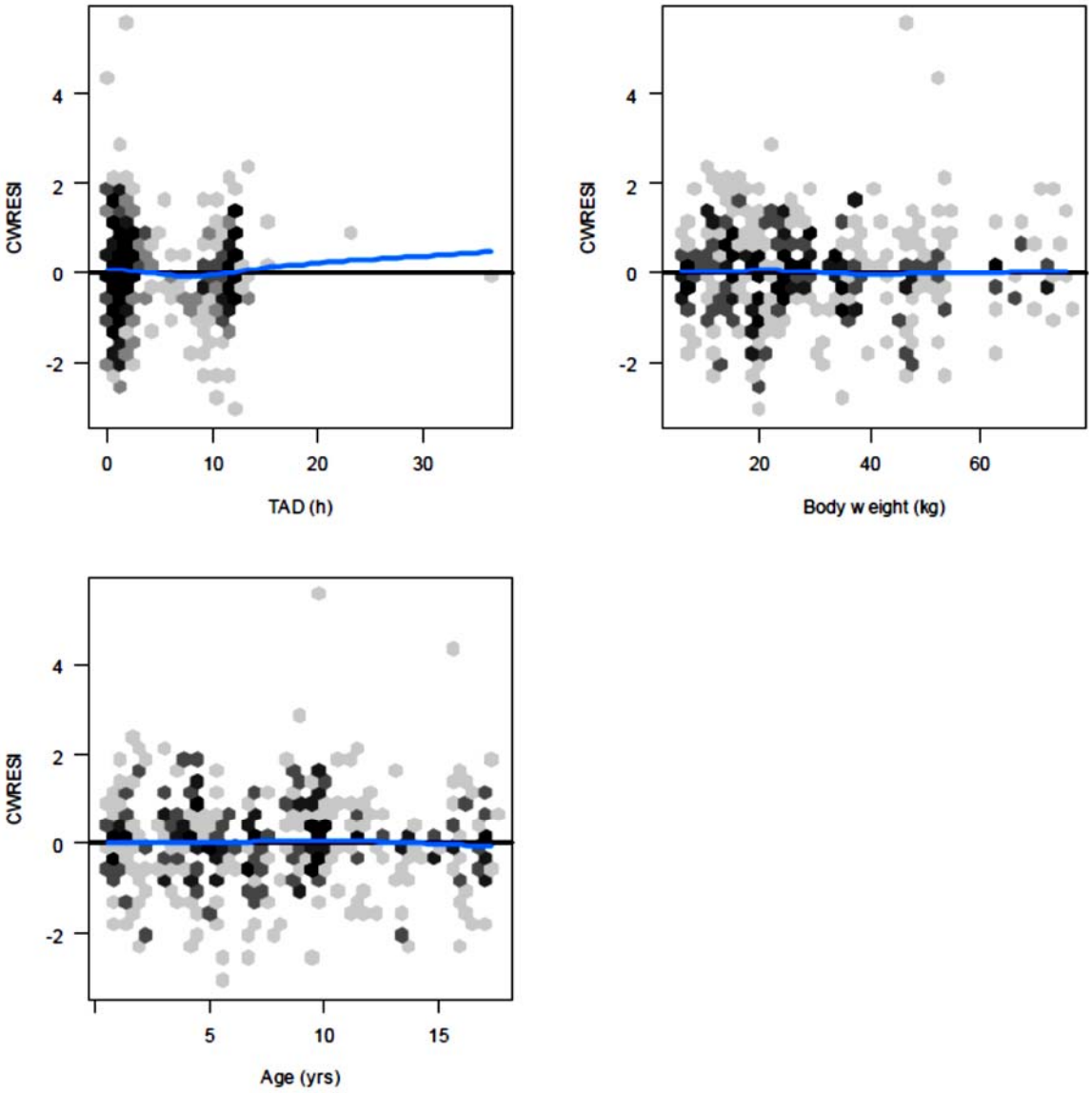
Table 6: PK Parameter Estimates for the Final PK Model in Pediatric Subjects with Partial Epilepsy

Parameter	Estimate	SE[1] (%CV)	95% CI [2]	IIV[3]	Shrinkage (%)
CL/F[4] (L/h) (θ3)	2.37	6.9%	2.05/ 2.69	32.3%	6.7%
V/F[5] (L) (θ4)	50.6	6.7%	44.0/ 57.3	24.0%	42.4%
Ka (1/h) (θ5)	2.45	19.5%	1.51/ 3.38	55.1%	51.3%
Allometric scaling factor CL/F (θ6)	0.624	8.8%	0.516/ 0.732		
Change in CL with IND co-administration (%) (θ7)	53.5%	21.0%	23.4%/ 76.6%		
Proportional residual error (SD/mean) (θ1)	0.194	12.5%	0.146/ 0.242		
Additive residual error (SD) (θ2)	0.283	38.1%	0.0716/ 0.495		

Source: Page 45 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

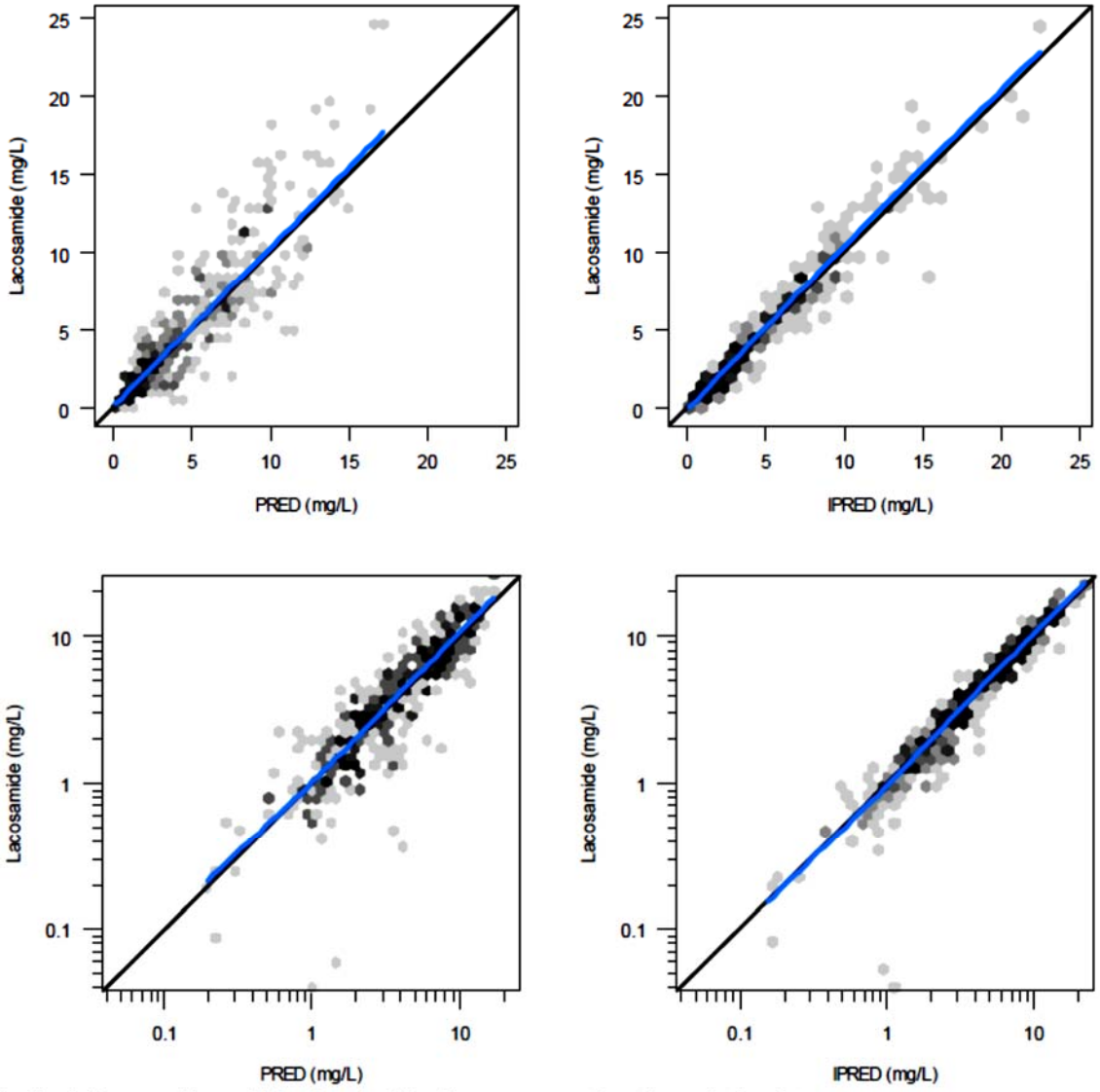
Model diagnostics are presented in the figures below.

Figure 7: Diagnostic Plots for the LCM Pediatric Population PK Model



Source: Page 46 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

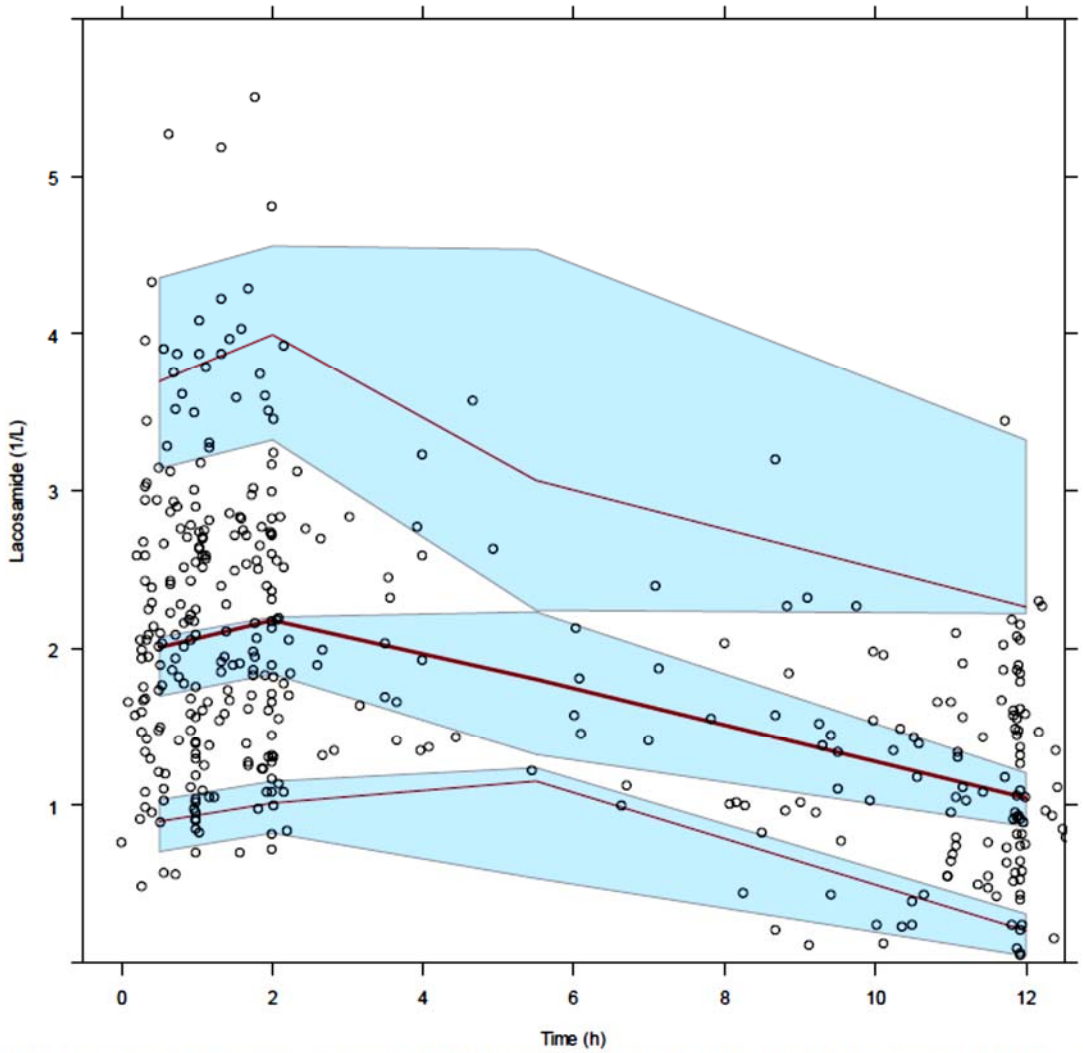
Figure 8: Diagnostic Plots for the LCM Pediatric Population PK Model



The black lines are lines of identity, the blue lines are smoothes through the data.

Source: Page 49 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

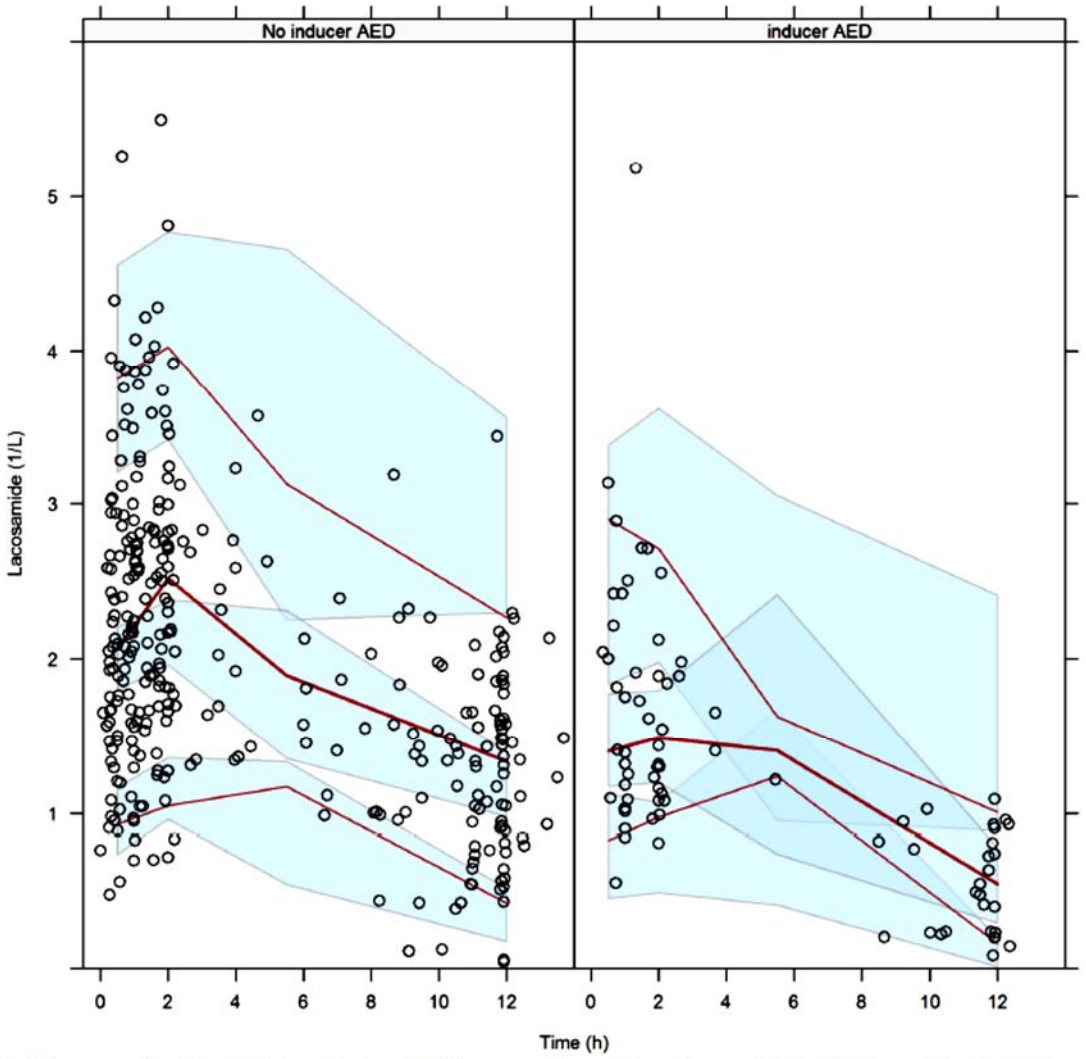
Figure 8: VPC Plot for the LCM Pediatric Population PK Model



Red lines are the 5th, 50th (median) and 95th percentiles of the observed data (dots) and the light blue areas contain 95% of the simulated quantiles using runS613a.

Source: Page 52 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

Figure 9: VPC Plot for the LCM Pediatric Population PK Model by Inducer AED Status



Red lines are the 5th, 50th (median) and 95th percentiles of the observed data (dots) and the light blue areas contain 95% of the simulated quantiles using runS613a.

Source: Page 55 of 125, cl0177-lcm-pediatrics-extension-report.pdf (sequence 0191)

[*Reviewer comment: Based on the diagnostic plots, there is no apparent systematic bias across the dosing interval, across the range of LCM concentrations, by age, or by weight.*

The Applicant determined that concomitant use of enzyme-inducing AEDs is a covariate for both Cl/F and V/F. Allometric scaling normalized to 70 kg was implemented to account for changes in LCM Cl/F and V/F due to maturation of organ systems involved in LCM disposition, which is acceptable.

Similar to the adult PK model, enzyme-inducing AEDs was included as a covariate on Cl/F. However, in the adult model inducers increase Cl/F by 34% yet in the pediatric model inducers increase Cl/F by 53.5%. The effect of enzyme-inducing AED on LCM PK is expected to be similar in adults as in pediatrics and may be due to other factors (e.g. sample size, study design, or variability) and may not represent a true difference between the two populations. In addition,

when viewing a VPC in subpopulations stratified by inducer AED use, the confidence intervals appear wider for patients receiving concomitant inducer AEDs than patients who did not receive concomitant inducer AEDs (Figure 9). For these reasons, the reviewer's PK simulations described in Section 7 were conducted with the inducer term inactive for both the adult model and the pediatric model.

Overall, the Applicant's pediatric population PK model building procedure appears reasonable. However, the pediatric PK model generates pediatric clearance values at 70 kg which are lower than the same weight for the adult PK model. Please refer to the comments at the end of Appendix B for details.

Based upon concerns regarding the reliability of drug interaction estimation in pediatric patients, simulations with the pediatric PK model should be performed only in a scenario without concomitant enzyme-inducing AEDs.]

Appendix B:

Adult Population PK Model Review

Applicant developed a population PK model to characterize the PK of LCM in adult patients with epilepsy and to assess the relationship of LCM exposure with demographics and other covariates. This PK model was used to generate a "reference range" of exposures expected in adult epilepsy patients receiving the approved LCM dose.

Summary of PK Data: Applicant collected 4272 LCM concentration measurements from n=906 adult epilepsy patients for use in the PK analyses.

Trials: Applicant incorporated PK data from adult patients in trial EP0008 (n=342), SP754 (n=277), and SP755 (n=287). The following table provides key details for these 3 studies.

Table 7: Clinical Studies from Which PK Data Were Sourced for Population PK Analyses

Trial No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/ Route of Administration	Duration of treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
Population PK Report for: SP754/ US	Describe the population PK characteristics of LCM in subjects with partial-onset seizures with or without secondary generalization as part of the Phase 3 trial SP754 and characterize the inter- and intra-individual variability of the population PK parameters of LCM within the trial population	Double-blind, placebo-controlled, multi-center	LCM/ 400mg/day and 600mg/day (200 and 300mg bid)/ oral tablet	Up to 21 weeks	104 placebo, 204 LCM 400mg/day, 97 LCM 600mg/day/ 49.4%M/ 50.6%F	38.3 years/ (16-71)	Complete/ Population PK report
Population PK Report for: SP755/ Australia, Europe	Describe the population PK characteristics of LCM in subjects with partial-onset seizures with or without secondary generalization as part of the Phase 3 trial SP755 and characterize the inter- and intra-individual variability of the PK parameters of LCM within the trial population	Double-blind, placebo-controlled, multi-center	LCM/ 200mg/day and 400mg/day (100 and 200mg bid)/ oral tablet	Up to 18 weeks	163 placebo[e], 163 LCM 200mg/day, 159 LCM 400mg/day/ 51.5%M/ 48.5%F	37.8 years/ (16-70)	Complete/ Population PK report
EP0008 **China, Japan**	**Evaluate efficacy, safety, tolerability, dose-response, and steady-state plasma concentrations of LCM administered concomitantly with 1 to 3 AED(s) in Japanese and Chinese subjects with or without additional VNS who currently had uncontrolled partial-onset seizures with or without secondary generalization.**	**Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel-group study.**	**LCM** **100 mg twice daily or 200 mg twice daily.**	**Up to 16 weeks**	**N=547 (n=184 placebo, n=183 LCM 100 mg twice daily, n=180 LCM 200 mg twice daily)**	**31.4 years (16-67)**	**Clinical Study Report**

Sources: Page 16-17 of 35, tabular-listing.pdf (sequence 0000), page 83 of 279 ep0008-bodytext-global-amend-1.pdf (sequence 0191)

Dosing: In study SP755 and trial EP0008, patients underwent 4-weeks titration starting at 50 mg twice daily with a dose increase of 100 mg/day every week (or matching placebo). In Study 754 the titration dosing was the same but titration lasted up to 6 weeks.

In study SP755 as well as Trial EP0008 the target dose was 100 mg twice daily, 200 mg twice daily or matching placebo. Afterwards, patients randomized to LCM in SP755 and EP0008 received 100 mg twice daily or 200 mg twice daily for 12 weeks in Study SP755.

In Study SP754 the target dose was 200 mg twice daily, 300 mg twice daily, or matching placebo. After titration, patients randomized to LCM received 200 mg twice daily or 300 mg twice daily for 12 weeks.

Adult Population PK Model:

The structural model was a one-compartment model with first-order oral absorption. PK parameters were Cl/f, V/f and k_a (absorption constant for the tablet).

Allometric Scaling: Weight-based allometric scaling applied to Cl/f and, V/f normalized to 70 kg.

Inter-individual Variability: exponential

Residual Variability: additive and proportional

Final Model: Cl/F and V/F were expressed using the following equations

$$CL/F\ (L/h) = 1.92 \cdot (0.827)^{RACE} \cdot (1.34)^{INDUC} \cdot (WT/70)^{0.375} \quad \text{(equation 7)}$$

$$V/F\ (L) = 59.5 \cdot (WT/70)^{0.625} \quad \text{(equation 8)}$$

where RACEGRP=1 for Asians and =0 for non-Asians, and INDUC=1 for inducer AEDs present and =0 for inducer AEDs not present

Source: page 46 of 111, cl0261-pk-report.pdf (sequence 0191)

The PK parameter estimates for the final model are shown in the table below

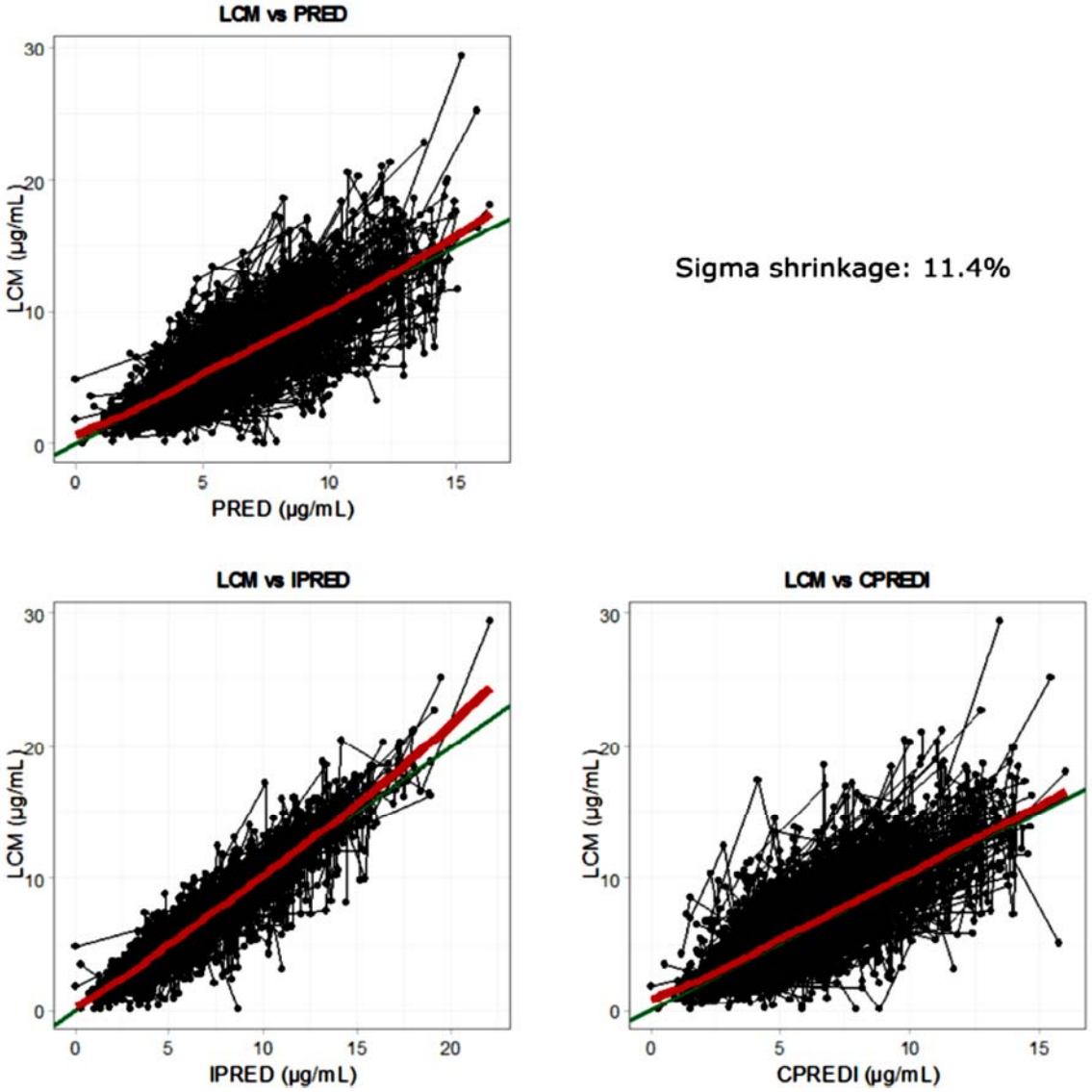
Table 8: PK Parameter Estimates for the Final PK Model in Adult Subjects with Partial Epilepsy

Parameter	*Estimate*	*SE**	*CV (%)*	*95% CI***
Thetas				
CL (L/h)	1.92	0.0301	1.57	1.86 / 1.98
V (L)	59.5	3.19	5.36	53.3 / 65.8
KA (1/h)	1.74	0.222	12.8	1.30 / 2.17
CL_RACEGRP	0.827	0.0179	2.17	0.791 / 0.862
CL_INDUC	1.34	0.0245	1.83	1.29 / 1.38
F1_WTBSL_power	0.375	0.0408	10.9	0.295 / 0.455
Residual error (proportional)	0.160	0.00977	6.11	0.141 / 0.179
Residual error (additive; µg/mL)	0.688	0.0684	9.94	0.554 / 0.822
	Estimate	*SE**	*CV (%)*	*100*sqrt(Omega²)*
Random effects				
Omega² CL	0.0353	0.0135	38.4	18.8%
Omega² V	0.426	0.0518	12.2	65.3%
Omega² F1	0.0201	0.0127	63.5	14.2%

Source: page 45 of 111, cl0261-pk-report.pdf (sequence 0191)

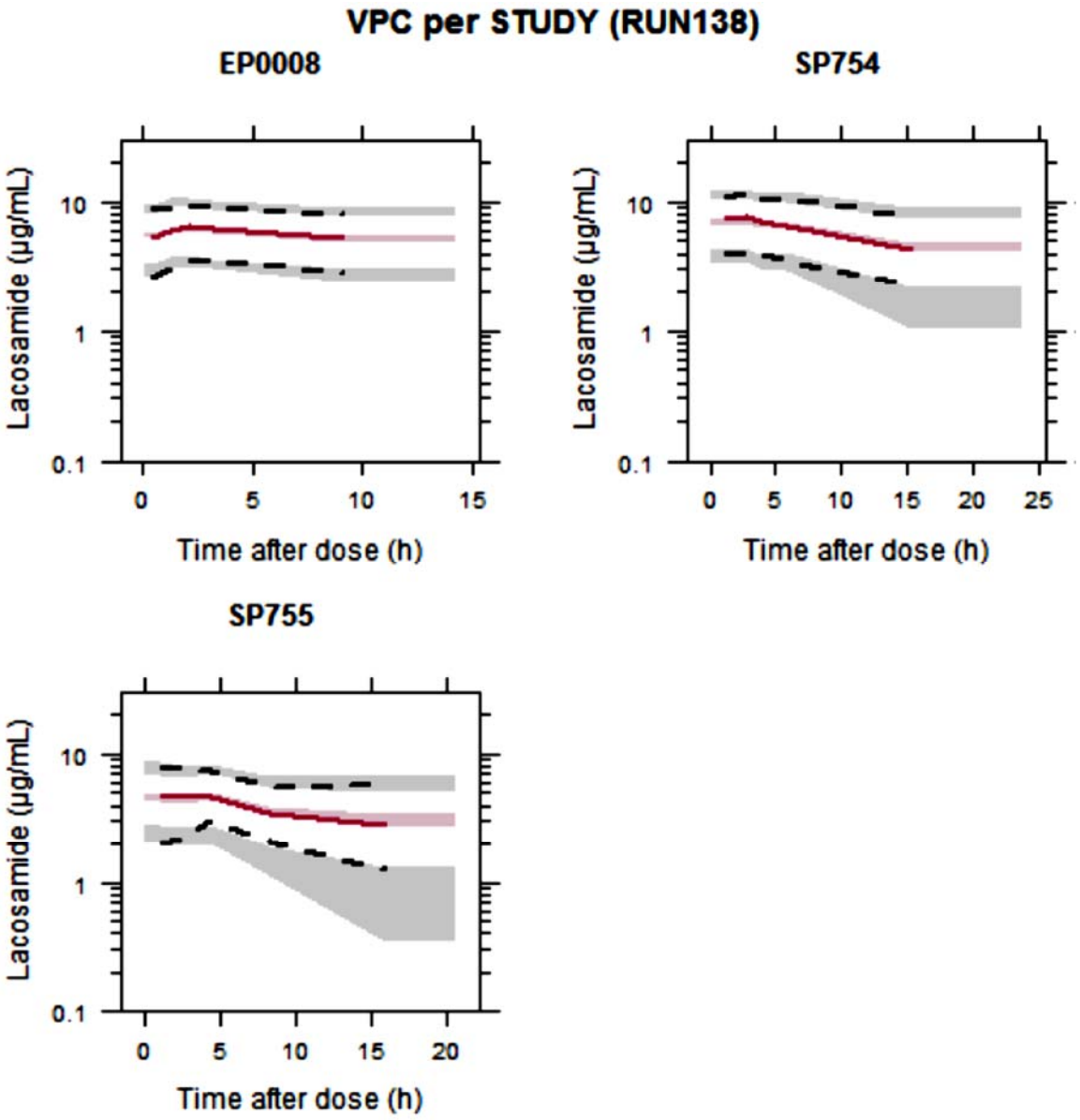
Model diagnostics are presented in the figures below.

Figure 10: Diagnostic Plots for the LCM Adult Population PK Model



Source: page 46 of 111, cl0261-pk-report.pdf (sequence 0191)

Figure 11: VPC per Study for the LCM Adult Population PK Model



Source: page 47 of 111, cl0261-pk-report.pdf (sequence 0191)

[*Reviewer comment: the 95% CI interval for the 5th percentile of the observed data is wider for the studies in the Western studies (SP754 and SP755) than for study EP0008 conducted in east Asia. However, at its widest, the 95% CI of the lower 5th percentile spans ~ 1.5 µg/mL to ~0.5 µg/mL. As the PK simulations utilized C_{avss}, then the uncertainty at the lowest concentrations near the end of the dosing interval is not likely to have a relevant impact on the PK simulations listed in this review.*

Concomitant use of inducers is a mechanistically plausible covariate for Cl/F. However, as the magnitude of the inducer effect on adults (34.5% Cl/F increase) is unexpectedly different than the

inducer effect in pediatric patients (53.5% Cl/F increase), then the inducer effect was deactivated for PK simulations conducted by the reviewer (see section 7 for details).

Race is not a covariate in the pediatric model. However, the pediatric PK dataset includes only 2.5% Asians and thus it is not reasonable to expect such a small representation of Asians in the pediatric study would permit assessment of a race effect on pediatric PK. However, to reduce a race effect from confounding PK simulations, the PK simulations excluded pediatric as well as adult patients that are Asian.

Aside from the wide confidence interval at lower concentration, near the end of the dosing interval, the VPC suggests that the adult model represents the data well. ***Overall, the Applicant's adult population PK model building procedure appears reasonable.***

However, the adult population PK model and pediatric PK model predict different clearance values for adults as for the higher age range of pediatric patients with a comparable body weight. For example, a 70 kg non-Asian patient not receiving concomitant inducers is predicted to have a 1.92 L/h Cl/F based on the adult model yet the pediatric PK model predicts a 2.37 L/h Cl/F (23% higher than for an adult). At this weight, the Cl/F estimate for pediatric patients at 70 kg is expected to be comparable with adults.

It is not clear whether the pediatric exposures are under-predicted, adult exposures are over-predicted or a combination. One approach to address the differing Cl/F predictions at 70 kg is to pool the adult and pediatric population PK data and build a population PK model to represent both populations.

However, assuming the pediatric clearance were underestimated, it is unlikely that the dosing recommendation would change. For example, when using a pediatric Cl/F value 23% lower (which would result in comparable Cl/F for 70 kg adult as a 70-kg pediatric patient), the steady-state exposure in pediatric patients would be expected to increase by ~30% (e.g. using AUC=Dose/CL, AUC increases ~30% when Cl/F decreases Cl by 23%). Even in such a scenario, based upon inspection of the reviewer's PK simulations (Figures 5 and 6) the proposed doses would result in an acceptable match to exposures in adults at the approved dose.]

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/s/

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11/02/2017

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