Summary Review

Date	April 25, 2023
From	Philip H. Sheridan, MD Paul R. Lee, MD, PhD
Subject	Summary Review
NDA/BLA # and Supplement#	022253 (S-50) / 022254 (S-40) / 022255 (S-32)
Applicant	UCB, Inc.
Dates of Submission	June 30, 2022
PDUFA Goal Date	April 30, 2023
Proprietary Name	Vimpat
Established or Proper Name	Lacosamide
Dosage Form(s)	50 mg, 100 mg, 150 mg, 200 mg tablets (NDA 22253); 200 mg/20 ml single-dose vial for intravenous use (NDA 22254); 10 mg/ml oral solution (NDA 22255)
Applicant Proposed Indication(s)/Population(s)	For extension of the use of the oral formulations and intravenous formulation for: • Alternate initial dosing (loading dose) for initiation of treatment of partial-onset seizures in patients 1 month of age and older • Alternate initial dosing (loading dose) for initiation of treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older

Applicant Proposed Dosing Regimen(s)	From the Applicant's proposed labeling: **Recommended Dosages for Partial-Onset Seizures (Monotherapy or Adjunctive Therapy) in Patients 1 Month and Older, and for Primary Generalized Tonic-Clonic Seizures (Adjunctive Therapy) in Patients 4 Years of Age and Older*** (b) (4)

	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	For extension of the use of the oral formulations and intravenous formulation for:

	• Alternate initial dosing (loading dose) for initiation of treatment of partial-onset seizures in patients 1 month of age and older • Alternate initial dosing (loading dose) for initiation of treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older
Recommended Dosing Regimen(s) (if applicable)	See approved labeling

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The overall benefit-risk analysis of lacosamide (LCM) for the treatment of partial-onset seizures (POS) in patients down to 1 month of age, for the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients down to 4 years of age, and for use of a loading dose in adult patients has previously been found to be acceptable.

LCM was approved as VIMPAT in the United States in 2008 for the treatment of partial-onset seizures (POS) in adults in both oral tablet and intravenous (IV) formulations. An oral solution was approved in 2010. The approvals of the oral formulations were extended down to patients age 4 years and older in 2017 using a pediatric extrapolation approach to demonstrate evidence of effectiveness. The IV formulation was approved in pediatric patients down to age 4 years in 2020. The indication of POS for all formulations was extended to pediatric patients 1 month and older in 2021, based on extrapolation of efficacy and demonstration of safety from a randomized, double-blind, placebo-controlled safety and efficacy study in 255 pediatric patients age greater than or equal to 1 month to less than 4 years, an open-label, long-term safety study on the same population, and an open-label safety and tolerability study of the IV formulation in pediatric patients as young as 1 month old.

The safety of VIMPAT at doses in current approved labeling has been well-characterized in adults, and common adverse events noted in pediatric patients are similar to those seen in adults. In this supplemental new drug application (sNDA), the Applicant submitted safety data from a retrospective cohort study which used electronic health record data from the database of a clinical research network which comprises 8 pediatric health systems in the United States. Comparison of pediatric patients between 1 month to less than 17 years who received a first dose of IV LCM which was at or above the proposed loading dose with patients who received a first dose of IV LCM which was below the proposed loading dose did not demonstrate obvious new adverse events (AEs) or obvious increased frequency of AEs in the group who received the higher loading dose, except for an increased risk of rash. Reviews of postmarketing cases compatible with the use of an LCM loading dose in pediatric patients and of publications involving LCM loading doses in pediatric patients provide supportive safety data. The proposed loading dose will allow for rapid titration to maintenance dosing and associated steady-state levels, which has potential benefit in patients who are having an increase in seizure frequency. Loading doses in pediatric patients should be administered with medical supervision because of the increased incidence of central nervous system and cardiac conduction reactions, as is recommended in the previously approved labeling. Cardiac monitoring should continue to be conducted in patients with underlying cardiovascular disease, including cardiac conduction abnormalities, or who are on cardiac medications.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Both partial-onset seizures (POS) and primary generalized tonic clonic seizures (PGTCS) are common in pediatric patients, although POS typically appear at a younger age than PGTCS. • Pediatric patients with epilepsy may have episodes of increased seizure frequency. • Frequent seizures increase the risk of life-threatening conditions such as status epilepticus, as well as the risk for sudden death. • Rapid achievement of a potentially therapeutic concentration level of an antiseizure medication (ASM) may prevent complications of frequent seizures such as status epilepticus, sudden death, emergency department admission, or prolonged hospitalization.	A loading dose which achieves a potentially therapeutic concentration level of an antiseizure medication (ASM) more rapidly than the standard initiation of an ASM would achieve a therapeutic serum level more rapidly and may prevent complications of frequent seizures.
Current Treatment Options	• Approximately 12 currently approved drugs have clearly defined indications for use in pediatric patients with POS and/or PGTCS. • Of the available drugs for the treatment of seizures, only three are labeled for loading doses in pediatric patients.	The treatment armamentarium would benefit from more therapeutic options for achieving a potentially therapeutic concentration level of an ASM rapidly and safely.
Benefit	• Efficacy has already been demonstrated to support approval of the current labeled maintenance dosing of lacosamide (LCM), which was extended in 2017 from adults down to age 4 years and in 2021 down to age 1 month.	Achievement of the currently labeled maintenance dosing more rapidly with an alternate initial dosing regimen which includes a loading dose would be expected to result in comparable efficacy and possibly more rapid achievement of the treatment goal.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The goal of treatment of a patient who has ongoing, frequent seizures is to efficiently stop and prevent further seizures. More rapid achievement of the currently labeled maintenance dosing may result in more rapid cessation of seizures.	

Risk and Risk Management	• Common adverse events (AEs) noted in pediatric subjects in studies with LCM are similar to those seen in adults and include central nervous system AEs such as dizziness, somnolence, and headache, and nausea and vomiting.
	• Common AEs with loading doses of LCM in adults are similar to those seen in other studies but may be more frequent with faster infusion rates (15 minutes versus 30 to 60 minutes).
	• In the open-label study of rapid infusion of adjunctive LCM in LCM-naïve adults with POS which supported the 2014 addition of a loading dose for adults, dose-dependent PR and QRS interval prolongation was seen during or shortly after infusions. An adult subject who was on a concomitant beta blocker for a history of hypertension had severe bradycardia at 7 minutes into a 15-minute infusion.
	• Simulations of the pharmacokinetic (PK) profile using the proposed loading dose and subsequent titration regimen as performed by the Office of Clinical Pharmacology demonstrate more rapid achievement of the steady-state exposures achieved by the approved recommended dosing regimen (without loading dose) and continued rise of exposure levels.
	• Given the bioequivalence of IV and oral formulations, results can be extended to oral dosing.
	• A real world evidence (RWE) study of patients who
		• A large proportion of patients at the 8 pediatric healthcare systems in the PEDSnet network received loading doses of LCM which are higher than recommended labeled dosing.
		• Based on mechanism of action and pediatric physiology, AEs with a loading dose of LCM in pediatric patients with epilepsy are expected to be similar to those in adults.
		• The submitted RWE study demonstrated increased rash in pediatric patients who received a loading dose equal to or higher than the proposed loading doses, but did not demonstrate an increase in cardiac conduction abnormalities.
		• Labeling must continue to provide risk mitigation strategies including:
		  • Consideration of clinical response and tolerability to determine the need for dosing changes and titration;
		  • Discussion of the risk of DRESS and hypersensitivity;
		  • Discussion of the need for precautions including administration under medical supervision and close monitoring of patients with known cardiac conduction problems, on concomitant medications that prolong the PR interval, or with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	received an IV LCM dose at one of eight pediatric health systems was conducted. Analysis of the data as extracted from electronic health records through a mean follow-up period of 13.5 days (range 0 to 37 days, median 8 days) after the index IV LCM dose did not demonstrate higher incidence of AEs related to cardiac conduction abnormalities in the 321/686 (46.8%) subjects who received doses equal to or higher than the proposed loading doses as compared to the 365/686 subjects who received doses lower than the proposed loading doses. • The RWE study demonstrated a higher incidence of rash in the loading dose cohort. There was no higher incidence of drug reaction with eosinophilia and systemic symptoms (DRESS) or of hypersensitivity; however, the sample size was not large enough to be able to detect a difference in incidence of such rare events.	severe cardiac disease.

2. Background

This supplemental application to the NDAs for all formulations of LCM, submitted on June 30, 2022, contains data intended to support the safety of an alternate initial dosing for initiation of treatment of POS down to 1 month of age, and of an alternate initial dosing for initiation of treatment of PGTCS down to 4 years of age. These supplemental applications were originally submitted on December 15, 2020, but the Agency issued a Refuse to File decision due to a lack of the necessary datasets to allow for complete review of the application. Therefore, this application is a resubmission and contains the requested datasets needed for review.

LCM (tradename Vimpat) is currently approved as a tablet, oral solution, and injection for intravenous infusion for the treatment of partial-onset seizures (POS) in patients 1 month and older and treatment of primary generalized tonic clonic seizures (PGTCS) in patients 4 years and older.

LCM was approved in 2008 for the adjunctive treatment of POS in adults 17 years and older in both oral and intravenous formulations; the oral solution was added in 2010, and the use of an alternate initial dosage ("loading dose") and monotherapy for the treatment of POS in adults were added in 2014. The indication for the treatment of POS was extended down to 4 years of age in 2017 for oral formulations only. In 2020, LCM was approved for adjunctive treatment of PGTCS in patients 4 years and older, and the IV formulation was approved for pediatric patients 4 years and older for temporary replacement of oral maintenance treatment of both POS and PGTCS. In 2021, the indication for the treatment of POS was extended down to age 1 month for all formulations.

3. Product Quality

Not applicable. There is no Office of Product Quality (OPQ) review because no new chemistry, manufacturing, and control (CMC) data were submitted.

4. Nonclinical Pharmacology/Toxicology

Not applicable. There is no nonclinical pharmacology/toxicology review because no new nonclinical data were submitted.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Adarsh Gandhi (clinical pharmacology reviewer), Dr. Gopichand Gottipati (clinical pharmacology Team Leader), and Dr. Atul Bhattaram (Pharmacometrics Team Leader).

The clinical pharmacology of LCM was previously described in the clinical pharmacology team's review of the findings submitted in the original NDA submissions.

The OCP review team reviewed the information from Study EP0147 that was submitted in NDA 022253/S-050 (with cross-reference to NDA 022254/S-040 and NDA 022255/S-032). The primary focus of the OCP review of this supplement to the NDA was to evaluate the appropriateness of the Applicant's proposed alternate initial dosage regimen in pediatric patients based on findings of Study EP0147.

Specifically, the OCP review team conducted PK modeling and simulation in pediatric patients comparing the LCM pharmacokinetics (PK) profiles following the previously approved dosing regimen (without the initial loading dose), and the newly proposed alternate dosing regimen, (with initial loading dose), over 8 weeks, which included sufficient time for dose initiation, titration, and maintenance.

The OCP review team's exploratory PK analyses in pediatric patients showed that LCM mean concentrations achieved with the proposed alternate initial dosage, titration, and maintenance pediatric regimen are higher than those achieved using the currently approved pediatric regimen (i.e., without the alternate initial dosing regimen).

The OCP review concludes that the clinical relevance of these differences in exposures is unclear. Therefore, the OCP review defers to the clinical team's conclusion regarding the acceptability of the proposed alternate initial dosage, titration, and maintenance regimen for inclusion in labeling. The OCP team subsequently agreed with the clinical review team's conclusion that the proposed alternate initial dosing regimen is appropriate and safe. The clinical review team's basis for this conclusion is provided in Section 8 of this Summary Review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Efficacy is not addressed in this submission.

The efficacy of LCM in the treatment of POS and PGTCS, and the currently labeled titration and maintenance dosing for LCM in pediatric patients, were previously established by the findings supporting approval of NDAs 022253, 022254, and 022255. The efficacy of LCM would not be expected to be diminished with administration of an initial dosing regimen which achieves labeled maintenance dosing more quickly, as is proposed in this application.

8. Clinical – Safety

Dr. Amy Kao performed the clinical safety review of this application.

Dr. Kao's review focused primarily on the data from Study EP0147, a retrospective cohort study utilizing electronic health records (EHR) data (b) (4) from the PEDSnet clinical research network (PEDSnet.org). The PEDSnet data network integrates and standardizes health system EHR data across members into a common data repository, managed by a Centralized Coordinating Center at the Children's Hospital of Philadelphia. The database for Study EP0147 included 686 patients aged ≥1 month to <17 years and 28 neonates. The Applicant used these data to support the use of an alternate dosing regimen to achieve the maintenance dosage in a shorter timeframe in pediatrics.

The application also included a literature review of publications provided by the Applicant in which LCM loading doses were administered to patients 1 month to less than 17 years of age. The Applicant also provided a sample from their postmarketing safety database focusing on safety findings for a pediatric patient population. Dr. Kao conducted reviews of the publications and the postmarketing database to inform specific aspects of the safety labeling as described below.

The principal conclusions of Dr. Kao's safety review of the application are summarized below.

Review of the Safety Database (Study EP0147)

Overall Exposure

In Study EP0147, 686 subjects met the inclusion criteria of age 1 month to less than 17 years AND receipt of at least one IV administration of LCM, without exposure to either oral or IV LCM within the 3 months previous to the initial IV LCM dose.

The Applicant divided these subjects into two cohorts which were defined by cut-off doses which were estimated to achieve the same exposure as a single 200 mg dose (the initial loading dose of the approved alternate initial dosing regimen in adults). The Applicant-designated "recommended dose" cohort received an initial IV LCM dose which was less than the cut-offs listed below, and the Applicant-designated "loading dose" cohort received an initial IV LCM dose which was equal to or greater than the cut-off doses listed below:

- <6 months of age and <30 kg: 4 mg/kg
- ≥6 months of age and <30 kg: 6 mg/kg
- 30-50 kg: 4 mg/kg
- >50 kg: 200 mg.

Using the Applicant-designated cut-offs, 471 subjects (68.7%) fell within in the "recommended dose" cohort, and 215 subjects (31.3%) were within the "loading dose" cohort.

However, Dr. Kao performed an analysis using cut-off doses that aligned with the loading doses proposed for labeling by the Applicant. Thus, her loading dose categories were as follows:

- <6 kg: 2.5 mg/kg ("lower dose")
- 6 to less than 30 kg: 4.5 mg/kg. ("proposed loading dose")

Utilizing these cut-off doses, Dr. Kao compared 365 subjects (53.2%) in the "lower dose" cohort to 321 subjects (46.8%) in the "proposed loading dose" cohort (as displayed in Table 1 below). Dr. Kao's categorization, not the applicant's, will be used in the remainder of this memorandum.

Table 1 Total exposure by weight of subjects who received either the "lower dose" (365 subjects) or the proposed dosing or higher (321 subjects) as their index IV dose

Weight Group	Number of patients n (% of total)	Labeled dosing (Increase dosage based on clinical response and tolerability)	Proposed alternate initial (loading) dosing	Administered loading dose (LD) range (mg/kg)	Mean LD (mg/kg)	Median LD (mg/kg)	Patients who received ≥ proposed dose n (% of weight group)
< 6 kg	46 (6.7)	**IV**: initial 0.66 mg/kg TID; Increase by 0.66 mg/kg TID every week to maintenance 2.5 to 5 mg/kg TID	IV: 2.5 mg/kg TID	0.5 to 19.15	6.38 (SD 3.88)	5.02	38/46 (82.6%) • Range 2.99-19.15 mg/kg • 19/46 (41.3%) got ≥7.5 mg/kg (proposed daily dose) *EP0147 data is IV only*
		PO: initial 1 mg/kg BID; Increase by 1 mg/kg BID every week to maintenance 3.75 to 7.5 mg/kg BID	PO: 3.75 mg/kg BID				
6 to <11 kg	106 (15.5)	Initial 1 mg/kg BID; Increase by 1 mg/kg BID every week to Maintenance 3 to 6 mg/kg BID	4.5 mg/kg followed 12 hrs. later by 3/kg BID	0.47 to 14.9	4.45 (SD 2.76)	4.14	52/106 (49.1%) • Range 4.57-14.9 mg/kg • (29-150 mg absolute)
11 to <30 kg	309 (45)			0.44 to 20.2	4.32 (SD 2.89)	3.98	126/309 (40.8%) • Range 4.5-20.2 mg/kg • (52-327 mg absolute)
30 to <50 kg	127 (18.5)	Initial 1 mg/kg BID; Increase by 1 mg/kg BID every week to Maintenance 2 to 4 mg/kg BID	4 mg/kg followed 12 hrs. later by 2/kg BID	0.93 to 10.31	3.99 (SD 2.53)	3.36	60/127 (47.2%) • Range 4-10.31 mg/kg • (139-400 mg absolute)

≥50 kg	98 (14.3)	Initial 50 mg BID; Increase by 50 mg BID every week to Maintenance of: Monotherapy 150-200 mg BID Adjunctive 100-200 mg BID	200 mg followed 12 hrs. later by 100 mg BID	0.42 to 8.77 (25 to 600 mg)	2.72 (SD 1.67) (177.89 mg)	2.14 (175.68 mg)	45/98 (46%) • Range 200 to 500 mg • (1.35-8.77 mg/kg)
Total	**686**						**321 (46.8%)**

Abbreviations: BID = twice daily; TID = three times daily
Source: Clinical Reviewer Table 3

Dr. Kao noted that, although the overall sample size may not be large enough to detect a difference in incidence rates of rare events between the proposed loading dose group and the lower dose group, the administration of the proposed loading doses or higher in nearly half (46.8%) of the subjects in the trial indicates that healthcare providers are already prescribing off-label doses which are larger than the current labeled/recommended doses in a significant proportion of patients and therefore the data in this submission likely will represent an accurate readout of the safety performance of the proposed regimen.

Relevant characteristics of the safety population

The baseline demographic characteristics are summarized below in Tables 2.

Table 2 Demographic characteristics

	lower dose (N=365)	proposed loading dose (N=321)	Total (N=686)
Age (years unless otherwise specified)			
Mean (SD)	7.6 (5.01)	6.7 (5.52)	7.1 (5.27)
Median (Min, Max)	7.3 (38 days, 16.99 years)	5.6 (30 days, 17 years)	6.8 (30 days, 17 years)
Sex			
FEMALE	164 (44.9)	139 (43.3)	303 (44.2)
MALE	201 (55.1)	182 (56.7)	383 (55.8)
Race			
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.1)
American Indian or Alaska Native	1 (0.3)	3 (0.9)	4 (0.6)
No information	3 (0.8)	2 (0.6)	5 (0.7)
Refuse to answer	8 (2.2)	1 (0.3)	9 (1.3)
Asian	18 (4.9)	11 (3.4)	29 (4.2)
Other	20 (5.5)	13 (4.0)	33 (4.8)
Unknown	29 (7.9)	5 (1.6)	34 (5.0)
Multiple race	14 (3.8)	28 (8.7)	42 (6.1)
Black or African American	53 (14.5)	44 (13.7)	97 (14.1)
White	218 (59.7)	214 (66.7)	432 (63.0)
Weight group			
<6 kg	8 (2.2)	38 (11.8)	46 (6.7)
6 to <11 kg	54 (14.8)	52 (16.2)	106 (15.5)
11 to <30 kg	183 (50.1)	126 (39.3)	309 (45.0)
30 to <50 kg	67 (18.4)	60 (18.7)	127 (18.5)
50 kg or greater	53 (14.5)	45 (14.0)	98 (14.3)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics (joining of FR_DEM [demographics], FR_IND [index drug exposure]); Filter: None. Age, Sex, Race, Weight group - Dataset: Demographics; Filter: None. SD = Standard Deviation.

Dr. Kao notes that there are some slight imbalances across the two cohorts involving race and weight groups, but she concludes it is unlikely that these imbalances would impact safety outcomes.

The numbers of subjects in each cohort per site (displayed in Table 3 below) are overall relatively well distributed.

Table 3 Number of subjects in each cohort per site

SITE*	lower dose	proposed loading dose	Total
site_1084	43	43	86
site_1156	53	26	79
site_1836	65	86	151
site_1840	3	9	12
site_1962	127	13	140
site_403927	35	120	155
site_1036771	39	21	60
site_1037158	0	3	3
Total	**365**	**321**	**686**

Source: FR_DEM (demographics), JMP analysis

* Distribution of subjects by the specific PEDSnet institution at which they received IV LCM cannot be determined, because site identifiers are masked for confidentiality.

Dr. Kao notes that direct measures of seizure or epilepsy severity, such as number of seizures, were not collected in the database for EP0107. Therefore, possible indirect indicators of acute and chronic seizure severity in the two dose cohorts are displayed in Table 4 below.

Table 4 Possible indirect indicators of seizure severity

	lower dose (N=365)	proposed loading dose (N=321)	Total (N=686)
Indications for IV LCM			
Diagnosed epilepsy	170 (46.6)	148 (46.1)	318 (46.4)
Status epilepticus	108 (29.6)	98 (30.5)	206 (30.0)
Seizures without a diagnosis	67 (18.4)	53 (16.5)	120 (17.5)
Traumatic brain injury	3 (0.8)	7 (2.2)	10 (1.5)
Seizure with fever	5 (1.4)	3 (0.9)	8 (1.2)
Brain tumor	2 (0.5)	3 (0.9)	5 (0.7)
Other	4 (1.1)	0	4 (0.6)
Posterior reversible encephalopathy syndrome	0	4 (1.2)	4 (0.6)
Cerebral bleed	1 (0.3)	2 (0.6)	3 (0.4)
Infection	1 (0.3)	1 (0.3)	2 (0.3)
Hydrocephalus	0	1 (0.3)	1 (0.1)
Hypoxic brain injury	1 (0.3)	0	1 (0.1)
Metabolic encephalopathy	1 (0.3)	0	1 (0.1)
Prophylaxis	1 (0.3)	0	1 (0.1)
Pseudoseizure	1 (0.3)	0	1 (0.1)
Stroke	0	1 (0.3)	1 (0.1)
Location of IV LCM administration			
ICU	190 (52.1)	176 (54.8)	366 (53.4)
Inpatient	156 (42.7)	137 (42.7)	293 (42.7)
ED	19 (5.2)	8 (2.5)	27 (3.9)
Total number of IV LCM administrations Mean (SD) Median (Min, Max)	 9.5 (14.5) 3 (1, 110)	 8.1 (15.5) 2 (1, 141)	 8.9 (15) 3 (1, 141)
Number of other prior ASMs (benzodiazepines plus non-benzodiazepines) Mean (SD) Median (Min, Max)	 5.98 (2.74) 5 (2, 18)	 5.38 (2.59) 5 (2, 16)	 5.71 (2.69) 5 (2, 18)
Number of other ASMs on same date as IV LCM Mean (SD) Median (Min, Max)	 3.8 (1.4) 4 (2, 8)	 3.6 (1.3) 3 (2, 8)	 3.7 (1.3) 3 (2, 8)

	lower dose (N=365)	proposed loading dose (N=321)	Total (N=686)
Abbreviations: ASM = antiseizure medication, ED = emergency department, ICU = intensive care unit, IV = intravenous, LCM = lacosamide, Max = maximum, Min = minimum, SD = standard deviation Source: OCS Analysis Studio, Custom Table Tool. Columns, Indications for IV LCM, Location of IV LCM administration - Dataset: Demographics (joining of FR_DEM and FR_IND); Filter: None. Source for Total number of IV LCM administrations, Number of prior ASMs, Number of other ASMs on same date: joining of FR_IND (index drug exposure), FR_LCM (counts of IV and oral LCM doses during the follow-up period), FR_IND1 (information about index visit), FR_AED (ASM exposures before and concomitant with LCM) with 4 missing PERSONS added; JMP analysis.			

Dr. Kao suggests that the relatively greater number of subjects in the proposed loading dose group who received IV LCM in an intensive care unit (ICU) may indicate a bias towards use in in this setting. There was also a slight disparity in the acuity of the indications in the proposed loading dose group (e.g., traumatic brain injury, brain tumor, and posterior reversible encephalopathy syndrome) compared to the lower dose group (e.g., seizure with fever, prophylaxis, and pseudoseizure); however, the numbers of each diagnosis are relatively small and, as discussed below, there did not appear to be a statistical bias towards more serious indications obscuring the safety of the proposed loading dose.

Dr. Kao further notes there were a higher number of IV LCM administrations, and a minimally higher number of exposures to other ASMs, both prior to and on the same date as the index IV LCM dose in the lower dose cohort; however, the absolute total dosage of LCM and of other ASMs was not collected. Through a response to an IR, the Applicant noted that it was not considered practicable to conduct a chart review and verification of all dose amounts subsequent to the initial index IV LCM dose. Therefore, there is the potential for higher exposure to LCM and other ASMs that could impact safety interpretability of the proposed dosing regimen, but subsequent analyses of safety did not suggest a safety signal clearly indicative of toxic LCM exposure nor safety issues clearly attributable to other ASMs.

Adequacy of the safety database

Dr. Kao observes that, in the context of established experience with LCM in pediatric patients and of LCM loading doses in adults, the relatively large proportion (46.8%) of subjects in Study EP0147 who received the proposed loading doses or higher doses provides an adequate pool of pediatric subjects to assess for any novel or unique AEs in this higher dose cohort which were not seen in the lower dose group, in previous clinical trials in adults, or in postmarketing reports. The potential confounding by disparities between cohorts with respect to acuity of diagnosis and ASM exposure illustrates the inherent limitations of a retrospective/observational study which do not allow for as thorough a quantitative comparison of the two cohorts as would be possible in a prospectively enrolled cohort. Nevertheless, even allowing for the potential for small disparities between the two cohorts, in the setting of an approved therapy with extensive pre- and postmarketing safety, Dr. Kao concludes that the relatively large proportion of subjects who received the proposed loading doses or higher is adequate to allow a reliable qualitative assessment of the safety of the proposed alternate initial dosing.

Safety results

There were 657 AEs recorded amongst 286 subjects (41.7% of the total 686 subjects). AEs were recorded in 159 (43.6%) of the 365 subjects in the lower dose cohort and in 127 (39.6%) of the 321 subjects in the proposed loading dose cohort.

Although the documented AEs are described as "newly diagnosed health conditions recorded by the chart reviewer during the follow up period after the index drug exposure," some of these diagnoses which were interpreted as treatment emergent AEs could have been chronic rather than new onset. Many of the documented AEs could also have possibly been the diagnoses which provided the need for an ASM. Some of the documented AEs were symptoms versus conditions, e.g., "spinal stenosis in cervical region" and "magnetic resonance imaging of cervical spine abnormal." Dr. Kao recoded some terms to consolidate similar terms, based on Medical Dictionary for Regulatory Activities (MedDRA) version 25.1, as displayed in Table 7 below. However, she did not alter conditions relating to cardiac conduction abnormalities so as to retain the ability to qualitatively assess these AEs. She also did not alter terms which implied a cause or severity or terms which were general symptoms/signs and for which a definitive cause could not be assumed.

Because Study EP0147 was a real world evidence study, safety monitoring was performed by the healthcare providers as part of the routine clinical care. Particular clinical tests were not captured in a structured format; rather, abnormalities would have been captured by documentation of AEs.

Deaths:

As displayed in Table 5 below, there were a total of 48 deaths; 25/365 (6.8%) in the proposed dose group and 23/321 (7.2%) in the lower dose group. Of the 48 subjects, 26 did not receive LCM on the date of death, and 22 received LCM on date of death.

Table 5 Deaths per cohort and receipt of LCM on date of death

LCM on date of death?	Cause of death (adjudicated by PEDSnet clinician investigators)	lower dose	proposed loading dose	Total
No	Cardiorespiratory arrest	2	1	3
	Multiple organ failure	3	2	5
	Status epilepticus	0	2	2
	Cerebral herniation	0	1	1
	Acute disseminated encephalomyelitis	1	0	1
	Hemophagocytic lymphohistiocytosis	0	1	1
	Hemorrhage of abdominal cavity structure	0	1	1
	Hepatic failure	0	1	1
	Invasive aspergillosis	1	0	1
	Motor vehicle accident	1	0	1
	Necrotizing enterocolitis	0	1	1
	Neuroblastoma	1	0	1
	Progressive multifocal leukoencephalopathy	0	1	1
	Pseudomonas meningitis	1	0	1
	Retinoblastoma	0	1	1
	Sepsis	0	1	1
	Traumatic brain injury	1	0	1
	Unknown	1	0	1
	Vascular insufficiency of intestine	1	0	1
	Total who did not receive LCM on date of death	**13**	**13**	**26**
Yes	Cardiorespiratory arrest	1	2	3
	Multiple organ failure	0	1	1
	Status epilepticus	3	1	4
	Anoxic encephalopathy	3	0	3
	Hypoxic ischemic encephalopathy	1	2	3
	Cerebral herniation	1	0	1
	Apnea	0	1	1
	Cardiac arrest	0	1	1
	Cerebral infarction	0	1	1
	Glioblastoma	1	0	1
	Perforation of intestine	0	1	1
	Subdural intracranial hemorrhage	0	1	1
	Traumatic intracranial subdural hematoma	0	1	1
	Total who received LCM on date of death	**10**	**12**	**22**
	Total	23	25	48

Source: "ADSL" dataset (FR_DEM, FR_IND) joined with FR_DEA, JMP analysis

For each death, because there was no narrative available, Dr. Kao reviewed the indication for LCM and cause of death, in particular those subjects for which "cardiorespiratory arrest" or "cardiac arrest" were documented as the cause of death. She also reviewed previous health

conditions, body systems for which the patient had received a related diagnosis prior to the encounter in which he/she received the IV LCM, and newly diagnosed health conditions recorded by the Study EP0147 chart reviewer during the follow up period after the index drug exposure. She often concluded that the cause of death was clearly related to complications of the underlying cause of the seizures and not attributable to LCM.

For the subjects who died from cardiac or cardiorespiratory arrest and had received LCM on the date of death, the indications and cause of death are shown in Table 6 below.

Table 6 Indications for IV LCM in subjects who died from cardiac/cardiorespiratory arrest

LCM on date of death?	Indication for IV LCM	Cause of death	lower dose	proposed loading dose
No	Status epilepticus	Cardiorespiratory arrest	1	1
	Hypoxic brain injury	Cardiorespiratory arrest	1	0
Yes	Status epilepticus	Cardiac arrest	0	1
	Diagnosed epilepsy	Cardiorespiratory arrest	1	0
	Seizures without a diagnosis	Cardiorespiratory arrest	0	2
Total			**3**	**4**

Source: "ADSL" dataset (FR_DEM, FR_IND) joined with FR_DEA, JMP analysis

Dr. Kao observed that there are no obvious indicators that the deaths from cardiorespiratory or cardiac arrest which were captured in Study EP0147 were caused by LCM; however, a definitive understanding of whether LCM was potentially causative is not possible without additional details about the subjects who died. She believes that it is likely that the majority, if not all, of the deaths occurring within the study duration were related to the underlying cause of the seizures and/or comorbidities. Regardless, she recommends that labeling indicate that the administration a loading dose of LCM or IV LCM should be performed in a setting with appropriate cardiac monitoring, and that the risks and benefits of LCM treatment should be considered before treating a patient with underlying cardiac concerns.

Serious Adverse Events (SAEs):

Other than deaths, categorization of AEs as serious was not captured in Study EP0147.

Discontinuations Due to Treatment-Emergent Adverse Events (TEAEs):

Study EP 0147 was a retrospective study; therefore, dropouts and discontinuations due to AEs are not applicable.

TEAEs of All Severities:

Dr. Kao comments that no unexpected AEs were documented in the proposed loading dose cohort. In fact, she notes that AEs (based on System Organ Class) for almost all categories appeared to occur more frequently in the lower dose cohort. This paradoxical observation could be due to unmeasured confounding factors. However, in that context, she notes that

lethargy/somnolence occurred at a greater frequency in the proposed loading dose cohort; it is expected that this AE, which is common with LCM administration, would occur more frequently with a larger IV dose. In addition, although arrhythmias were not observed at higher frequency in the proposed loading dose cohort, hypotension was seen at essentially the same frequency between the cohorts. Cardiac arrest was also seen at the same frequency between the cohorts; however, if cardiac arrest were due to an arrhythmia, one would expect that an arrhythmia would have been recognized, documented, and treated. Rash also occurred in a slightly higher percentage of subjects in the proposed loading dose cohort compared to the lower dose cohort, and Stevens-Johnson syndrome (SJS) occurred in one subject in the proposed loading dose cohort but did not occur in the lower dose cohort. In summary, the TEAEs observed in this study appear largely consistent with the established safety profile of LCM. Somnolence, arrhythmias (including the rare arrythmias leading to cardiac arrest), rash, and hypersensitivity are already discussed in the approved label and no alterations to the current approved labeling text for these AEs appear necessary based on the findings of this study.

Laboratory Findings:

Because Study EP0147 was a real world evidence study, safety monitoring was performed by healthcare providers as part of the routine clinical care the patients were receiving. Particular clinical tests were not captured in a structured format; rather, abnormalities were captured by the documentation of AEs encountered as part of standard clinical care.

Overall, there were no consistent or clinically relevant treatment-related changes in hematology or clinical chemistry values.

There were abnormalities in liver function tests, as well as reports of neutropenia, anemia, and agranulocytosis noted in the study. These lab abnormalities, and the need for monitoring for them, are included in the current approved labeling for LCM.

Vital Signs:

Vital signs were not specifically captured in a structured format, but abnormalities were expected to have been captured in AEs as part of standard clinical care.

There were no clinically relevant changes from baseline in vital signs that were consistently observed.

Dr. Kao concludes that there were no new safety signals identified from her review of the vital signs post-infusion.

Cardiac AEs and Electrocardiograms:

Current approved labeling describes a risk of cardiac rhythm and conduction abnormalities associated with LCM. Therefore, the safety review focused particular attention to the potential for cardiac AEs and rhythm abnormalities associated with the proposed loading dose.

In Study EP0147, 85 subjects had 102 AEs related to conduction abnormalities or cardiac/sinus arrest (arrhythmia, AV block, AV block second degree, bradyarrhythmia, bradycardia, cardiac arrest, prolonged QT interval, sinus arrest, tachyarrhythmia, tachycardia, ventricular tachyarrhythmia).

Because AV block and AV block second degree were only seen in the proposed loading dose group (in one subject each), Dr. Kao reviewed all datasets for additional information to potentially inform the clinical context, including the indication for LCM, previous health conditions, body systems for which the patient had received a related diagnosis prior to the encounter in which he/she received the IV LCM, and all newly diagnosed health conditions (considered AEs) recorded by the chart reviewer during the follow up period after the index drug exposure. Both patients with AV block received IV LCM for status epilepticus. One of these patients only received a single IV dose of LCM and the event of AV block occurred 3 days after, making LCM unlikely to have contributed. Other potential risk factors were found in the previous health conditions noted (genetic, neurological, mental health) and newly diagnosed health conditions (cardiac arrest, rash, cellulitis, cerebral infarction, ventilator-acquired pneumonia). The other patient had the event of AV block 9 days after receiving the index IV dose, while still receiving either IV or oral LCM, and was noted to have had a previous cardiac condition.

Table 7 Cardiac AEs based on initial IV LCM dose

	lower dose (N=365)	proposed loading dose (N=321)	Total (N=686)
Number of patients with cardiac event			
Bradycardia	26 (7.1)	8 (2.5)	34 (5.0)
Tachycardia	16 (4.4)	7 (2.2)	23 (3.4)
Tachyarrhythmia	11 (3.0)	8 (2.5)	19 (2.8)
Cardiac arrest	8 (2.2)	7 (2.2)	15 (2.2)
Prolonged QT interval	2 (0.5)	1 (0.3)	3 (0.4)
Arrhythmia	2 (0.5)	0	2 (0.3)
Bradyarrhythmia	1 (0.3)	1 (0.3)	2 (0.3)
Atrioventricular (AV) block	0	1 (0.3)	1 (0.1)
Atrioventricular (AV) block second degree	0	1 (0.3)	1 (0.1)
Sinus arrest	1 (0.3)	0	1 (0.1)
Ventricular tachyarrhythmia	1 (0.3)	0	1 (0.1)
Total number of patients with cardiac event	**68 (18.6)**	**34 (10.6)**	**102 (14.9)**
Time to cardiac AE in general (in days)			
Mean (SD)	7.0 (7.99)	6.5 (8.18)	6.8 (8.02)
Median (Min, Max)	3.0 (0, 34)	4.0 (0, 36)	3.0 (0, 36)
Time to bradycardia (in days)			
Mean (SD)	7.2 (9.20)	13.8 (12.67)	8.8 (10.30)
Median (Min, Max)	2.0 (0,34)	9.5 (1, 36)	5.0 (0,36)
Time to tachycardia (in days)			
Mean (SD)	7.8 (7.19)	2.9 (2.79)	6.3 (6.54)
Median (Min, Max)	5.5 (1,22)	3.0 (0.7)	3.0 (0,22)
Time to tachyarrhythmia (in days)			
Mean (SD)	8.3 (9.21)	3.2 (2.92)	6.2 (7.54)
Median (Min, Max)	7.0 (0, 25)	3.0 (0, 8)	3.0 (0, 25)
Time to cardiac arrest (in days)			
Mean (SD)	5.9 (6.62)	6.0 (6.95)	5.9 (6.53)
Median (Min, Max)	4.5 (1, 21)	3.0 (0, 19)	4.0 (0, 21)
Time to prolonged QT interval (in days)	1.0	0.0	
Time to arrhythmia	6, 11	-	
Time to bradyarrhythmia (in days)	0.0	12.0	
Time to AV block (in days)	-	9.0	
Time to AV block second degree (in days)	-	9.0	
Time to sinus arrest (in days)	3.0	-	
Time to ventricular tachyarrhythmia (in days)	1.0	-	
Days of follow-up			
Mean (SD)	21.4 (12.57)	26.7 (13.04)	23.1 (12.91)
Median (Min, Max)	20.0 (1, 37)	35.5 (1, 37)	24.0 (1, 37)

	lower dose (N=365)	proposed loading dose (N=321)	Total (N=686)
Number of IV LCM doses subsequent to index dose			
Mean (SD)	13.9 (16.23)	22.6 (31.21)	16.8 (22.59)
Median (Min, Max)	6.0 (1, 80)	14.5 (1, 141)	9.0 (1, 141)
Number of oral LCM doses subsequent to index dose			
Mean (SD)	27.6 (25.56)	24.3 (28.84)	26.6 (26.37)
Median (Min, Max)	22.0 (1, 95)	16.0 (3, 114)	19.5 (1, 114)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics ("ADSL" dataset formed by FR_DEM, FR_IND)
Cardiac AE, Time to cardiac AE, Days of follow-up, Number of IV LCM doses subsequent to index dose, Number of oral LCM doses subsequent to index dose - Dataset: Adverse Events ("ADAE" dataset formed by FR_IND, FR_NEW). Filter: None.
Max = Maximum, Min = Minimum, SD = Standard Deviation

Based on findings as displayed in Table 7 above, Dr. Kao concluded that cardiac AEs, including cardiac conduction abnormalities, were not seen more frequently in the proposed loading dose cohort. This finding is in the context of an adequate time of follow-up and despite a higher number of IV LCM doses in the proposed loading dose group (although, as previously discussed, the absolute total dosage of LCM is not known). Cardiac arrest was seen at equal frequency between the two groups; cardiac arrest in this setting can occur for many reasons other than the known cardiac conduction abnormalities attributable to LCM. Cardiac arrest occurred at similar number of days after the initial IV dose in both the low and proposed dose cohorts, which suggests that cardiac arrest was not dose-dependent on the initial IV dose.

The AE, "bradyarrhythmia" was also seen at equal frequency in the two groups; although the sample size was low (n=1 in each group), Dr. Kao performed an additional analysis which combined all AEs which could lead to a bradyarrhythmia or bradycardia (bradycardia, bradyarrhythmia, atrioventricular block, atrioventricular block second degree). Her analysis demonstrated that potential bradyarrhythmia-causing AEs remained higher in the lower dose group (n=27) than in the proposed loading dose group (n=11). Although AV block was only seen in the proposed loading dose group, risk factors other than LCM were suggested to be the primary etiologies for cardiac blocks in these patients.

QT interval prolongation:

Dr. Kao noted prolonged QT interval was noted as an AE in two subjects (0.5%) in the lower dose cohort and in a single subject (0.3%) in the proposed loading dose cohort. Per the approved label, in a thorough QT study, LCM did not prolong QTc interval. Dr. Kao reviewed the Applicant's datasets FR_PRE (previous health conditions), FR_NEW (newly diagnosed health conditions during the follow-up period after the index drug exposure which informed the study outcome variables of AE categories), and FR_DEA (death details for patients who died within the follow-up period) in order to attempt to better understand the clinical context of each of the three subjects for whom the AE of "prolonged qt interval" was noted. All three subjects received IV LCM for the indication of status epilepticus. One subject in the lower

dose cohort had had previous health condition(s), and conditions newly diagnosed after the index LCM dose which included tachycardia, abdominal compartment syndrome, septic shock, torsion of ovary, hyperglycemia, and lactic acidosis. Other ASMs that this subject was prescribed are not known to prolong QT. The other subject in the lower dose cohort had newly diagnosed conditions of bradycardia; hypertensive disorder, systemic arterial; on examination – fixed, dilated pupils; and petechia. This patient died with a diagnosis of neuroblastoma. This subject was also prescribed fosphenytoin, which can prolong the QT interval. The subject who was in the proposed loading dose cohort was also prescribed fosphenytoin and died of cerebral herniation. Dr. Kao observes that these three subjects who had an AE of "prolonged qt interval" had severe illnesses, and two subjects were prescribed other drugs with an established risk of QT prolongation. Therefore, while definitive conclusions cannot be made with the information provided, there was no clear evidence that QT prolongation was associated with the proposed loading dose of LCM.

Dermatologic or Hypersensitivity Abnormalities:

During the review of the original NDA for Vimpat, particular attention was paid to the analysis of potential multiorgan hypersensitivity reactions. Hepatitis/nephritis in a healthy volunteer was determined to be consistent with a delayed drug-induced multiorgan hypersensitivity reaction. The association of ASMs with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was increasingly recognized, and DRESS is recognized in the current approved Vimpat labeling with a Warning and Precaution statement.

Dr. Kao found that 46 subjects in Study EP0147 had 51 AEs of DRESS, hypersensitivity, rash, skin peeling, or SJS (displayed in Table 8 below). Because of the potential overlap of symptoms and signs, she also reviewed the available data for individual subjects who had several skin or hypersensitivity AEs. One subject had rash documented first, then hypersensitivity noted 18 days later. One subject had rash documented first, then a diagnosis of DRESS 2 days later. One subject had hypersensitivity documented first, then DRESS was noted 3 days later. Two subjects had rash and hypersensitivity or DRESS reported on the same day.

The single patient with SJS was in the proposed loading dose group and received two IV doses of LCM only; SJS was reported 13 days after the first IV LCM dose. The single patient with peeling of skin was in the proposed loading dose group and received 14 IV LCM doses; the event was reported 14 days after the first IV LCM dose. Narratives were not able to be provided for my independent review; however, no events of DRESS, hypersensitivity, peeling of skin, or SJS were attributed by the treating providers to LCM exposure. Two AEs of rash in the lower dose group and one event of rash in the proposed loading dose group were attributed in the available notes to LCM.

Table 8 Skin or hypersensitivity AEs based on initial IV LCM dose

	lower dose (N=365)	proposed loading dose (N=321)	Total (N=686)
Number of patients with event			
Rash	22 (6.0)	20 (6.2)	42 (6.1)
Drug reaction with eosinophilia and systemic symptoms (DRESS)	2 (0.5)	2 (0.6)	4 (0.6)
Hypersensitivity	2 (0.5)	1 (0.3)	3 (0.4)
Peeling of skin	0	1 (0.3)	1 (0.1)
Stevens-Johnson syndrome (SJS)	0	1 (0.3)	1 (0.1)
Total number of patients with any event*	**23**	**23**	**46**
Time to event in general (in days) **Mean (SD)** **Median (Min, Max)**	 12.8 (9.33) 11.0 (0, 36)	 9.6 (7.61) 7.0 (0, 34)	 11.2 (8.62) 9.5 (0, 36)
Time to rash (in days) Mean Median (Min, Max)	 12.1 10 (0, 36)	 9.9 7 (0, 34)	 11.0 10 (0, 36)
Time to DRESS (in days)	9, 17	3, 11	
Time to hypersensitivity (in days)	17, 24	0	
Time to peeling of skin (in days)	-	14	
Time to SJS (in days)	-	13	
Days of follow-up **Mean (SD)** **Median (Min, Max)**	 29.5 (9.14) 34.0 (6, 37)	 21.2 (12.72) 19.0 (1, 37)	 25.5 (11.68) 29.0 (1, 37)
Number of IV LCM doses subsequent to index dose **Mean (SD)** **Median (Min, Max)**	 20.6 (23.91) 14.0 (1, 80)	 15.0 (21.83) 7.0 (1, 89)	 17.9 (22.89) 10.5 (1, 89)
Number of oral LCM doses subsequent to index dose **Mean (SD)** **Median (Min, Max)**	 30.8 (26.64) 21.0 (1, 87)	 29.6 (19.98) 25.0 (3, 64)	 30.1 (22.68) 24.0 (1, 87)

* Some subjects had more than one skin or hypersensitivity AE.
Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics ("ADSL" dataset formed by FR_DEM, FR_IND)
Number of patients with event, Time to event in general (in days), Day of follow-up, Number of IV LCM doses subsequent to index dose, Number of oral LCM doses subsequent to index dose - Dataset: Adverse Events ("ADAE" dataset formed by FR_IND, FR_NEW). Filter: None.
Max = Maximum, Min = Minimum, SD = Standard Deviation

Dr. Kao noted that rash occurred at increased frequency (6.2% vs. 6.0%) in the proposed loading dose cohort. In addition, when considering DRESS, hypersensitivity, and SJS (conditions of which there may be overlap of clinical signs/symptoms and diagnoses)

together, there is a numerical difference of 1.2% favoring the proposed loading dose group. It is notable that the time to onset of rash is over 2 days shorter in the proposed loading dose group which is potentially supportive of an immune-mediated reaction being more likely with this proposed dose. Although any conclusions regarding whether rash may be an early sign of or risk factor for more severe hypersensitivity reactions including DRESS and SJS cannot be made based on the information available in this retrospective dataset study, the potential association should be considered relevant to clinical care and the data support that the existing warnings regarding DRESS certainly are applicable to patients receiving the proposed loading dose.

Additional Safety Assessments/Concerns from Other Disciplines (Office of Clinical Pharmacology, Division of Epidemiology I , and Division of Biometrics VII):

The OCP reviewers and clinical reviewers had noted that precise data regarding doses subsequent to the initial IV loading dose were not collected in Study EP0147. In its response to an IR, the Applicant noted that, "In the original protocol, the loading dose was defined as 'The iv LCM loading dose will be defined, where possible, as the single, initial high iv LCM dose which is followed within approximately 12 hours by a subsequent lower maintenance dose.' This definition was simplified to define dose cohorts by the initial dose at the recommended or loading doses previously mentioned, and not require a lower subsequent dose 12 hours later, as this was more complicated to determine programmatically and patients with higher initial doses might continue to receive the higher dose and not necessarily receive lower doses."

At the time of approval of LCM loading dose for adults in 2014, it was determined based on safety review of adults who received IV loading doses that labeling should inform that patients with known cardiac conduction problems, on concomitant medications that prolong PR interval, or with severe cardiac disease (e.g., myocardial ischemia, heart failure), must be monitored closely, as IV infusion of VIMPAT may cause bradycardia or AV blocks in these patients, and that 30 to 60-minute infusions are preferable to 15-minute infusions.

The OCP review teams **(**Clinical Pharmacology and Pharmacometrics) raised the concern that the PK profile resulting from the proposed alternate initial dosing regimen was different than the PK profile resulting from the approved adult loading dose, specifically exposure levels rose more rapidly and continued to rise beyond the first day and week of administration. In the context of lack of observed safety data to support the precise proposed regimen beyond just the initial IV loading dose, the concern for potential increased AEs with the Applicant's proposed alternate initial dosing regimen for pediatric patients in particular was extensively discussed across the Clinical review team and the Clinical Pharmacology and Pharmacometrics review teams. Ultimately, it was determined that, based on the practice of medicine and the context of a clinical need to quickly administer a higher dose of LCM, it is likely that the prescribing providers in Study EP0147 would have prescribed currently labeled pediatric maintenance dosing rather than lower currently labeled initial dosing after having administered a high loading dose. In addition, the risk for life-threatening AEs, specifically cardiac conduction abnormalities/arrhythmias, would be highest in the immediate loading dose administration

period, either during infusion or shortly after; this timeframe was adequately included in the follow-up of all subjects in Study EP0147. Therefore, the OCP review teams and the clinical review team concurred that the proposed alternate initial dosing was adequately supported. The OCP reviewers and clinical reviewers collaborated closely in editing the corresponding and necessary changes to the LCM labeling to ensure safe use of the proposed loading regimen in the pediatric patient population.

The Division of Epidemiology I, Office of Surveillance and Epidemiology provided a detailed consultation review of the methodology and conduct of Study EP0147, dated April 19, 2923. The review concluded, "The Sponsor adequately designed and executed a study with appropriate methodology to minimize risk of bias and confounding. Even with this approach, residual differences in comparator groups existed, favoring sicker patients in the recommended dose group. While this increases the difficultly for interpreting the study results, this study overall demonstrated rates of adverse events, consistent with current labeling for these adverse effects [in adults], and without raising significant safety concerns with the loading dose aside from an increased rate of rash."

A consultation review from the **Division of Biometrics VII (DB-VII) of the Office of Biostatistics** (dated April 19, 2023) provided another detailed assessment of the design, conduct, and data of Study EP0147. The biometrics team review concluded that while both the data and design of Study EP0147 have some limitations, but the study conduct meets regulatory requirements. Specifically, the DB-VII review team raised concerns relating to the discrepancy between the observed higher risk for AEs and higher incidence of comorbidities in the cohort who received lower doses of LCM, and the clinically expected increased severity of seizures and higher vigilance for AEs in patients who are typically administered (off-label) loading doses of LCM. In an attempt to reconcile these discrepancies, DB-VII and Dr. Kao requested additional sensitivity analyses that attempted to adjust for all imbalanced factors. An analysis using inverse probability of treatment weighting did not suggest that comorbidity differences favoring patients with more severe epilepsy being treated with the recommended dose could mask a potential safety signal with the proposed loading dose. Nevertheless, a theoretical concern that unadjusted confounding could be interacting with the safety data still remained. The DB-VII review concluded that "[f]rom a statistical perspective, the limitations observed result in uncertainties as to whether the RWE study EP0147 provides sufficient scientific evidence on the safety of the proposed loading dose. While the limitations of unmeasured and residual confounding were not addressed through statistical assessment, they may be explained based on clinical judgement which we defer to the clinical review team." After extensive discussion with DB-VII, Dr. Kao concluded that it is likely that there are many variables considered during clinical care that are unaccounted for/not documented and which may cause imbalance in different directions, both favoring and opposing the safety of the proposed loading dose. It is possible that chronic diagnoses and certain AEs (subject-reported, not life threatening) are less likely to be captured in charting in the intensive care setting where the focus is on stabilization of acute issues. In addition, conditions which would potentially predispose to cardiac or central nervous system AEs of LCM could influence treatment decisions toward using lower/recommended LCM dosing. The clinical team concluded that while confounding persisted despite reasonable statistical attempts to eliminate it, the

confounding was not so significant as to prevent rendering a conclusion regarding the safety of the proposed loading dose.

Applicant's Published Literature Review:

The Applicant submitted 5 studies, only one of which was prospective, and one case series, to provide support for the safety of the proposed loading dose regimen. The total number of patients amongst the 5 studies is 110, so each study contributed a small sample size (an average of 22 patients per study.) Qualitatively, the range of loading doses in these publications ranged from 2 mg/kg up to 11 mg/kg. The doses at the higher end of that range seemed to be used more commonly with the median or mean loading dose being approximately 4-8 mg/kg which is approximate to the loading dose proposed in this application.

In terms of safety signals, the publications described bradycardia, central nervous system symptoms (e.g., sedation and ataxia), and rash most prominently.

Dr. Kao concluded that no unique or unexpected AEs were noted in these publications but also noted the majority of the published studies were retrospective, and the pooled safety database provided by these publications was very small.

Safety Concerns Identified Through Postmarket Experience:

The Applicant submitted a review of its global safety database between August 29, 2008, and February 29, 2020, which included 335 postmarketing cases compatible with the use of an LCM loading dose in pediatric patients 1 month to less than 17 years. The criteria that the Applicant used to identify these cases included a first/initial dose of 200 mg or more regardless of weight, 4 mg/kg or more for 30-50 kg patients, 6 mg/kg or more for patients 6 months of age or older, and 4 mg/kg for patients less than 6 months of age; if weight was unavailable, the 3rd percentile weight was used.

Six hundred eight-four (684) AEs occurred across the 335 cases. The Applicant reports that the majority (73.7%) of the cases had an epilepsy-related indication for LCM (excluding status epilepticus); these included such diagnoses as epilepsy, seizure, Lennox-Gastaut syndrome, generalized tonic-clonic seizure, and other specified epilepsy syndromes. Status epilepticus was the indication in 3.6% of the cases; the indication was unknown in 21.8% of the cases. The majority (58.5%) of cases involved an unknown formulation of LCM; 37.6% were noted to involve an oral formulation (tablet, syrup, oral solution), and 3.9% of cases were noted to involve solution for infusion.

Events occurring with a frequency greater than 2% included somnolence and dizziness, which accounted for 2.5% and 2.0% of the total events, respectively.

Cases or cardiac abnormalities were also noted to occur: bradycardia 3 (0,4%), electrocardiogram abnormality 1 (0.1%), AV block first degree 1 (0.1%), electrocardiogram PR prolongation 1 (0.1%), heart rate irregular 1 (0.1%), and ventricular tachycardia 1 (0.1%). When Dr. Kao reviewed the narratives, she found that details were usually insufficient to make a determination of likelihood of causality, although she did conclude that LCM contributed to only one of the three observed cases of bradycardia.

No cases of syncope, presyncope, loss of consciousness (based on MedDRA preferred terms); multiorgan hypersensitivity, DRESS (using MedDRA SMQ broad); severe cutaneous adverse reactions (based on MedDRA SMQ narrow) were identified.

Dr. Kao notes that, because of the relatively small number of cases reported in pediatric patients from this database, a definitive conclusion cannot be made regarding whether the frequencies are the same or higher than those in adults. In addition, because postmarketing cases are reported voluntarily from a population of uncertain size without a comparator condition, an estimate of frequency and a conclusion of a causal relationship cannot be reliably made.

Dr. Kao concluded that no new safety concerns were identified from the postmarketing safety database. However, given the known, established risks with LCM, the prescribing information should continue to note the need for cardiac monitoring in all patients receiving loading doses and the increased risk for cardiac conduction abnormalities in patients with underlying cardiovascular disease or on cardiac medications.

Safety Conclusion

Although there were extensive pre-submission discussions between the Agency and the applicant regarding the design of a RWE study which had the potential to fulfill the postmarketing requirements and to support labeling revisions, there remained several challenges to data interpretation which relate to the inherent limitations of retrospective cohort studies. The absence of randomization and undocumented/unidentified confounding factors in this retrospective means that the comparability of the two examined cohorts is not established to the same extent that would be achieved in a prospectively enrolled clinical trial. This potential lack of equivalence between the two examine cohorts may restrict the ability to detect new safety signals, particularly rare safety signals. However, the safety findings observed in the retrospective Study EP0147, the product safety database for pediatric patients, and the published literature provided by the Applicant are consistent with the established safety profile of LCM. Even a prospective interventional trial has limitations with respect to the capability of detecting rare safety events, and the limitations of the data submitted in this supplemental application do not preclude the ability to generate meaningful conclusions to support a decision regarding of the proposed dosing regimen.

Dr. Kao observes that the data submitted in this application suggests a slightly higher risk of rash but does not suggest a higher risk of cardiac conduction AEs in children at the eight tertiary care pediatric hospitals in Study EP047 who received a loading dose of LCM and a consequential higher rate of acute exposure. While rash is concerning for a more serious

hypersensitivity reaction, the numbers of patients with DRESS or SJS were small and not so different between the two cohorts to suggest a higher risk associated with the proposed loading dose. The overall similarity in safety findings between the two cohorts and the consistency of the observed AEs with the labeled risks of LCM, support the safety and approval of the proposed alternate initial dosing regimen, which will provide an additional option for children who are experiencing increased seizure frequency. However, the safety findings confirm there remains a need for labeled precautions including cardiac monitoring, during and after administration as well as vigilance for rash and hypersensitivity reactions. The currently approved label reflects the need for cardiac monitoring and the risk of multi-organ hypersensitivity, and the warnings certainly apply to pediatric patients exposed to the proposed loading dose.

Study EP0147 and the postmarketing data submitted found no safety signals that were unique to the proposed alternate initial dosing of LCM and that the safety profile of the proposed alternate initial dosing of intravenous LCM is similar in pediatric patients to that in adult patients as described in previously approved labeling.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because the clinical study design of EP0147 was acceptable and the safety profile of the alternate initial dosing of LCM appeared similar to that of the previously approved initial dosing.

10. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified in Dr. Kao's clinical review.

- Dr. Kao concludes in her clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

11. Pediatrics

Study EP0147 was submitted in response to the following Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs):

- 2774-2: A study that will examine safety and tolerability of an oral loading dose that will allow a more rapid achievement of the final recommended therapeutic dose in pediatric patients greater than or equal to 1 month to < 17 years of age.
- 2774-3: A study that will examine safety and tolerability of an intravenous loading dose that will allow a more rapid achievement of steady-state exposures of the final

recommended therapeutic dose in pediatric patients greater than or equal to 1 month to < 17 years of age.

- 3957-1: A study that will examine safety and tolerability of an oral loading dose of Vimpat (lacosamide) that will allow a more rapid achievement of the final recommended therapeutic dose in pediatric patients 4 to <17 years of age. (This PMR was a revision of 2774-2 to encompass pediatric patients with PGTCS).
- 3957-2: A study that will examine safety and tolerability of an intravenous loading dose of Vimpat (lacosamide) that will allow a more rapid achievement of steady-state exposures of the final recommended therapeutic dose in pediatric patients 4 to <17 years of age. (This was a revision of 2774-3 to encompass pediatric patients with PGTCS).

These PREA PMRs are considered fulfilled by this submission.

12. Labeling

Please refer to the final negotiated product labeling. Labeling negotiations with the applicant have been completed, and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations (PMRs)

There are no new recommended PMRs.

14. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
04/27/2023 09:44:10 PM

PAUL R LEE
04/28/2023 09:46:17 AM