CLINICAL REVIEW

Application Type	NDA efficacy supplement
Application Number(s)	022253 (S-46) / 022254 (S-36) / 022255 (S-27)
Priority or Standard	Standard
Submit Date(s)	January 16, 2020
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Division/Office	Division of Neurology 2/ Office of Neuroscience
Reviewer Name(s)	Emily R. Freilich, MD
Review Completion Date	October 16, 2020
Established/Proper Name	Lacosamide
(Proposed) Trade Name	Vimpat
Applicant	UCB, Inc
Dosage Form(s)	Oral tablet, solution, injection
Applicant Proposed Dosing Regimen(s)	50, 100, 150 and 200 mg (oral tablet), 10 mg/ML Adults (17 years and older): - Initial dosage for adjunctive therapy for the treatment of primary generalized tonic clonic seizures is 50 mg twice daily - Maximum recommended dosage is 200 mg twice daily Pediatric patients 4 years to less than 17 years: - The recommended dosage is based on body weight and is administered twice daily
Applicant Proposed Indication(s)/Population(s)	For adjunctive therapy in the treatment of primary generalized tonic clonic seizures in patients (b) (4) 4 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adjunctive therapy in the treatment of primary generalized tonic clonic seizures in patients 4 years of age and older

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AV	atrioventricular
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EEG	electroencephalogram
ET	early termination
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GCS	Glasgow Coma Scale
GRMP	good review management practice

HR	hazards ratio
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
IND	Investigational New Drug Application
IMP	investigational medicinal product
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
LCM	lacosamide
LEV	levetiracetam
LFT	liver function tests
LTG	lamotrigine
MAO-I	monoamine oxidase A
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PET	polyethylene terephthalate
PER	perampanel
PGTCS	primary generalized tonic clonic seizures
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POS	partial-onset seizure
PP	per protocol

PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SPA	special protocol agreement
SS	safety set
SUDEP	sudden unexpected death in epilepsy patients
TEAE	treatment emergent adverse event
TPM	topiramate
ULN	upper limit of normal
VNS	vagal nerve stimulator
VPA	valproate

1. Executive Summary

1.1. Product Introduction

Lacosamide (LCM), a slow sodium channel antagonist, is currently approved for the treatment of partial-onset seizures (POS) in patients 4 years and older in both tablet and oral solution, and in patients 16 years and older in injection for infusion. LCM is believed to exert its antiepileptic effect through selectively enhancing slow inactivation of voltage-gated sodium channels, thereby increasing activation thresholds and leading to reduction of neuronal hyperexcitability.

In this supplemental application, the Applicant proposes a new indication for LCM (tradename VIMPAT) tablets, oral solution and injection for infusion for the adjunctive treatment of primary generalized tonic clonic seizures (PGTCS) in patients 4 years of age and older (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of effectiveness for LCM for the adjunctive treatment of PGTCS in patients 4 years of age and older (b) (4) is based on the positive results from a single, multicenter, double-blind, placebo-controlled pivotal study.

The level of evidence provided is adequate to support the conclusion that LCM is effective for the treatment of PGTCS in the population studied, given that LCM is already indicated for the treatment of POS in patients 4 years and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Lacosamide (LCM) is currently approved for the treatment of partial-onset seizures (POS) in patients 4 years of age and older. The current application seeks approval for the new indication of the adjunctive treatment of primary generalized seizures (PGTCS) in patients 4 years and older.

Despite the fact that there are a few currently approved therapies for PGTCS, up to 40% of patients with PGTCS remain refractory to current treatment and may have difficult-to- treat seizures, with increased risk for both status epilepticus as well as sudden death in epilepsy patients (SUDEP). Additionally, having even a sporadic generalized convulsion can significantly affect the quality of life of these patients who are then unable to drive, work certain jobs, or attend school regularly. There are significantly fewer approved treatment options for PGTCS than those available for the treatment of POS, and some of the treatments used for POS can actually worsen or exacerbate seizures in IGE. Of the treatments that are approved for PGTCS, some have significant risks for adverse events, including risks for Stevens-Johnson syndrome and risks of teratogenicity.

The efficacy of LCM for the adjunctive treatment of PGTCS is based on a single, multicenter, double-blind, placebo-controlled efficacy and safety study (Study SP0982) in patients 4 years of age and older with idiopathic generalized epilepsy (IGE). The study utilized a time-to-event study design, and the primary efficacy endpoint was based on the time-to-second PGTC seizure, as determined by seizure diary, after a minimum 6-week Titration Period, and for a maximum 24-week Treatment Period, after which patients were censored. The study demonstrated effectiveness at the same dosing that is utilized in the treatment of POS, 400 mg/day for adults, 8 mg/kg/day for pediatric patients weighing between 30 and < 50 kg, and 12 mg/kg/day for pediatric patients < 30 kg.

The safety profile of LCM is well-characterized in adults with POS based on multiple controlled studies, and it was found to be quite similar in pediatric patients with POS age 4 years and above. The current application provides safety data on 242 patients age 4 years and older with PGTCS from Study SP0982. The controlled safety data demonstrated a similar safety profile to that of patients with POS, with the most common adverse events of dizziness, somnolence, headache, and nausea being the same. Additionally, a new adverse event of myoclonic seizures was noted in 3% of patients receiving LCM, compared to only 1% of patients in the placebo arm. While these events were mild and only led to one study discontinuation, it is important to note because patients receiving LCM also reported more days with myoclonic seizures compared to patients in the placebo arm, and because this is a known potential adverse reaction of sodium channel blockers in IGE. There were also 2 serious adverse events of worsening seizures, including status epilepticus, that occurred during the Titration Period, and led to treatment

discontinuation. Providers should be aware that, although rare, it is possible for LCM to worsen seizures in patients with PGTCS. There were no other safety signals unique to the population of patients with PGTCS.

Another advantage of LCM is that it is bioequivalent in both oral and intravenous dosage forms, allowing for easy transition to intravenous therapy if patients are not tolerating oral medications or need to avoid taking anything by mouth while in the hospital. It also allows for a rapid titration with a loading dose in adult patients, which helps to achieve a more rapid steady-state and can be advantageous in patients who have recently had an increase in seizure frequency. The loading dose is not yet studied in pediatric patients < 17 years of age.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PGTCS remain refractory to currently available treatments in up to 40% of patients. • Untreated PGTCS increase the risk for SUDEP as well as status epilepticus and can significantly impact quality of life. • PGTCS are typically found as part of epilepsy syndromes, that are most commonly felt to have an underlying genetic or idiopathic etiology. • PGTCS may begin in patients as young as age 4 years, although it is rare for it to become refractory prior to age 12 years.	PGTCS represent a serious seizure disorder with several serious potential sequalae. Although not as common, patients as young as 4 years of age may present with PGTCS as part of their generalized epilepsy syndromes.
Current Treatment Options	• The approved treatments for PGTCS include levetiracetam, perampanel, lamotrigine, topiramate, and valproate. • Many of the treatments approved for POS patients may be ineffective or even worsen seizures in patients with PGTCS.	The current treatment options in PGTCS are limited, and may have risks of Stevens-Johnson syndrome or risks of teratogenicity with valproate. Many other non-FDA approved therapies are used off-label, but some may worsen seizures in patients with PGTCS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In a single, adequate, and well-controlled pivotal Study SP0982, LCM demonstrated effectiveness at 400 mg/day (adult) or comparable weight-based pediatric dosing compared to placebo in the time-to-2nd PGTC seizure study design, with a statistically significant hazards ratio favoring treatment with LCM. • The key secondary endpoint was percent of patients free from PGTC seizures over the 24-week Treatment Period, which also demonstrated a statistically significant treatment benefit for LCM over placebo. • LCM has a unique benefit among many other AEDs in that it can be used interchangeably in both oral and intravenous formulations.	LCM would be a useful addition to the relatively short list of drugs currently approved for the treatment of PGTCS. Because LCM is bioequivalent in both oral and intravenous dosage forms, it has the benefit of allowing easy transition to intravenous therapy if patients are not tolerating oral medications. It also allows for a rapid titration with a loading dose in adult patients, which helps to achieve a more rapid steady-state and can be advantageous in patients who have recently had an increase in seizure frequency. The loading dose is not yet studied in pediatric patients < 17 years of age.
Risk and Risk Management	• LCM was well tolerated by patients age 4 years and older with PGTCS. • In general, the safety profile was consistent with the known adverse reactions seen in pediatric and adult patients with POS. • Three percent (3%) of patients receiving LCM had worsening of myoclonic seizures, compared to 1% of patients receiving placebo. • There were two patients with serious adverse events of worsening seizures, including one with status epilepticus, during the Titration Period, shortly after starting the treatment, that also led to study discontinuation.	LCM was generally safe and well-tolerated in patients with PGTCS, with a similar adverse event profile to patients treated for POS. The only adverse event that was not previously reported was worsening of myoclonic seizures in a small percentage of patients, which may be unique to patients with PGTCS. There were also 2 patients with serious adverse events of worsening seizures. Although it was only a few patients, seizure worsening has previously been reported in the postmarketing section of the prescribing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		information, and providers should be aware of the potential risk in patients with PGTCS.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		x	Patient reported outcome (PRO)	Sec 6.1.1 Study design
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Epilepsy is a common neurological disease characterized by recurrent seizures, which are classified by their electrical and clinical features. Approximately 65 million people worldwide are estimated to have epilepsy.[1] The most common seizure type in patients with epilepsy is POS (57%), followed by the 3 major types of generalized seizures: tonic clonic seizures (23%), absence seizures (6%) and myoclonic seizures (3%).[2] Generalized seizures are those that have apparent clinical or electrical onset (on an electroencephalogram [EEG]) in both hemispheres of the brain, with no clear focus of initiation. Consciousness is often impaired and motor manifestations are bilateral. One critical EEG hallmark of a susceptibility to generalized seizures is the presence of well-formed, generalized, spike-wave discharges. These are occasionally seen, but are not well-developed, widely distributed, and/or highly stereotyped until 2-3 years of age.

Generalized epilepsy syndromes are further classified as primary (idiopathic) and secondary (symptomatic). IGE is a category of disorders defined by strict clinical and EEG features proposed by the International League Against Epilepsy (ILAE) classification of epileptic syndromes.[3] The IGEs, while representing a heterogenous patient population with multiple factors, are generally assumed to have a genetic etiology. The IGEs typically starts in older children, adolescents and young adults, but may be present in children as young as 4 years of age. There are a number of different epilepsy syndromes within the group of IGEs, but patients with the most common IGE syndromes often experience some PGTCS. These syndromes include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with grand mal seizures on awakening. Additionally, there is the more newly defined syndrome of "IGE with PGTCS only", which includes patients who have PGTCS without also having absence or myoclonic jerks.[4]

Although some patients with IGE may respond well to treatment options, research has suggested that approximately 35-40% of patients with some IGE syndromes may not achieve long-term seizure remission, and the PGTCS associated with IGE are a known risk factor for seizure-related injury and SUDEP.[5]

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[1] Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011; 52 Suppl:2-26
[2] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;34:453-68.
[3] ILAE 1989. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classifications of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.
[4] Engel J, Jr. Report of the ILAE classification Core Group. Epilepsia. 2006; 47:1558-68.
[5] French JA, Krauss GL, Wechsler RT, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: A randomized trial. Neurology 2015; 85(11): 950-957.

2.2. Analysis of Current Treatment Options

The newer antiepileptic drugs (AEDs) differ from older agents in several important ways, including mechanism of action, spectrum of activity, and pharmacokinetic (PK) characteristics. However, between 15% and 40% of patients with IGE remain refractory to therapy or do not tolerate the AEDs commonly used in this population: phenobarbital, valproate, ethosuximide (absence seizures only), lamotrigine, topiramate, and levetiracetam[6,7]. More recently, perampanel was also approved for the treatment of PGTCS in patients 12 years and older. Some of these AEDs can induce serious, life-threatening adverse events. Generalized tonic-clonic seizures may also respond to drugs that can potentially aggravate other generalized seizure types, such as absence seizures and/or myoclonic jerks[7,8]. Absence and myoclonic seizures are particularly prone to aggravation by certain AEDs, including carbamazepine, vigabatrin, tiagabine, phenytoin, and oxcarbazepine. Of these, carbamazepine, phenytoin, and oxcarbazepine are sodium channel blockers which is thought to potentially play a role in the exacerbation of the generalized seizures.

Table 1 Summary of Available Treatments for PGTCS in Patients with Idiopathic Generalized Epilepsy

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Admin	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]					
Lamotrigine (LTG)	Adjunctive therapy of PGTCS in patients ≥ 2 years of age	2006	Oral, BID	Single multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥ 2 years of age. Primary endpoint was percentage change from baseline in PGTC seizures, with a median percent reduction of 66% with LTG and 34% with placebo	BOX Warning: serious rash, including Stevens Johnson syndrome, toxic epidermal necrolysis Warnings: hypersensitivity reactions, hemophagocytic lymphohistiocytosis, suicidal behavior/ideation, and withdrawal seizures. Other: Risk of serious rash increased when on concomitant valproate; slow titration of dose decreases risk
Levetiracetam (LEV)	Adjunctive therapy of PGTCS in	2007	Oral, BID	Single multicenter, double-blind, placebo-	Warnings: behavioral abnormalities including psychotic

[6] Bartolomei F, Roger J, Bureau M, et al. Prognostic factors for childhood and juvenile absence epilepsies. Eur Neurol. 1997;37:169-75.
[7] Verrotti A, Greco R, Giannuzzi R, et al. Old and new antiepileptic drugs for the treatment of idiopathic generalized epilepsies. Curr Clin Pharmacol. 2007;2(3):249-59.
[8] Genton P. When antiepileptic drugs aggravate epilepsy. Brain Dev 2000;22:75-80.

	patients ≥ 6 years of age			controlled trial in 165 patients with IGE with PGTCS. Primary endpoint was percent reduction from baseline in weekly PGTCS frequency, with a median percent reduction of 77.6% with LEV and 44.6% with placebo.	symptoms, suicidal ideation, and aggressive behavior, somnolence and fatigue, serious dermatologic reactions, coordination difficulties, and withdrawal seizures.
Perampanel (PER)	Adjunctive therapy of PGTCS in patients ≥ 12 years of age	2015	Oral, Daily	Single, multicenter, double-blind, placebo-controlled trial in idiopathic generalized epilepsy with PGTCS. The primary endpoint was percent reduction from baseline in PGTCS frequency per 28 days, with a median percent reduction of 76% with PER and 38% with placebo.	Warnings: psychiatric and behavioral adverse reactions including aggression, irritability, anger, suicidality, dizziness, somnolence (including caution when driving), falls, DRESS/multi-organ hypersensitivity, and withdrawal seizures.
Topiramate (TPM)	Adjunctive therapy and monotherapy of PGTCS in patients ≥ 2 years of age	1996	Oral, BID	Single, multicenter, double-blind, placebo-controlled study in patients with PGTCS. Primary endpoint was change from baseline in frequency of PGTCS, with a median percent reduction in seizure frequency of 57% with TPM and 9% on placebo.	Warnings: acute myopia and secondary angle closure glaucoma, visual field defects, oligohidrosis and hyperthermia, metabolic acidosis, suicidal behavior and ideation, cognitive /neuropsychiatric adverse reaction, fetal toxicity, serious skin reactions, hyperammonemia/encephalopathy, kidney stones, and hypothermia with concomitant valproic acid use.
Other Treatments – [Combine by Pharmacologic Class, if relevant]					
Valproic acid (VPA)	Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure	1983	Oral, BID Also available as an injection	Unclear	Box Warning: hepatotoxicity, fetal risk, pancreatitis Contraindicated in patients with hepatic disease, known mitochondrial disorders with mutations in POLG, urea cycle disorders Warnings: Birth defects, decreased IQ and neurodevelopmental disorders

	types that include absence seizures				following in utero exposure, pancreatitis, suicidal behavior, bleeding and other hematopoietic disorders, hyperammonemia and hyperammonemic encephalopathy, hypothermia, drug reaction with eosinophilia and systemic symptoms (DRESSS), somnolence in elderly

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LCM was approved in the United States in October 2008 for the adjunctive treatment of partial-onset seizures (POS) in adults 17 years of age and older (NDA 022253, oral tablet) and for the short-term management of seizures in adult patients with POS unable to tolerate oral therapy (NDA 022254, injection). The oral solution (NDA 022255) was later approved in April 2010, and all formulations were approved for use as monotherapy and with an oral and intravenous loading dose option in August 2014. Finally, in November 2017, the approval was expanded to include treatment of POS in pediatric patients 4 years of age and older (oral tablet and suspension only). The injection has not yet been approved for use in pediatric patients.

The pivotal study SP0982 to assess the efficacy and safety of LCM as adjunctive therapy for uncontrolled PGTCS in patients 4 years of age and older with IGE has been the subject of a Special Protocol Assessment (SPA) agreement since August 2, 2013. The SPA was amended in November 2017 as detailed below to stop participation after the 125th event was observed and to enroll ongoing patients into the open-label extension study, with FDA agreement.

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-NDA meeting was conducted via Written Responses in April 2019 to discuss the format and requirements for the current submission.

The Applicant also requested priority review for the current submission, because of a significant unmet medical need in the population of patients with refractory PGTCS, as well as the risk for SUDEP. Priority review was denied because of the availability of several FDA-approved alternate treatment options, and because LCM is already marketed and available for off-label use, if necessary.

3.3. Foreign Regulatory Actions and Marketing History

LCM is approved worldwide in more than 70 countries, although in the European Union it remains marketed only for treatment of POS in patients 4 years and above.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI planned inspections of three foreign sites to evaluate data integrity and quality. However, due to the world-wide Covid19 pandemic, these sites were deemed non-mission critical and the inspections were not able to be completed.

4.2. Product Quality

Vimpat is an already approved product.

4.3. Clinical Microbiology

No new clinical microbiology studies were included in this NDA supplement.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were included in this NDA supplement.

4.5. Clinical Pharmacology

The proposed doses are the same as the already approved doses for treatment of POS. See Office of Clinical Pharmacology review of the proposed doses.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 2 Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
SP0982	NCT 02408523	Double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy	Oral, divided BID Total daily dose: < 30 kg: 12 mg/kg/day ≥ 30 to < 50 kg: 8 mg/kg/day ≥ 50 kg: 400 mg/day	Primary endpoint: Time to second PGTCS during 24-week Treatment Period Key secondary endpoint: Seizure freedom for PGTCS during the 24-week Treatment Period	Min 6 weeks to Max 24 weeks Treatment Period, with 30-day Safety Follow-Up Period	242	Patients 4 years and older with IGE taking 1 to 3 concomitant AEDS	US, Europe, Asia, Australia
		Studies to Support Safety						
EP0012	NCT 02408549	Phase 3, open-label, multicenter extension study to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy	Oral, divided BID Total daily dose: < 30 kg: 10 mg/kg/day ≥30 to < 50 kg: 8 mg/kg/day ≥ 50 kg: 400 mg/day	Safety	Minimum 2 years up to 5 years, 30 day Safety Follow-Up	250	Baseline failures and those who completed study SP0982	US, Canada, Europe, Asia, Australia
EP0060	NCT 0271	Phase 2/3, multicenter, open-label study to evaluate the safety and	IV, single-dose *potential for	Safety	Minimum 1 day, up to 5	Approx 88 patients	Patients 1 month to < 17	North America, Europe, Asia

	0890	tolerability of intravenous LCM in pediatric subjects ≥ 1 month to < 1 years of age with epilepsy	Q12 dosing up to 10 doses Dose ranged: 2-12 mg/kg/day or 100 -600 mg/day		days with a final visit following the last dose and telephone visit 1-3 days after Final Visit		years of age with epilepsy and: Open-label LCM (OLL): patients currently receiving oral LCM in an open-label long-term study Prescribed LCM (RxL): patients currently receiving prescribed oral LCM from commercial supply Initiating iv LCM (IIL): patients not currently receiving LCM and receiving first dose in the study	
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
SP0961		Phase 2, open-label, pilot study to assess the safety of oral LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy	Oral, BID 100 mg/day – 400 mg/day	Primary variables for safety: Change in seizure days with absence	Total duration 16 weeks: baseline (4 weeks, titration (3	49	Patients with uncontrolled PGTCS with IGE age 16 to 65 years	US only

				seizures from baseline to maintenance and Change in seizure days with myoclonic seizures from baseline to maintenance	weeks), maintenance (6 weeks) and end-of-study period (3 weeks)			
SP0962		Phase 2, open-label extension study to assess the safety and seizure frequency associated with long-term oral LCM for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy	Oral, BID 200 mg/day – 800 mg/day	Primary variable was safety	56-week Treatment Period, with 3-week Taper	39	Patients who completed Study SP0961	US only

5.2. Review Strategy

This clinical review will primarily examine Study SP0982, a single double-blind, placebo-controlled, pivotal study in the treatment of PGTCs in patients with idiopathic generalized epilepsy, which is considered sufficient to demonstrate evidence of effectiveness in this indication given the prior approvals with demonstration of effectiveness in the treatment of patients with POS across the same age range.

A separate Biometrics review will provide Dr. Xiangmin Zhang's statistical analysis. I will also discuss the clinical relevance of the Applicant-provided analyses for efficacy from Study SP0982. Section 7 is not relevant to this application because there is reliance on a single pivotal study for efficacy.

I will perform my own safety analyses based on data provided by the Applicant from pivotal study SP0982, as well as the open-label, long term extension study EP0012. Further supportive safety information will be reviewed from open-label Phase 2 studies SP0961 and SP0962 in patients with PGTC seizures.

The data from open-label study EP0060 examined the safety and tolerability of intravenous LCM in pediatric patients with epilepsy, and did not distinguish between treatment of PGTCs and POS. A second supplemental NDA was submitted by the Applicant in May 2020 to expand the use of intravenous LCM down to age 4 years for the treatment of POS. Although an interim study report from EP0060 was submitted with this application to support the treatment of pediatric patients with PGTC seizures with intravenous LCM, the review of the final EP0060 study report will be done completely in the review for that NDA supplement (sNDA 022254 S-38).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Double-Blind, Randomized, Placebo-Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Lacosamide As Adjunctive therapy for Uncontrolled Primary Generalized Tonic-Clonic Seizures in Subjects with Idiopathic Generalized Epilepsy

6.1.1. Study Design

Overview and Objective

Study SP0982 is a Phase 3, double-blind, placebo-controlled, parallel-group, multicenter study

to evaluate the efficacy and safety of lacosamide (LCM) in patients with idiopathic generalized epilepsy with uncontrolled PGTCs in patients ≥ 4 years of age. The objectives were to demonstrate efficacy, safety and tolerability of adjunctive therapy with LCM in patients taking 1 to 3 concomitant AEDs.

Trial Design

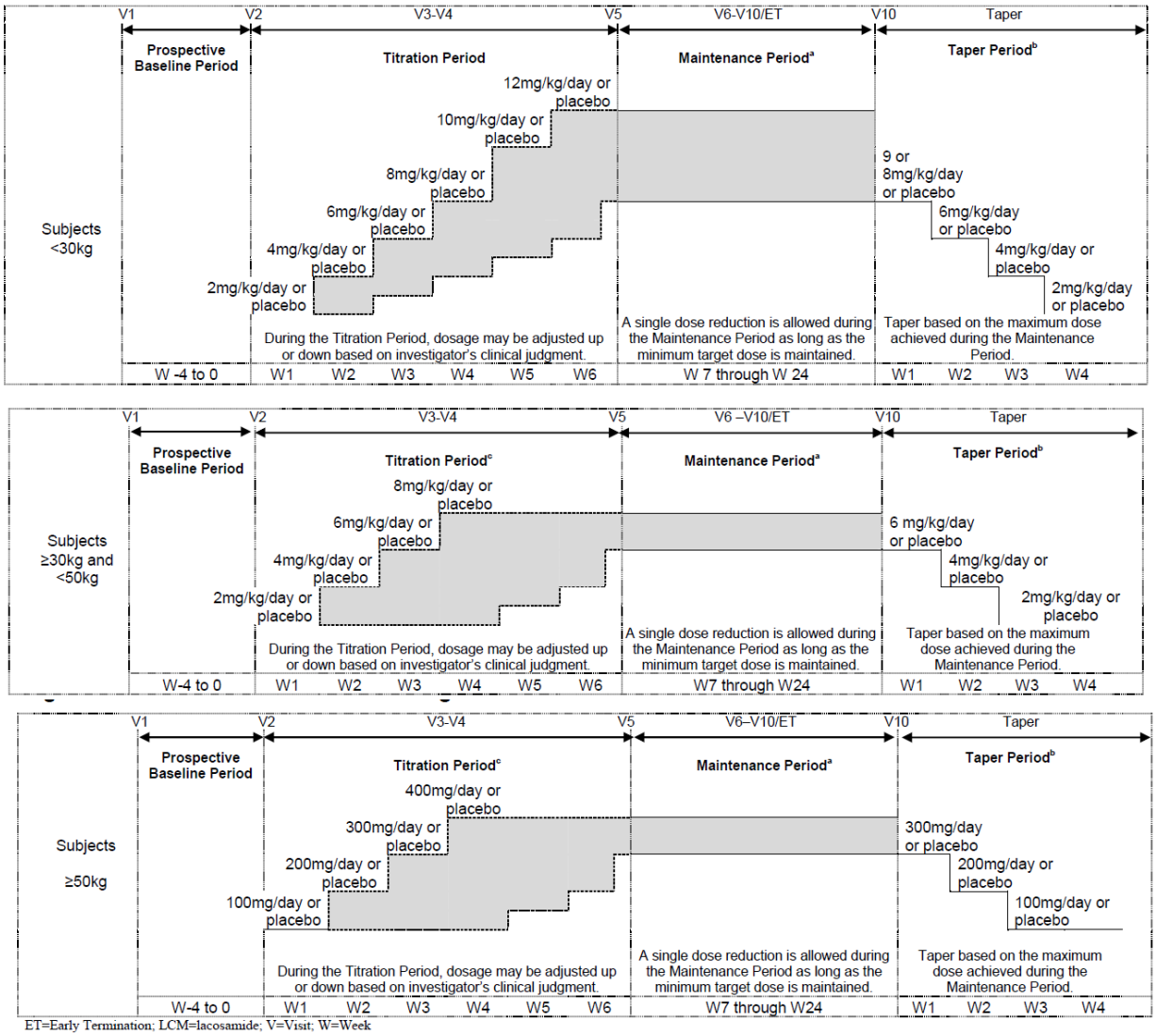
- Basic study design
  The study was a Phase 3, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy of oral LCM vs. placebo as adjunctive therapy for uncontrolled PGTC seizures in patients with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs. The study also assessed the safety, tolerability, and PK of LCM use in this population. The study included a 4-week prospective baseline period, and a 6-week (minimum) to 24-week (maximum) Treatment Period, including a 6-week Titration period and an 18-week (maximum) Maintenance Period (see Figure 1).

  The study utilized a novel primary endpoint, time to second PGTC seizure, rather than utilizing the more traditional endpoint of percent reduction in seizure frequency over the entire Treatment Period. The study design attempted to reduce the duration of the prospective baseline period and the required frequency of baseline seizures required for eligibility into the study, as no percent decrease in the number of seizures is required for the primary analysis. Patients were allowed to exit the study after they experienced ≥ 2 seizures, after a minimum of 6 weeks of double-blind treatment, rather than continue to remain on treatment and having frequent seizures. Patients who did exit early were still eligible to receive LCM in the open-label extension study.

  Reviewer's comment: The "time to nth seizure" design is an innovative "time to event" study design for seizure trials which is aimed to minimize exposure to placebo, as well as decrease the required seizure frequency for eligibility into the study. The original rationale for the study design was established from a post-hoc analysis using data from a traditional, adjunctive study in patients with PGTC seizures comparing lamotrigine to placebo[9]. This post-hoc analysis revealed that the time to third seizure was statistically significant with a hazard ratio of 0.533 (lamotrigine 48.2%, placebo 25.4%). Since the majority of the events in the lamotrigine study occurred prior to Day 21, it was hypothesized that fewer events would occur using LCM in a similarly-designed study, as LCM reaches an effective steady-state dose earlier, given the slow titration required for lamotrigine. Therefore, time to second seizure was chosen for this study from a clinical and statistical perspective.

[9] French JA, Tempkin NR, Hammer AE, et al. Time to Nth seizure analysis of Lamotrigine as Adjunctive Therapy in Subjects with Primary Generalized Tonic Clonic Seizures. Epilepsia. 2007; 48(S6):77-8.(abstract 1.211)

Figure 1 Study Design Schematic Overall, Baseline Period through Taper Period



ET=Early Termination; LCM=lacosamide; V=Visit; W=Week

Note: Lacosamide dosing is designated as "mg/kg/day" (oral solution) and "mg/day" (tablets) and matching placebo is shown as "placebo."

[a] Subjects will be required to achieve and maintain a minimum LCM (or matching placebo) dose for at least the final 3 days of Week 6 to be eligible for entry into the Maintenance Period.

[b] If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit. There will be a 30-day Safety Follow-up Period for subjects who complete the End of Taper Visit. After the 125th event occurs, the 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

[c] If the subject is in the Titration Period when the 125th event occurs, the subject will proceed to the Transition/Taper period directly after their ET/V10 Visit.

- Trial Location

  The study enrolled patients across 115 sites in the United States, Europe, Asia, and Australia.

Reviewer's comment: Given the proposed patient population targeted by this indication, although limited patients from the United States were enrolled in this study, the international population of patients with PGTCs is not felt to differ significantly from the patients in the United States with the same condition.

- Choice of Control Group
  The use of placebo was the appropriate choice for a control group in this patient population and for this indication. Comparison to a placebo arm is felt to be necessary to fulfill the scientific objectives and regulatory requirements to demonstrate both efficacy and safety in this population, as a comparator is required to reliably assess the impact on seizure frequency, given the variability amongst patients at baseline in terms of seizure frequency, severity, type, and variable time between seizures. The use of the novel endpoint, "Time to 2nd seizure" was introduced to be able to reduce time patients would have to spend on placebo if they were continuing to have seizures, and to reduce the seizure frequency required for entry into the study as described above.

- Diagnostic Criteria
  Patients must have a diagnosis of idiopathic generalized epilepsy with PGTC seizures (see below Inclusion and Exclusion criteria as well). Eligibility to enroll in the study was based on a 12-week historical baseline prior to screening to evaluate for PGTCs frequency. The following 3 criteria must have been met:
  - The patient must have experiences at least 3 PCGTS during the 16-week Combined Baseline Period (12-week historical baseline plus 4-week prospective baseline)
  - The study participant must have experienced at least 2 PGTCS during the 12-week historical baseline period
  - Of the above seizures, at least 1 PGTCS should have occurred during the first 8 weeks and at least 1 PGTCS should have occurred during the second 8 weeks of the 16 week Combined Baseline Period

- Key Inclusion/Exclusion Criteria

  Key Inclusion Criteria:
  - Male and female patients ≥ 4 years of age
  - Patients with a confirmed diagnosis at least 24 weeks prior to Visit 1 and a disease onset prior to 30 years of age, consistent with IGE experiencing PGTC seizures (Type IIE) that are classifiable according to the ILE Classification of Epileptic Seizures (ILAE, 1981).
  - Patient has ≥ 3 PGTC seizures during the 16-week Combined Baseline as described above in diagnostic criteria
  - No evidence of progressive abnormality or any lesion likely to be associated with partial-onset seizures on MRI or CT scan, if performed.

- Patient has been maintained on a stable regimen of 1-2 non-benzodiazepine marketed AEDs with no benzodiazepine AEDs, OR 1 benzodiazepine marketed AED with 1-2 non benzodiazepine marketed AEDs for at least 28 days with or without concurrent stable Vagal Nerve Stimulator (VNS).
- EEG report consistent with IGE (e.g., generalized ≥ 3 Hz epileptiform discharges and a normal EEG background), confirmed by a Central Reviewer.

Key Exclusion Criteria:

- Patient has history of partial-onset seizures or EEG findings indicative of partial-onset seizures
- Patient has symptomatic generalized epilepsy (e.g. Lennox-Gastaut Syndrome typically presenting with seizures including tonic seizures), some other related syndrome like Doose's syndrome (typically presenting with myoclonic-atonic seizures) or evidence of both generalized and focal epilepsy
- Patient has a history of convulsive status epilepticus 1 year prior to screening
- Patient has a current or previous diagnosis of pseudoseizures, conversion disorder, or other nonepileptic ictal events which could be confused with seizures.
- Patient has a lifetime history of suicide attempt or has suicidal ideation in the past 6 months as indicated on the Columbia-Suicide Severity Rating Scale at Screening
- At Visit 1, patient has ≥ 2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or > ULN total bilirubin (≥ 1.5x ULN total bilirubin if known Gilbert's syndrome). If patient has elevations only in total bilirubin that are >ULN and < 1.5x ULN, fractionate bilirubin to identify possibly undiagnosed Gilbert's syndrome.
- Patient has impaired renal function (i.e., creatinine clearance [CLcr] is < 30 mL/min at screening
- Patient has a known cardiac channelopathy, such as Brugada syndrome
- Patient has sick sinus syndrome without a pacemaker, or second- or third-degree atrioventricular (AV) block, or any other clinically significant ECG abnormalities
- Patient has New York Heart Association Class III or Class IV heart failure
- Patient has been taking 1 or more of the following medications on a regular basis within 28 days prior to Visit 1: monoamine oxidase A (MAO-A) inhibitors, barbiturates for indications other than epilepsy, or clozapine
- Patient has been treated with felbamate and experienced any serious toxicity issues with this treatment. Patients treated with felbamate for < 12 months are excluded. Patients treated with felbamate ≥ 12 months without serious toxicity issues are eligible.
- Patient has taken vigabatrin in the preceding 6 months.

- Dose Selection
  For adult patients, the LCM 100 mg/day dose was selected to be the starting dose for the

study with a 300- 400 mg/day target maintenance dose. The 400 mg/day maintenance dose was previously well-tolerated and demonstrated efficacy in 3 primary efficacy studies in patients with partial-onset seizures. In the prior Phase 2 study of adult patients with uncontrolled PGTC seizures with IGE, the 400 mg/day dose was also well tolerated.

The pediatric dose recommendations were made based on currently available LCM pediatric safety and PK data from prior studies to achieve similar plasma concentrations to the average steady-state LCM plasma concentration reached after a 400 mg/day dose administration in adult studies. A population PK model (CL0177) was also developed and different pediatric dosing adaptation schemes were simulated with the aim of reaching the range of average steady-state plasma concentrations in adults reaching LCM 400 mg/day, which is approximately 8 µg/mL. This was achieved with a target dosing scheme of 12 mg/kg/day in children < 30 kg, 8 mg/kg/day in children weighing 30 kg to < 50 kg, and 400 mg/day in children weighing ≥ 50 kg.

- Study Treatments
  The investigational medicinal product was provided as LCM oral solution (syrup, 10 mg/mL), LCM tablets (50 mg) and matching placebos. The medication was administered orally twice daily at approximately 12-hour intervals in the morning and in the evening. The tablet may not be broken and must be swallowed whole.

- Assignment to Treatment
  Interactive response technology (IRT) will be utilized to assign eligible patients to a treatment regimen based on a predetermined production randomization and/or packaging schedule by the Applicant. The randomization schedule will be produced by the IRT vendor, who is otherwise not involved in the study, and the IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

- Blinding
  The treatment randomization schedule was generated by the Applicant (or designee) in a manner that ensured the study team remained blinded in accordance with standard operating procedures. The randomization schedule was maintained in a secure location until the study was unblinded for the final statistical analysis.

  The LCM and matching placebos were manufactured, packaged, and labeled according to GMP guidelines. The tablets and matching placebo tablets were packaged in high density polyethylene bottles. The oral solution and matching placebo were packaged in amber polyethylene terephthalate (PET) bottles and measured and administered via a dosing syringe.

Reviewer's comment: The study was conducted using matching placebos and was thus

adequately blinded with minimal opportunity for unintentional unblinding.

An interim futility assessment was planned to allow the Applicant to consider terminating the study should the likelihood of a positive outcome be unacceptably low based on an unblinded assessment of interim data by an independent data monitoring committee (IDMC). The interim assessment was to be conducted in a manner to ensure blinding was not compromised for individuals involved with operational aspects of the study or with planning and conduct of the final statistical analysis. The 3 planned interim safety analyses were conducted similarly to assure that blinding was maintained.

- Dose modification, Dose discontinuation
  During the Maintenance Period, a single dose reduction was permitted as long as the minimum target dose was maintained. No further dose reductions were allowed. If the patient did not tolerate the drug after one dose reduction, the patient would enter the taper period and be withdrawn from the study. Once the dose had been reduced, it could not be increased.

- Administrative Structure
  An independent data monitoring committee (IDMC) would oversee the safety of the study by reviewing the safety data periodically, and it was outlined in an IDMC charter. The three interim safety analyses were to be performed by the IDMC with a single futility assessment at the second interim analysis.

- Procedures and Schedule
  See the below for the SP0982 Schedule of Assessments through the Maintenance Period or Early Termination Visit (Error! Reference source not found.).

Table 3 Schedule of Key Assessments for SP0982

	Prospective Baseline			Treatment Period											Unscheduled
				6-24 weeks											
				Titration Period (6 weeks)					Maintenance Period (18 weeks)						
Visit Number	V1	TC	V2	TC	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ET[a]	Visit
Study Week	-4	-2		1	2	3	4	5	6	8	12	16	20	24	NA
Study Assessments															
Inclusion/Exclusion criteria	X	X	X												
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X		X		X		X		X		X		X	X	
Vital signs and weight	X		X		X		X		X	X	X	X	X	X	
EEG[b]	X														
Clinical Laboratory Tests[c]	X		X		X				X		X		X	X	
LCM plasma concentration									X					X	
Contact IRT	X		X		X		X		X	X	X	X	X	X	X
Randomization			X												
Subject diary return/review			X		X		X		X	X	X	X	X	X	
Dispense study drug			X		X		X		X	X	X	X	X	X	
Study drug return/review					X		X		X	X	X	X	X	X	
Adverse Event reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[d]	X		X		X		X		X	X	X	X	X	X	
Behavior/QOL assessments[e]			X											X	

ECG = electrocardiogram; EEG = electroencephalogram; LCM = lacosamide; IRT = interactive response technology; C-SSRS = Columbia Suicide Severity Rating Scale; QOL= quality of life; TC = telephone contact; V = visit

[a] Once the patient has experienced 2 PGTC seizures, the site may contact the medical monitor to confirm whether the patient has met exit criteria, and if so, sites will be advised to have the patient return for their ET visit within 1 week of the patient's second seizures.

[b] Patients are required to have an EEG showing discharges consistent with Idiopathic Generalized Epilepsy prior to Visit 1. A confirmatory EEG may be performed during the prospective baseline, if approved by the Central reviewer.

[c] Clinical laboratory tests include chemistry, hematology, and urinalysis.

[d] C-SSRS will be completed for all patients ≥ 6 years of age only.

[e] The PROs utilized were the Achenbach CBCL (Child Behavior Check List), BRIEF-P/BRIEF (Behavior Rating Inventory of Executive Function), EQ-5D-3L (European Quality of Life), and QOLIE-31-P/PedsQL (Patient -Weighted Quality of Life in Epilepsy Inventory Form 31/ Pediatric Quality of Life Inventory). -Achenbach CBCL/1 ½ -5 is for children < 5 years and 11 months of age, and the CBCL/6-18 is for children ≥ 6 years to < 18 years of age and is completed by the parent/legal representative. The BRIEF-P was used for patients < 5 years of age and the BRIEF was used for patients ≥ 5 years of age. The EQ-5D-3L was performed on all patients ≥ 12 years of age. The QOLIE-31-P was used for all patients ≥ 18 years of age and the PedsQL was used for patients < 18 years of age.

- Concurrent Medications
  Patients were permitted to be maintained on their stable dose regimen of 1-2 non-benzodiazepine marketed AEDs OR a regimen of 2-3 AEDs, with 1 AED identified as a benzodiazepine if stable for at least 28 days prior to Visit 1, with or without additional concurrent stable VNS.
    - Intermittent use of benzodiazepines were limited to 2 doses per 28 days and allowed only for epilepsy indications if established at least 28 days prior to Visit 1.
    - Contraceptive treatment is allowed as per the Exclusion Criteria (and recommended based on whether the patients were on enzyme-inducing AEDs or not).
    - Stable use of amphetamines and sedative antihistamines were allowed.
    - Neuroleptics other than clozapine were allowed during study but efforts were made to maintain stable dosing.

  - Prohibited medications included clozapine, MAO-inhibitors, barbiturates (except as antiepileptic medications), and herbal medicines for epilepsy.
  - Any patient taking non-benzodiazepine anxiolytics or once-daily hypnotics must remain on stable dose throughout the study.

- Treatment Compliance
  At each visit after the investigational drug is dispensed, the patients were to return any unused IMP and empty IMP kits. Drug accountability was completed in the patient's presence to obtain explanations regarding any discrepancies in compliance. If a patient was found to be persistently noncompliant (< 75% or more than 125% compliant with the dosing schedule) then the Applicant and the investigator would decide if it required withdrawal from the study.

  Patients were also monitored for compliance with timely completion of the seizure diary for evaluation of safety and efficacy. Patient diary completion was evaluated at ever clinic visit and telephone contact, and sites were encouraged to call patients to inquire about diary completion. Patients were reminded to include daily entries even if no seizures occurred.

- Subject Completion, Discontinuation, or Withdrawal
  Patients were required to exit the study if any of the following events occurred:
  - Patient completed the first 6 weeks of the treatment period (after randomization) and experienced ≥ 2 PGTC seizures during that time
  - Patient experienced a second PGTC seizures after the first 6 weeks of Treatment Period
  - The 125th event occurred in the study

  If a patient met exit criteria, the patient would return for their early termination (ET) visit within 1 week of the patient's second seizure, unless the 2nd seizure occurred during the first 6weeks of the treatment period, and then the patient would wait for the end of the first 6 weeks of the treatment period to complete the ET visit.

  Patients could withdraw from the study at any time for any reason. Patients were <u>required</u> to be withdrawn from the study if any of the following events occurred:
  - The patient is unable to attain at least the minimum Maintenance Period target dose.
  - The patient required a subsequent dose increase after dose reduction during the Maintenance period or required more than 1 dose reduction during the Maintenance Period.
  - Patient developed second- or third-degree AV block.
  - The patient became pregnant, as evidenced by a positive pregnancy test.
  - The sponsor or a regulatory agency requests withdrawal of the patient.
  - The patient is unwilling or unable to continue and withdraws consent.
  - In the case of liver function test (LFT) results of transaminases (AST and/or ALT) ≥ 3x

ULN to <5x ULN and total bilirubin ≥ 2x ULN, or transaminases (AST and/or ALT) ≥ 5x ULN, LCM must be immediately discontinued, and the patient withdrawn from the study.
- Patient ≥ 6 years of age had actual suicidal ideation, patient would be withdrawn from the study and referred immediately to a mental healthcare professional.

Patient may be withdrawn from the study if any of the following events occurred:
- Patient requires a medication that was not permitted.
- Patient requires a modification to a concomitant AED dose during the study
- The patient is unable to manage completion of the diary or is noncompliant.
- Patient had an episode of status epilepticus, prolongation of seizure duration, worsening of seizure frequency, or emergence of a new seizure type considered by the investigator to require intervention.
- Patient developed an intolerable adverse event or a clinically relevant change in medical condition that the investigator felt it is in the interest of the patient to withdraw.

Further criteria were provided for potential drug-induced liver injury (PDILI) discontinuation criteria.
The following criteria required immediate and permanent discontinuation of study drug:
- ALT or AST ≥ 5x ULN
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN
- Patients with ALT or AST ≥ 3x ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever without alternative cause, rash, or eosinophilia).

The following criteria allowed for continuation at the discretion of the investigator:
- Patients with ALT or AST ≥ 3x ULN (and > 2x baseline) and < 5x ULN, total bilirubin < 2x ULN, and no eosinophilia (i.e. ≤ 5%) with no fever, rash or symptoms of hepatitis.

Study Endpoints

- Primary Efficacy Endpoint
  The primary efficacy variable is the time to second PGTC seizure during the 24-week Treatment Period.

  The patients were to keep a diary to record daily seizure activity from Visit 1 until the end of study. The patient was to complete the diaries daily even if no seizures had occurred. The following information was recorded on a daily basis as applicable: seizure type and number of PGTC seizures. If more than one PGTC seizure occurred on a single day, each seizure would be counted separately, provided there was complete recovery of consciousness between seizures.

Reviewer's comment: The primary efficacy endpoint was evaluated based on seizure diary, as is typical for other similar trials in patients with PGTC seizures and with partial-onset seizures. However, the time to 2nd seizure was a novel endpoint as discussed above. The primary endpoint was agreed upon as part of the Special Protocol Agreement (SPA).

- Secondary Efficacy Endpoint
  The key secondary efficacy variable is seizure freedom from PGTC seizures during the 24-week Treatment Period, estimated using Kaplan-Meier analysis.

Reviewer's comment: The key secondary endpoint was agreed upon as part of the SPA. However, while it is important to note which patients did not have any PGTC seizures during the treatment period, it is not as clinically meaningful as it would be if the patients were free of all seizure types. Further evaluation for complete seizure freedom was a later efficacy endpoint that was not included in the statistical hierarchy.

Other secondary efficacy variables are the percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period relative to the Combined Baseline (historical and prospective baseline), the percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline, and time to the first PGTC seizure during the Treatment Period.

There were a number of other pre-specified other efficacy endpoints that were exploratory including seizure freedom, change in days with absence and/or myoclonic seizures, seizure responder rates, and change from baseline in the quality of life scales.

- Safety Endpoints

The safety and tolerability of LCM was assessed through evaluation of adverse events and serious adverse events. The Applicant included a list of anticipated serious adverse events which are anticipated to occur in the patient population at some frequency independent of drug exposure. The following anticipated SAEs were still documented and recorded throughout the study.

Table 4 Anticipated SAEs for the Epilepsy Population

System Organ Class	Preferred Term
Congenital, Familial and Genetic Disorders	Teratogenicity
General disorders and Administration Site Conditions	Sudden unexplained death in epilepsy
Nervous System Disorders	Convulsion
	Incontinence
	Status epilepticus
Pregnancy, Puerperium and Perinatal Disorders	Abortion spontaneous
Psychiatric Disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder
Reproductive System and Breast Disorders	Menstrual disorder
	Impotence

SAE=serious adverse event

There were also the following AEs of special interest for LCM:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree, Type I and II, and third degree) and marked bradycardia (< 45 bpm)
- Syncope or loss of consciousness (other than seizure-related)
- Serious suspected multiorgan hypersensitivity reactions (as defined and agreed to in the protocol)
- Emergence of non-preexisting or worsening of any existing epileptic seizure type
- Potential Hy's Law, defined as ≥ 3x ULN ALT or AST with co-existing ≥ 2x ULN total bilirubin in absence of ≥ 2x ULN ALP, with no alternative explanation for the biochemical abnormality, must always be reported to the sponsor as an AE of special interest.

Other safety measurements include:

- Laboratory assessments (hematology, chemistry, endocrinology, urinalysis, and pregnancy testing)
- 12-lead ECG
- Vital signs, body weight, and height
- Incidence of new seizure types or increase in absence seizure days or myoclonic seizure days per 28 days
- Physical and neurologic examinations
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Achenbach Child Behavior Checklist (CBCL)
- Behavior Rating Inventory of Executive Function (BRIEF/ BRIEF-P)

Statistical Analysis Plan

The original statistical analysis plan (SAP) was dated August 9, 2016, and agreed to as part of the SPA. There were 4 SAP amendments and the last version was finalized March 28, 2019, prior to the database lock.

Primary Endpoint analysis
The primary efficacy variable, time to second PGTC seizure during the 24-week Treatment Period, was evaluated using a Cox proportional hazards regression model with an effect for treatment, stratifying for the patients' Baseline PGTC seizure frequency (≤ 2 per 28 days vs. > 2 per 28 days in the 16 week prior to treatment) and age at informed consent (≥ 4 to < 12 years of age, ≥ 12 to < 18 years of age and ≥ 18 years of age). Pooling strategies for strata with a low number of events were defined in the SAP prior to unblinding. Patients who prematurely discontinued from the study were to be censored on the date of the last dose of study drug during the Treatment Period. A Kaplan-Meier (KM) plot for time to second PGTC seizure as well as the KM estimate for the median time to second PGTC seizure was to be provided using the full analysis set (FAS) population.

Testing for the primary endpoint would be done at the 5% level (2-sided alpha). A gatekeeping strategy was to be used for the key secondary efficacy variable if the primary efficacy endpoint was statistically significant. No additional adjustments for multiplicity were required.

The following additional sensitivity analyses on the primary efficacy endpoint were planned to assess the effect of dropouts, protocol deviations, and operational bias on the primary endpoint:

- Repeat primary analysis using the Per-Protocol-Set (PPS).
- Repeat primary analysis using the FAS, except all patients who prematurely discontinue due to lack of efficacy, consent withdrawn, or lost to follow-up will be analyzed as treatment failures.
- Repeat primary analysis using the FAS, except all patients who prematurely discontinue due to lack of efficacy of AEs only will be analyzed as treatment failures.
- Repeat primary analysis using the FAS, comparing the event rates at each interim analysis to examine possible operational bias due to unblinding.

Key Secondary Endpoint Analysis
The analysis of the key secondary endpoint, seizure freedom from PGTC seizures for the 24-week Treatment Period, would be analyzed in the same manner as the primary endpoint using the FAS. The percentage of seizure-free patients at 24 weeks would be estimated from the Kaplan-Meier estimates of time to first seizure using 2-sided 95% confidence intervals.
A gatekeeping strategy was employed to control Type I error, such that the key secondary efficacy endpoint would be assessed at the 5% significance level, only if the primary endpoint is statistically significant at the 5% level.

All other secondary efficacy analyses were described in the SAP and were performed using the FAS and in a descriptive manner only.

Missing Data
All data will be used to the maximum possible extent, but without any imputations for missing data for any parameter, unless otherwise specified in the SAP.

Interim Analysis
Three interim analyses for safety were to be performed by the IDMC with a single futility assessment planned at the second interim analysis. The analyses were planned when 25%, 50% and 75% of patients experienced an event (31, 62, and 93 events, respectively) or 24 weeks after 50, 100, and 150 patients have been randomized, respectively, whichever came first. Analysis of the primary endpoint was only to be examined at the planned futility assessment; it was unexpected to have impact on the Type I error as there were no stopping rules for success in place. However, the significance level was set using a Haybittle-Peto boundary at alpha = 0.0001 so as not to require any adjustment to the overall alpha for the final analysis.

Sample Size Justification
The Applicant determined that observing 125 events (patients who have a second PGTC seizure during the 24-week Treatment Period), would provide 90% power to observe a hazard ration of 0.56 at the 2-sided 5% level, assuming a dropout rate of 15%. The observed hazard ration was based on the prior study comparing lamotrigine and placebo, with a 25.4% survival rate for placebo and 48.2% for lamotrigine with an observed hazard ration of 0.533. The hazard ratio was increased by 5% to 0.56 to account for the possibility of an increased placebo response. Enrollment would continue up 125 events occurring or to a maximum of 250 patients randomized, whichever came first.

Protocol Amendments

The original study protocol was dated August 5, 2011. There were 5 subsequent protocol amendments which are summarized below in Table 5. The SPA was agreed to on August 2, 2013 and initiated April 23, 2015.

Table 5 Summary of Major Protocol Amendments in SP0982

Amendment Number	Date	Major Changes
1	September 25, 2012	• Included randomization stratification by age at informed consent (≥ 12 to < 18 years, vs ≥ 18 years of age) • Inclusion/exclusion criteria modified to include patients of normal intelligence for age • Clarified the use of benzodiazepines to allow for 1 of 3 AEDs to be a benzodiazepine (regardless of indication) and for the intermittent use of a benzodiazepine for epilepsy use, limited to 2 doses per 28 days • Modified the secondary efficacy endpoint of "time to first PGTC seizure" as a key secondary endpoint and added gatekeeping strategy to control Type I error. • Added additional assessments including the Pediatric Quality of Life Inventory, the Achenbach Child Behavior Checklist and the Behavior Rating Inventory of Executive Function • Interim assessments for safety and futility added to be performed by an IDMC due to the novel study design and primary endpoint. • Study was amended to reflect that the study was event-driven based upon number of events, not number of study participants. However, a maximum of 250 patients was introduced if 125 events were not observed on or before the 200th patient was randomized.
2	July 11, 2014	• Inclusion of pediatric study patients ≥4 to < 12 years of age. • Inclusion of stratification by age at informed consent for patients 4 to < 12 years of age • Exclusion criteria modified to exclude patients with developmental delay/mental retardation as less likely to have idiopathic epilepsy, and exclude patients with history of status epilepticus.
3	January 9, 2015	• Nonsubstantial amendment to allow ECGs to be evaluated locally and not centrally.
4	June 8, 2016	• Clarification for inclusion and exclusion criteria and exit criteria and duration of the Baseline Period • Procedure for dividing the daily dose without breaking tablets • Clarification of permitted and prohibited concomitant medications • Addition of text regarding potential drug-induced liver injury
5	November 7, 2017	• Stop all patient participation once 125 events have been observed to avoid exposure to placebo unnecessarily and allow for flexible dosing in the open-label extension study • A minimum number of pediatric patients were required (40) rather than a percent (20%) to adjust for fluctuating sample size based on the event rate

Source: Adapted from CSR for Study SP0982

Reviewer's comment: Initially there were concerns that the November 2017 protocol

amendment could lead to an SPA-nonagreement due to changes being made after the unblinded futility analysis. The Applicant clarified that the change was not going to interfere with the study integrity, as the analysis was always powered for 125 events, but just to clarify that all patients would exit the study after the 125th event had been reached, and be able to roll over into the open-label extension study at that time. Thus, the Division agreed to allow the amendment under the SPA.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that all studies were conducted in accordance with the CFR governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice.

Financial Disclosure

APPEARS THIS WAY ON ORIGINAL

See Section 12.2 Financial Disclosures.

Patient Disposition

There were a total of 350 patients screened at 115 sites, and 110 patients were considered screen failures, largely because of ineligibility. Three of these patients were later successfully re-screened and randomized into the study. There were 37 patients who were baseline failures due to their frequency of PGTC seizures during the baseline period. A total of 242 patients started the study and 213 (88.0%) completed the study. See Table 6.

Table 6 Patient Disposition

Disposition	Placebo	LCM	All Patients
Screened		350	
Randomized		242	
Started Study	121	121	242
Completed Study	110	103	213
Discontinued	11	18	29
Reasons for D/C:			
AE	4	10	14
Lack of Efficacy	0	1	1
Protocol Violation	1	2	3
Lost to Follow-up	2	3	5
Consent Withdrawn	3	1	4
Other	1	1	2
Completed Titration Period	114	107	221
Continued into Maintenance	70	82	152
Not Continuing into Maintenance	44	25	69
Did not complete Titration Pd	7	14	21
Completed Maintenance Period	66	78	144

Of those who started the Maintenance Period, 66 /70 patients in the placebo arm completed the maintenance period, and 78 / 82 patients on LCM completed the maintenance period. The reasons for discontinuation during Maintenance were for AE (4), lost to follow-up (1), consent withdrawn(2), and other(1).

The Randomized Set and Safety Set were the same, and included 121 patients in each arm. The Full Analysis Set (FAS) included 240 patients who had at least 1 seizure diary assessment during the treatment period, including 119 in the LCM arm (98.3%) and 121 in the placebo arm (100%).

Protocol Violations/Deviations

There were a number of protocol deviations that were considered important by the Applicant in 31.8% of patients. The number of patients with important protocol deviations was equal amongst the treatment arms with 38 (31.4%) in the placebo arm and 39 (32.2%) in the LCM

arm. A total of 35 patients (14.5%) were excluded from the per-protocol-set (PPS) for protocol deviations which may affect the interpretation of the primary efficacy analysis, with 15% in the placebo arm and 14% in the LCM arm. The main violations requiring exclusion from the PPS were violations related to the inclusion criteria (5 on LCM, 6 on Placebo), dosing regimen (5 on LCM, 4 on Placebo), and procedural noncompliance (completing fewer than 6 weeks of treatment, 6 on LCM, 8 on Placebo).

Reviewer comment: The individual protocol violations were reviewed and given that they were equally balanced between the treatment arms, the impact on the primary endpoint was not felt to be significant.

Table 7 Demographic Characteristics of Randomized Population (Same as Safety Population)

Demographic Parameters	Placebo (N = 121) n (%)	LCM (N = 121) n (%)	Total (N = 242) n (%)
Sex			
Male	45 (37)	55 (45)	100 (41)
Female	76 (63)	66 (55)	142 (59)
Age (years)			
Mean (SD)	28 (12.4)	28 (13.1)	28 (12.8)
Median	25	25	25
Min, Max	5, 65	4, 66	4, 66
Age Group			
≥ 4 to < 12 years	9 (7)	8 (7)	17 (7)
≥ 12 to < 18 years	16 (13)	16 (13)	32 (13)
≥ 18 to < 65 years	95 (79)	96 (79)	191 (79)
≥ 65 years	1 (1)	1 (1)	2 (1)
Weight (kg)			
Mean (SD)	73 (22.2)	70 (21.8)	72 (22.0)
Median	70	70.5	70.4
Min, Max	21.1, 154.3	15.8, 127.4	15.8, 154.3
BMI (kg/m^2)			
Mean (SD)	26.5 (6.8)	25.1 (6.2)	25.8 (6.5)
Median	25	24	24.5
Min, Max	14.2, 47.2	14.3, 50.0	14.2, 50.0
Race			
White	89 (76)	97 (82)	186 (79)
Black or African American	2 (2)	2 (2)	4 (2)
Asian	25 (21)	18 (15)	43 (18)
American Indian or Alaska Native	1 (1)	1 (1)	2 (1)
Other	4 (3)	3 (2)	7 (3)
Ethnicity			
Hispanic or Latino	18 (15)	10 (8)	28 (12)
Not Hispanic or Latino	103 (85)	111 (92)	214 (88)
Region			
United States	13 (11)	17 (14)	30 (12)
Latin America [A]	11 (9)	5 (4)	16 (7)
Western/Central Europe [B]	36 (30)	42 (35)	78 (32)
Eastern Europe [C]	22 (18)	29 (24)	51 (21)
Asia/Pacific/Other [D]	39 (32)	28 (23)	67 (28)

Source: Reviewer-adapted and verified from SP0982 CSR Table 3.1.1
[A] Latin American includes Brazil and Mexico
[B] Western/Central Europe includes Belgium, France, Germany, Italy, Spain, Portugal, Czech Republic, Hungary, Poland, Slovakia
[C] Eastern Europe includes Bulgaria, Romania, Russia
[D] Asia/Pacific/Other includes Japan, Korea, Taiwan, China, Israel, Australia

Reviewer's comment: The demographics were similar in general amongst the treatment arms, although there were a higher percentage of female patients in the placebo group. The regional distributions were slightly different amongst the treatment arms, with the placebo arm having more patients from Latin America and Asia/Pacific/Other, and the LCM arm having more patients from Europe. The majority of patients were non-Hispanic or Latino

white patients.

Table 8 Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline Characteristics	Placebo (N = 121)	LCM (N = 121)	Total (N = 242)
Time since Diagnosis (years)			
Mean (SD)	15.4 (13)	15.5 (13)	15.5 (13)
Median	11	11	11
Min, Max	0.5, 61	0.8, 65	0.5, 65
Seizures during Historical Baseline (per 28 days)			
Mean (SD)	1.7 (1.8)	1.7 (1.4)	1.7 (1.6)
Median	1.0	1.0	1.0
Min, Max	0.3, 14	0.3, 10	0.3, 14
Seizures during Prospective Baseline (per 28 days)			
Mean (SD)	3.0 (6.4)	2.5 (4.1)	2.8 (5.4)
Median	1.1	1.0	1.1
Min, Max	0, 54	0, 30	0, 54
Seizures during Combined Baseline (per 28 days)			
Mean (SD)	2.0 (2.4)	1.9 (1.7)	1.9 (2.1)
Median	1.2	1.2	1.2
Min, Max	0.7, 19	0.3, 12	0.3, 19
Number of PGTCS in Combined Baseline, n (%)			
≤ 2 PGTC Seizures	91 (75)	94 (78)	185 (76)
> 2 PGTC Seizures	30 (25)	27 (22)	57 (24)
Number of AEDs and Benzos at Baseline			
Mean (SD)	1.9 (0.8)	1.9 (0.7)	1.9 (0.8)
Median	2	2	2
Min, Max	0, 5	0, 3	0, 5
Seizure type (ILAE seizure classification)*	n(%)	n(%)	n(%)
Partial-onset seizures	0	1 (0.8)**	1 (0.4)
Generalized seizures	121 (100)	121 (100)	242 (100)
Absence	41 (34)	49 (41)	90 (37)
Atypical absence	2 (2)	2 (2)	4 (2)
Myoclonic	48 (40)	46 (38)	94 (39)
Clonic	2 (2)	3 (3)	5 (2)
Tonic	1 (1)	2 (2)	3 (1)
Tonic-Clonic	121 (100)	120 (99)	241 (100)
Atonic	3 (3)	2 (2)	5 (2)
Unclassified epileptic seizures	0	2 (2)	2 (1)

Source: Reviewer-adapted and verified from SP0982 CSR Table 3.2.1 and Table 4.1.1
AED = antiepileptic drug, PGTC = primary generalized tonic-clonic; ILAE = International League Against Epilepsy
**Seizures experienced at any time prior to study entry were summarized*
*** Patient was excluded from the Per-Protocol Set due to having a history of partial-onset seizures (exclusion criteria 3)*

Reviewer's comment: The LCM and placebo treatment arms were similar in their baseline characteristics related to time since diagnosis, number of AEDs at baseline, and the mean and median number of seizures that occurred during both the historical and prospective baseline periods. The treatment arms were also similar in the classification of seizures experienced prior to study entry.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The use of concomitant AEDs and benzodiazepines was overall similar between the treatment arms. The most common concomitant AEDs were valproate, levetiracetam, lamotrigine, and topiramate. (Table 9)

Table 9 Concomitant AEDs and benzodiazepines during the Treatment Period (SS)

Preferred Term Any AED and/or benzodiazepine	Placebo (N = 121) n (%)	LCM (N = 121) n (%)	Total (N = 242) n (%)
Levetiracetam	48 (40)	56 (46)	104 (43)
Lamotrigine	37 (31)	36 (30)	73 (30)
Topiramate	15 (12)	16 (13)	31 (13)
Zonisamide	7 (6)	7 (6)	14 (6)
Valproate*	68 (56)	59 (49)	127 (53)
Clonazepam	16 (13)	12 (10)	28 (12)
Clobazam	13 (11)	9 (7)**	22 (9)
Carbamazepine	5 (4)	9 (7)	14 (6)

Source: Reviewer-adapted and verified from SP0982 CSR Table 6.3
AED = antiepileptic drug, LCM = lacosamide; SS = safety set
**Valproate includes valproic acid, valproate semisodium, valproate sodium, valproate magnesium, ergenyl chrono, and valpromide.*
*** One additional patient was receiving clobazam reportedly for a headache indication and therefore was not counted in this group*

Non-AED concomitant medication use was similar between the two treatment groups. Excluding AEDS, 76 patients in the LCM group (63%) and 69 patients in the Placebo group (57%) took concomitant medications. The most common non-AED medications were anti-inflammatory products, analgesics, antibiotics, and sex hormones.

Efficacy Results – Primary Endpoint

The primary efficacy variable was time to second PGTC seizure during the 24-week Treatment Period. The primary efficacy assessment was based on the Full-Analysis Set (FAS). The comparison of LCM versus placebo was based on a Cox proportional hazards regression model with an effect for treatment, stratifying for the study participants' Baseline PGTCS frequency (≤ 2 per 28 days versus > 2 per 28 days in the Combined Baseline Period) and age at informed consent (≥ 4 to < 12 years of age , ≥ 12 to < 18 years of age, or ≥ 18 years of age). The reference group was placebo (Table 10).

The survival estimates at the end of the Treatment Period were 55.3% in the LCM treatment arm, and 33.4% in the Placebo treatment arm, with a resulting hazards ration (HR) of 0.540 [95% CI: 0.377, 0.774]; p< 0.001). For the LCM group the median time to second PGTC seizure could not be estimated by Kaplan-Meier (KM) methods because >50% of the patients did not experience a second PGTC seizure by Day 166. Of note, patient [redacted] (b) (6) (LCM) was randomized after the 125th event occurred and is not included in the analysis.

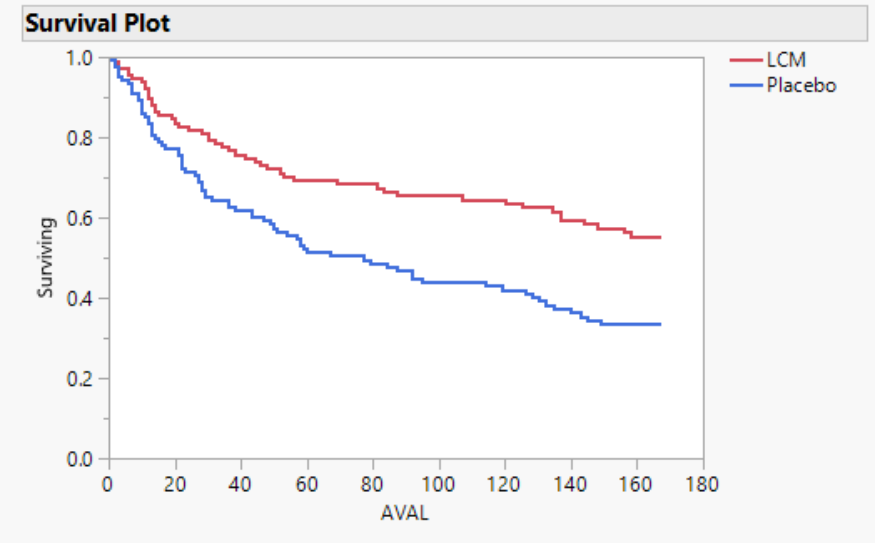
Table 10 Analysis of Time to Second PGTCS (FAS)

	Placebo (N = 121)		LCM (N = 118)	
	Cumulative Number of events	KM survival estimate (%)	Cumulative Number of events	KM survival estimate (%)
Treatment Period	76	33.37	49	55.27
KM analysis				
Patients censored*, n (%)	45 (37.2)		69 (58.5)	
Time to event (Days)				
Median	77.0		--	
95% CI	47.0, 126.0		137.0, --	
Treatment Comparison				
LCM vs. Placebo				
Hazard Ratio (HR)**	0.540			
95% CI of HR	0.377, 0.774			
p-value	<0.001			

Source: Reviewer verified and adapted from Sp0982 CSR Table 8.1.1
FAS = Full analysis Set; KM = Kaplan-Meier; LCM = lacosamide, CI = confidence interval, HR = hazard ratio, PGTCS = primary generalized tonic-clonic seizures
**Patients who completed the Treatment Period without having a second PGTCS during the Treatment Period were censored.*
*** An HR < 1 indicates time to second PGTCS was improved for LCM compared with Placebo*

Reviewer's comment: Please see Dr. Xiangmin Zhang's Statistical Review for further analysis of the primary efficacy endpoint. She notes that the Applicant used different strata in their primary analysis than those that were pre-specified in the SAP. The Applicant disclosed that the strata deviated from the pre-specified strata as a result of the low enrollment of pediatric patients in the 4-11 year age category. According to Dr. Zhang's review, had the Applicant followed the SAP pre-specification, there would be six strata, rather than the three used by the Applicant. The results based on the pre-specified strata had a hazard ratio of 0.548 (p-value = 0.001, 95% confidence interval = (0.381, 0.788)), also indicating the LCM group had a lower risk of developing a second PGTCS.

Figure 2 Kaplan-Meier Plot for Time to Second PGTC Seizure (FAS)



Source: Reviewer-created analysis of SP0982 ADTTE dataset for Time to Second PGTC Seizure
Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRTA

The Kaplan-Meier curve for time to second PGTCS during the 24-week Treatment Period is demonstrated above in Figure 2. The median survival time was 77 days for the placebo group; the median survival time was not estimated for the LCM group because more than 50% of the patients in the LCM group did not experience a second PGTC by the end of week 24. Treatment difference between the LCM group and placebo group is observed from the Kaplan-Meier curve.

Reviewer's comment: As noted in Dr. Zhang's Statistical Review, an additional analysis of the log-rank test was performed on the above Kaplan-Meier curve, which had a consistent conclusion with the primary analysis, favoring the treatment effect of LCM (nominal p-value = 0.001).

The primary endpoint demonstrates that there was a statistically significant and clinically meaningful treatment effect of LCM on the time that it took for patients to have a second PGTCS during the Treatment Period. The effect was noted both in patients with low baseline seizure frequency and high baseline seizure frequency.

Subgroup analyses were evaluated for the primary efficacy variable and are presented in the following table for the FAS (Table 11).

Table 11 Subgroup analyses of time to Second PGTC seizure during Treatment Period (FAS)

	Placebo (N = 121)			LCM (N = 118)			LCM-Placebo	
	N	Cumulative Number of events	KM survival estimate (%)	N	Cumulative Number of events	KM survival estimate (%)	HR*	95% CI
Age								
≥ 4 to 12 years	9	5	44.4	8	2	75.0	0.492	0.089, 2.731
≥ 12 to 18 years	16	9	41.3	16	7	54.1	0.740	0.265, 2.062
≥ 18 years	96	62	31.3	94	40	53.6	0.527	0.354, 0.786
Baseline PGTC frequency								
≤ 2 per 28 days	95	56	37.5	93	34	60.3	0.501	0.327, 0.767
>2 per 28 days	26	20	17.8	25	15	37.6	0.653	0.334, 1.277
Number of Concomitant AEDs								
0	0	0	-	1	0	100.0	-	-,-
1	44	22	44.77	34	12	63.22	0.570	0.279, 1.165
2	55	37	30.24	61	26	53.72	0.539	0.323, 0.900
≥ 3	22	17	19.39	22	11	44.43	0.440	0.201, 0.965
Race								
White	89	49	40.5	94	40	53.5	0.713	0.469, 1.083
Non-White	32	27	15.0	24	9	61.8	0.261	0.120, 0.565
Gender								
Male	45	26	39.7	54	15	70.7	0.397	0.209, 0.752
Female	76	50	29.4	64	34	42.2	0.685	0.442, 1.061
Region								
United States	13	10	16.9	16	7	53.0	0.446	0.158, 1.260
Latin America	11	8	24.2	5	3	30.0	0.946	0.238, 3.756
Western/Central Europe	36	16	48.3	41	21	46.2	1.298	0.671, 2.511
Eastern Europe	22	7	66.5	29	6	77.8	0.522	0.172, 1.585
Asia/Pacific/Other	39	35	10.3	27	12	52.3	0.263	0.134, 0.515

Source: Reviewer verified and adapted from SP0982 CSR Tables 8.1.8-8.1.14
AED = antiepileptic drug; CI = confidence interval; FAS = full-analysis set; HR = hazard ratio; LCM = lacosamide; PGTCS = primary generalized tonic clonic seizure;
**An HR < 1 indicates time to second PGTCS was improved for LCM compared with Placebo*

Reviewer's comment: The study was not powered to detect statistical significance within the subgroup analyses, and therefore the sample size for many of the subgroup categories in all subgroup analyses were relatively small. However, the subgroup analyses were directionally consistent with a treatment benefit of LCM compared to placebo with the exception of the Western/Central Europe subgroup, where there were more events in the LCM treatment arm, and the survival estimates were roughly equivalent (46.2% LCM and 48.3% Placebo, HR 1.3).

Data Quality and Integrity

Overall the data quality and analysis quality are adequate. I was able to perform independent review using the Applicant's submitted datasets and confirm the results. OSI was unable to complete clinical site inspections due to the world-wide COVID-19 pandemic. There was no evidence that any particular site was driving the efficacy results.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was seizure freedom from PGTCS at Day 166 of the Treatment Period. A seizure-free day was defined as a day where no PGTCS were reported in the seizure diary and PGTCS were assessed. The Kaplan-Meier proportion of patients with seizure freedom at Day 166 is provided for the FAS in Table 12. The estimated strata-weighted proportions of patients that did experience a PGTCS by the end of week 24 were 31.3% and 17.2% for the LCM group and placebo group, respectively; the LCM-placebo difference was 14.1% (95% CI = (3.2%, 25.1%) and statistically significant with p-value = 0.011.

Table 12 Proportion of patients with seizure freedom (For PGTCS) at Day 166

	Placebo (N = 121)			LCM (N = 118)		
	N	Number of patients with seizure n (%)	KM seizure-free (%) (95% CI)	N	Number of patients with seizure n (%)	KM seizure-free (%) (95% CI)
Overall						
Seizure Free from PGTCS	121	97 (80.2)	17.3 (10.3, 24.3)	118	79 (66.9)	31.0 (22.4, 39.6)
Stratum 1						
Baseline PGTCS ≤ 2 per 28 days and pediatric	21	18 (85.7)	14.3 (0.0, 29.3)	21	16 (76.2)	22.9 (4.4, 41.3)
Stratum 2						
Baseline PGTCS ≤ 2 per 28 days and adult	74	56 (75.7)	22.3 (12.5, 32.1)	72	46 (63.9)	34.2 (23.0, 45.5)
Stratum 3						
Baseline PGTCS > 2 per 28 days	26	23 (88.5)	4.9 (0.0, 14.3)	25	17 (68.0)	30.0 (11.3, 48.7)
Stratified*						
Seizure-Free from PGTCS			17.2 (10.4, 24.0)			31.3 (22.8, 39.9)
LCM-Placebo	14.1 (3.2, 25.1) p= 0.011					

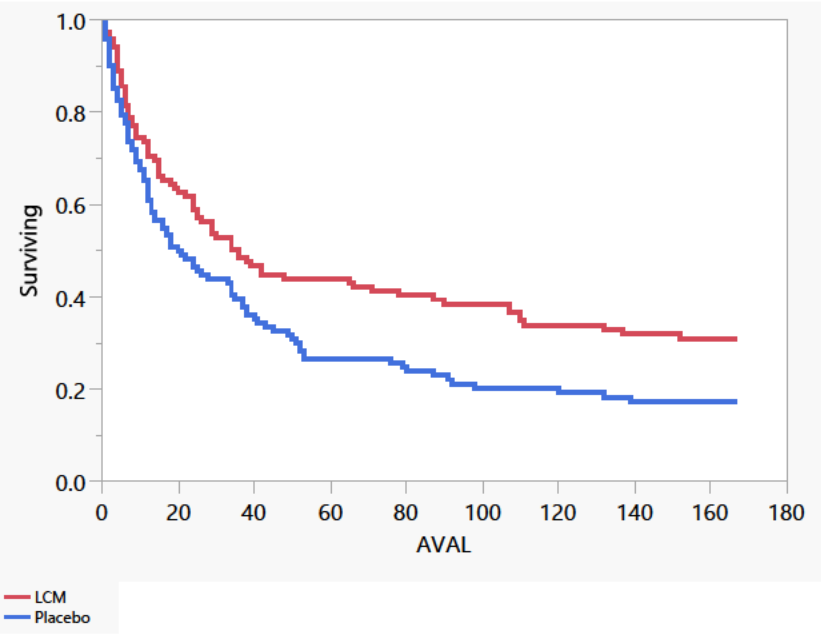
Source: Reviewer adapted and verified from SP0982 CSR Table 8.2.1
FAS = full analysis set; KM = Kaplan-Meier; LCM = lacosamide; PGTCS = primary generalized tonic clonic seizures
**Estimated by extended Mantel Haenszel methods*

Reviewer's comment: As noted in Dr. Zhang's Statistical Review, the three strata used in the analysis for the key secondary endpoint were the same as those pre-specified in the SAP and differed from the six strata that were included in the pre-specified analysis for the primary endpoint. Of note, the secondary endpoint is seizure freedom from PGTCS which is both clinically meaningful and statistically significant. PGTCS are the most clinically significant, high-risk, and life-threatening seizures that most patients with IGE experience, and that can significantly increase their risk of SUDEP. However, being free from PGTCS is not as clinically meaningful as if patients were completely seizure free from all seizure types because seizure freedom is a more important predictor for improvements in quality of life, ability to drive/be independent, and ability to potentially taper off other medications with significant adverse events.

The Applicant also analyzed the time to first PGTCS during the 24-week Treatment Period. The median survival time was 36 days for the LCM group and 20 days for the placebo group. The treatment difference between the LCM group and the placebo group is observed in the below

Kaplan Meier curve.

Figure 3 Kaplan-Meier curve for time (days) to First PGTCS during the 24-week Treatment Period (FAS)



Source: Reviewer-derived graph from SP0982 adtte Dataset using FAS, PARAMCD: TMFIPGTC
Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRTA

Table 13 Analysis of Time to First PGTCS (FAS)

	Placebo (N = 121)		LCM (N = 118)	
	Cumulative Number of events	KM survival estimate (%)	Cumulative Number of events	KM survival estimate (%)
Treatment Period	97	17.27	79	30.97
KM analysis				
Patients censored*, n (%)	24 (19.8)		39 (33.1)	
Time to event (Days)				
Median	20.0		36.0	
95% CI	13.0, 34.0		25.0, 78.0	
Treatment Comparison				
LCM vs. Placebo				
Hazard Ratio (HR)**	0.683			
95% CI of HR	0.507, 0.921			
p-value	0.012			

Source: Reviewer verified from SP0982 CSR Table 8.3.1
PGTCS = Primary generalized tonic clonic seizure; LCM = lacosamide; CI = confidence interval' HR = hazards ratio; FAS = full analysis set
**Patients who completed the Treatment Period without having a first PGTC seizure during the Treatment Period were censored. If the patient's Treatment Period participation was less than 166 days, they were censored on the date of the last dose of study medication.*
*** An HR < 1 indicates time to first PGTCS was improved for LCM compared to Placebo.*

Reviewer's comment: The above Kaplan-Meier curve for time to first PGTCS during the Treatment Period demonstrates a median survival time of 36 days to first PGTCS for patients receiving LCM and 20 days to first PGTCS for patients receiving placebo. The HR of 0.683 indicates improvement with treatment. This impact on time to first PGTCS is clinically meaningful as it increases the amount of time a patient can go without having a seizure.

Other secondary endpoints were also explored by the Applicant that were supportive of the findings demonstrated by the primary and key secondary endpoint. As comparison to other treatments previously approved for treatment of PGTCS, the PGTC Seizure frequency per 28 days results and percent change from Combined Baseline for the FAS are provided in Table 14 below.

Table 14 PGTC Seizure Frequency Per 28 days and Percent Change from Combine Baseline (FAS)

	Placebo (N = 121) n (%)			LCM (N = 121) n (%)		
Time Period	Mean (SD)	Median	% Change from Baseline Median	Mean (SD)	Median	% Change from Baseline Median
Combined Baseline	2.02 (2.42)	1.24	--	1.88 (1.76)	1.25	--
Titration Period	2.24 (7.18)	0.67	- 42.71	1.43 (5.0)	0.64	- 66.37
First 12 weeks	2.26 (7.17	0.66	- 55.69	1.4 (5.0)	0.33	- 71.33
Treatment Period	2.30 (7.17)	0.79	- 43.24	1.4 (5.0)	0.17	- 77.92

Source: Reviewer verified and adapted from SP0982 CSR Table 8.4.1
LCM = lacosamide; SD = standard deviation; FAS = full analysis set; PGTCS = primary generalized tonic clonic seizure

Results were based upon average seizures over 28 days

Reviewer's comment: Although the seizure frequency was low at baseline, it was similar in the two treatment arms. The study was not designed appropriately to assess a change in 28-day seizure frequency, especially as patients were discontinued from the study at various time points after the patient experienced a second PGTC seizure. Thus, this analysis is not particularly useful for interpreting the data. However, it is notable that the mean and median seizure frequencies were lower in the treatment group than the placebo treatment group for the entire treatment period.

The Applicant also provided analyses evaluating the frequency of days with absence and myoclonic seizures. The below table demonstrates that while days with absence seizures decreased more in the treatment group, the number of days with myoclonic seizures, (which was notably low to begin with), decreased more in the placebo arm than in the treatment arm.

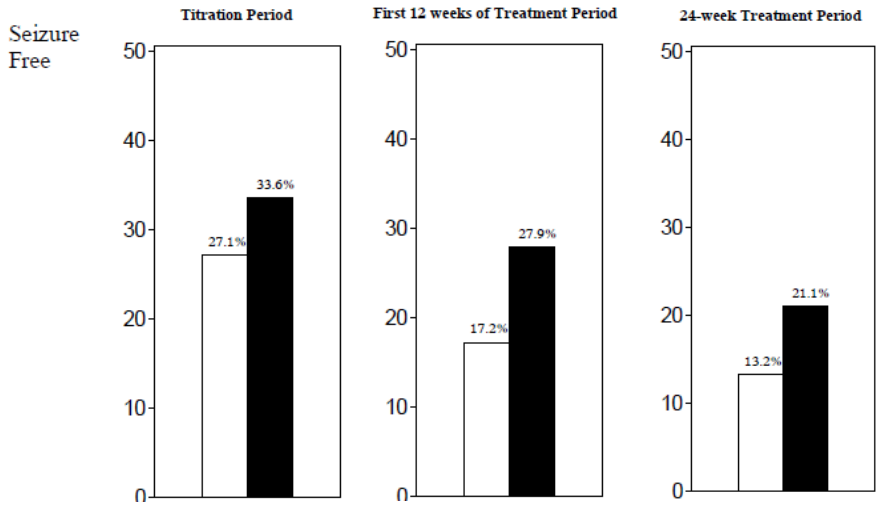
Table 15 Days with absence seizures and myoclonic seizures per 28 days observed results and % changes from baseline (Safety Set)

	Placebo			LCM		
Time Period	Mean (SD)	Median	% Change from Baseline Median	Mean (SD)	Median	% Change from Baseline Median
Absence Seizures	N = 42			N = 51		
Prospective Baseline	5.4 (8.1)	1.5		5.2 (8.1)	0.0	
Titration Period	4.6 (7.2)	0.0	-11.1	3.9 (7.1)	0.0	-24.6
First 12 weeks	4.6 (7.2)	0.2	-13.3	3.7 (6.8)	0.0	-30.4
Treatment Period	4.4 (7.2)	0.1	-15.3	3.6 (6.7)	0.0	-30.1
Myoclonic Seizures	N = 49			N = 47		
Combined Baseline	4.9 (7.7)	1.0		4.8 (6.9)	2.0	
Titration Period	3.5 (6.5)	0.0	-51.8	4.2 (6.8)	0.7	-32.5
First 12 weeks	3.5 (6.7)	0.0	-65.7	4.0 (6.9)	0.5	-43.8
Treatment Period	3.4 (6.7)	0.0	-65.7	3.7 (6.6)	0.6	-54.6

Source: Reviewer adapted from SP0982 CSR Table 8.6.2 and 8.7.2
LCM = lacosamide; SD = standard deviation; SS = safety set

Reviewer's comment: Overall there seemed to be a slight benefit on absence seizure days with treatment that was noted during the titration period and persisted through the first 12 weeks and the entire Treatment Period. The number of days with myoclonic seizures decreased in both the treatment arm and the placebo arm, but was slightly more improved in patients receiving placebo. This will be explored further in the Safety Assessment.

Figure 4 Seizure-Freedom from All Generalized Seizures (Safety Set)



Source: Reviewer-verified from SP0982 CSR Figure 8.4 (Reference Table 8.7.5)
Black bars = Lacosamide (N = 121)
White bars= Placebo (N = 121)

Reviewer's comment: The Applicant also supplied data on seizure-freedom from all generalized seizures and demonstrated that despite the fact that treatment with LCM did not seem to have a treatment benefit compared to placebo for treatment of myoclonic seizures, there is a trend demonstrating that more patients receiving LCM were free of all generalized seizures throughout treatment compared to patients receiving placebo. This effect was most prominent during the first 12 weeks of the Treatment Period.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There is only a single efficacy study included in this review and therefore this section is not applicable.

7.1.1. Primary Endpoints

There is only a single efficacy study included in this review.

7.1.2. Secondary and Other Endpoints

There is only a single efficacy study included in this review.

7.1.3. Subpopulations

There is only a single efficacy study included in this review.

7.1.4. Dose and Dose-Response

There is only a single efficacy study included in this review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There is only a single efficacy study included in this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The use of this drug in this patient population was studied in a way that was similar to how it will be used once approved and is already being used off-label in some patients, as it has been marketed in the US since 2008. It will provide another option for patients struggling with difficult to treat primary generalized tonic clonic seizures.

7.2.2. Other Relevant Benefits

Compared to some other antiepileptic drugs that are currently approved for PGTCS, LCM has the benefit that it is available and bioequivalent in both oral and IV formulations so can be used interchangeably when patients are unable to tolerate oral medications. This can be advantageous in patients who are inpatient and not able to take medications orally for any reason and can provide seamless transitions between IV and oral as needed.

7.3. Integrated Assessment of Effectiveness

Overall the data in this submission supports evidence of effectiveness of LCM in the treatment of primary generalized tonic clonic seizures at the same doses utilized in the treatment of partial-onset seizures.

SP0982 met its primary objective of demonstrating efficacy of oral LCM vs. placebo as adjunctive therapy for PGTCS in patients with IGE age 4 years and older. The primary endpoint and key secondary endpoints demonstrating statistically significant and clinically meaningful

improvements for LCM compared to placebo in this novel study design utilizing a "time to nth seizure" primary endpoint. Findings in the small number of enrolled pediatric patients were consistent with the results of the overall population for the primary and key secondary endpoints. General health outcomes scales show similar changes which were variable in both the LCM and placebo groups, but no worsening in any health outcome measure was observed.

8. Review of Safety

8.1. Safety Review Approach

Most of the safety analyses are presented for the double-blind treatment period (Titration and Maintenance Periods) in Study SP0982, with additional analyses provided for long-term safety from the open-label extension study, EP0012. The data from the open-label Phase 2 studies in patients with PGTCS (SP0961 and SP0962) as pooled by the Applicant (Pool SGTC-2) was also reviewed as part of the complete Integrated Summary of Safety (ISS) review. The data from the single placebo-controlled study and the open-label studies which lacked comparators were not pooled for the majority of the analyses.

The three safety populations analyzed were Controlled Data from Study SP0982 (n = 242), the safety pool of both of the Phase 3 studies for PGTCS (Applicant Pool SGTC-1, n = 255), and the entire ISS Safety Pool (n = 304). Pool SGTC-1 was all patients receiving at least one dose of LCM in either the SP0982 or the Open-label extension study EP0012.

EP0060 is a Phase 2/3 study open-label to investigate the safety and tolerability of intravenous LCM in children (≥ 1 month to < 17 years of age) with epilepsy. The interim clinical study report from EP0060 was submitted to support the safety of intravenous administration in pediatric patients treated for PGTCS. However, as noted above, the submitted data from EP0060 was not included as part of this review. The Applicant submitted a second supplement in May 2020 to support the safety of the intravenous formulation in pediatric patients 4 to < 17 years with epilepsy, either PGTC seizures or partial-onset seizures. The entirety of the safety data from EP0060 was reviewed with that supplement (NDA 022254, S-38).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Study SP0982 was composed of a Treatment Period that lasted a minimum 6 weeks up to 24 weeks, including a 6-week Titration Period and an 18-week (maximum) Maintenance Period. As SP0982 was a time-to-event study, patients were only required to complete a minimum of 6 weeks of treatment, and were enrolled until they experienced two PGTC seizures, or until the study observed 125 events.

The median study medication duration overall was 143.0 days in the LCM treatment arm, and 65.0 days in the Placebo arm. The majority of patients in both the LCM and placebo arms took a modal maintenance dose of 400 mg/day. Patients on Placebo or LCM had the option to transition to Study EP0012, the open-label extension study. The following Table (Table 16) is a summary of duration of exposure in the combined SP0982 and EP0012 studies.

Table 16 Summary of Exposure in Pool SGTC-1 (Phase 3 studies)

	Number of patients				
	≥ 1 dose	≥ 6 months	≥ 12 months	≥ 18 months	≥ 24 months
LCM exposure	255	202	147	114	81

Source: Reviewer verified from Summary Clinical Safety Table 4.1.1
LCM = lacosamide; a month was defined as 28 days

Table 17 Study medication duration during the Controlled Study SP0982 (SS)

Time Period	Placebo (N = 121) n (%)	LCM (N = 121) n (%)
Treatment (study medication duration, days)		
n	121	121
Mean (SD)	93.7 (57.7)	112.3 (61.2)
Median	65.0	143.0
Min, Max	7.0, 176.0	1.0, 176.0
Titration (study medication duration, days)		
n	121	121
Mean (SD)	41.0 (7.4)	40.4 (7.4)
Median	42.0	42.0
Min, Max	7.0, 57.0	1.0, 50.0
Maintenance (study medication duration, days)		
n	70	82
Mean (SD)	91.5 (44.0)	106.2 (37.6)
Median	120.5	126.0
Min, Max	3.0, 134.0	13.0, 135.0

Source: Reviewer adapted and verified from SP0982 CSR Table 10.1
LCM = lacosamide, max = maximum, Min = minimum, SD = standard deviation, SS = safety Set

8.2.2. Relevant characteristics of the safety population:

The key safety analyses were performed on the safety set from pivotal study SP0982, as well as the long-term extension study EP0012. See Table 7 above in Section 6.1.2 for a summary of demographic characteristics. There were no significant demographic or baseline medical history characteristic differences amongst the treatment groups.

8.2.3. Adequacy of the safety database:

Given that LCM has already been approved in the United States since 2008 with extensive experience in the approved indication for treatment of partial-onset seizures, the safety database for the additional indication studied here is considered adequate. The study only

included 12% of the patients from the United States, but the basic characteristics of the disease and response to medication are believed to be similar amongst patients in other countries, so the results of this study should be generalizable to patients in the United States.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the integrity of the data submitted for the safety review. The datasets provided by the Applicant were complete and not misleading, and I was sufficiently able to reproduce the safety analyses of the Applicant and perform my own analyses when necessary.

8.3.2. Categorization of Adverse Events

For Study SP0982, Study EP0012, and the combined Phase 2 Pool SGTC-2, MedDRA version 16.1 was used to code adverse events. For Phase 2 studies SP0961 and SP0962, Version 9.1 was used, however the Applicant's analyses of the Safety Pool SGTC-2 from these studies utilized MedDRA version 16.1 as well.

An Adverse Event (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. AN AE can therefore e any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medical product (IMP), whether or not related to the IMP.
Serious Adverse Event (SAE) were defined per the usual criteria:

- Death
- Life-threatening
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect
- Important medical event that based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in this definition
- Initial inpatient hospitalization or prolongation of hospitalization

AEs of Special Interest were listed as:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree and third degree) and marked bradycardia (< 45 bpm)
- Syncope or loss of consciousness (non-seizure related)
- Serious suspected multiorgan hypersensitivity reactions
- Emergence of non-preexisting or worsening of any existing epileptic seizure types

- Potential Hy's Law, defined as ≥ 3x ULN ALT or AST with coexisting ≥ 2x ULN total bilirubin in absence of ≥ 2x ULN ALP, with no alternative explanation for the biochemical abnormality.

Overall, the Applicant's coding of AE terms was sufficient. A few similar terms were grouped together during my review to avoid underestimating any potential safety signals/risks. The following terms were recoded as noted below in Table 18.

Table 18 Recoded AE codes to Group Similar Terms

Original Coded Terms	Recoded Term
Abdominal discomfort, abdominal pain, abdominal pain upper, abdominal pain lower	Abdominal pain
Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, transaminases increased	Transaminases increased
Body temperature increased, pyrexia	pyrexia
Clonic convulsion, grand mal convulsion	seizure
Depressed mood	depression
Dizziness, Dizziness postural	dizziness
Eosinophilia, eosinophil count increased	eosinophilia
Gastroenteritis, gastroenteritis viral	Gastroenteritis
Hypoaesthesia, hypoaesthesia eye, hypoesthesia oral	hypoasthesia
Myoclonus, myoclonic epilepsy	Myoclonic seizures
Rash, rash macular	rash
Respiratory tract infection, upper respiratory tract infection, respiratory tract infection viral	respiratory tract infection

Reviewer's comment: Overall, the categorization and coding of TEAEs was appropriate and sufficient, especially given the already well characterized safety profile in the treatment of both adult and pediatric patients 4 years and older with partial onset seizures.

8.3.3. Routine Clinical Tests

Refer to the above Schedule of Assessments (Table 3) in Section 6.1.1 for a summary of the performed clinical examinations. Routine clinical tests were performed including laboratory assessments, vital signs, ECG monitoring, physical exam, and neurologic exams.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in Study SP0982 or throughout the development program for the treatment of PGTCS.

8.4.2. Serious Adverse Events

There were 12 patients who experienced a total of 18 SAEs during the double-blind Treatment Period (Titration and Maintenance Periods). Of these 12 patients, 8 patients received LCM and 4 patients received placebo. The SAEs to occur in more than one patient on LCM were dizziness (2), and somnolence (2). There was one patient each on placebo and LCM who reported an SAE of increased transaminases. There was one patient each on LCM who had an SAE of status epilepticus and of worsening seizures (described below).

Additional SAEs occurred during the Transition/Taper period for 4 patients on LCM and 1 patient on placebo. These included additional reports of dizziness and nausea (1), and seizure (1) in patients receiving LCM, as well as 1 patient randomized to placebo who reported seizure worsening during the Post-Treatment period after tapering off study treatment.

- (b) (6), *Status Epilepticus*
  32-year-old man on concomitant lamotrigine and levetiracetam, as well as calcium, cholecalciferol and ibuprofen. Randomized to LCM and received first dose on (b) (6) Experienced SAE of status epilepticus on (b) (6) during the Titration Period, 10 days after study drug initiation. The event was severe and resulted in hospitalization. He had taken 100 mg/day from (b) (6) and then reduced the dose to 50 mg/day for one day. The drug was withdrawn, and the event resolved (b) (6)

- (b) (6), *Seizure aggravation, Contusion, Headache, Head Injury*
  21-year-old male patient on concomitant lamotrigine and levetiracetam. Randomized to LCM and received first dose on (b) (6) He had multiple SAEs related to seizures with hospitalization for a contusion on (b) (6) following a generalized tonic-clonic seizure, severe headache on (b) (6) following generalized tonic-clonic seizures, and 'tonic-clonic seizure aggravation' on (b) (6) with associated dizziness and post-ictal mental slowing, 30 days after initiation of the treatment. Finally, the same patient experienced an SAE of head injury following 2 episodes of tonic-clonic seizures on (b) (6) during the Transition/Taper period.

- (b) (6), *Epilepsy Aggravated*
  26-year-old female patient on concomitant valproic acid was randomized to LCM with first dose on (b) (6) She had an SAE of aggravated epilepsy on (b) (6) during the Transition/Taper period, 45 days after study drug initiation, which was severe in intensity. Patient had received 400 mg/day on (b) (6) but did not receive any LCM on day of the event and restarting 300 mg/day on (b) (6) Was hospitalized and received acetazolamide, amitriptyline, carbamazepine, mannitol, piracetam, and potassium magnesium aspartate as treatment medications. Event resolved on (b) (6)

(b) (6) and patient completed study.

Reviewer's comment: The above 3 patients had worsening of seizures (and/or status epilepticus) while on treatment. Patients (b) (6) had an episode of status epilepticus which temporally was related to treatment initiation 10 days prior to event. Patient (b) (6) had already had her 2 PGTC seizures and was starting to taper the drug when she developed worsening seizures, which appears to be related to potentially abruptly stopping the drug from 400 mg/day to no medication 1 day later. She also was stratified to the > 2 seizures per 28-day treatment group, so although she had 2 seizures in the 6-week Titration period, there was no indication that the treatment worsened her baseline seizure frequency. Finally, patient (b) (6) had several seizures during the 6-week Titration period, many resulting in hospitalization (head injury, laceration, headache), and was stratified to less than 2 seizures per 28 days at baseline, which indicates that the medication may have led to overall seizure worsening. This is concerning that there were 2 patients who had an SAE of seizure worsening and a potential mechanism for action of seizure worsening given potential seizure worsening properties of LCM. There was only one patient on placebo who had an SAE of seizure and that was in the Post-treatment Period. This indicates a potential for seizure worsening of PGTC seizures in some patients.

- (b) (6), *Dizziness, somnolence, nausea, vomiting*
  20-year-old female patient on concomitant levetiracetam and brivaracetam, eugynon (oral contraceptive), omeprazole and ibuprofen. Randomized to LCM, first dose (b) (6) Developed dizziness, nausea, somnolence, and vomiting on (b) (6) 16 days after drug initiation, moderate in intensity, and also experienced 1 episode of PGTC seizure. She was on 250 mg/day for one day at time of event. She was hospitalized for the symptoms, with normal laboratory and ECG values. Received medication for nausea and dizziness and was discharged the following day. The dose was reduced, and symptoms resolved.

- (b) (6), *Asthenia, Dizziness*
  26-year-old female patient on concomitant clobazam, lamotrigine, valproate, retinol, and vitamin B. She was randomized to LCM and received the first dose on (b) (6) During the Titration Period, 15 days after drug initiation, she experienced dizziness and asthenia on (b) (6) considered moderate in intensity, as well as non-serious abdominal pain without nausea, vomiting or diarrhea. She had a period of weakness where she felt unable to move and had a Glasgow Comas Scale (GCS) of 14 with an otherwise normal neurologic exam. Head CT was normal. She received metoclopramide, ondansetron, paracetamol, and sodium chloride and she was discharged the following day. She was unable to move her limbs for 45 minutes due to extreme fatigue. She denied a seizure in the past 24 hours prior to the event.

- [redacted], *Dizziness, Nausea*
  20-year-old female patient on concomitant lamotrigine. Enrolled [redacted] and received the first dose on [redacted] during the Transition/Taper Period, 194 days after drug initiation, she experienced dizziness and nausea, reported mild in intensity, 4 days after increasing the dose of 300 mg/day to 400 mg/day. She also experienced nonepileptic seizure and was hospitalized. She received metoclopramide, intravenous fluids and sodium chloride and held one dose. LCM was restarted the following day and final dose was 3 days later on [redacted]

- [redacted], *Somnolence*
  51-year-old male patient on concomitant valproic acid, who received his first dose [redacted] and experienced a nonserious AE of dizziness on [redacted] which resolved on the same day, and then experienced an SAE of somnolence on [redacted] 37 days after drug initiation, during the Titration Period. The event was reported as mild but requiring hospitalization. The dose was decreased from 400 mg/day to 300 mg/day and one dose was held. He felt better a week later and continued to complete the study.

  Reviewer's comment: The above episodes of dizziness and somnolence are likely related to the treatment but are already included in the prescribing information. There are no new safety signals identified and the events were rapidly resolved on their own or with dose reduction. Dizziness is currently included in the warnings and precautions section of the prescribing information.

- [redacted], *Increased transaminases*
  15-year-old female patient on concomitant valproic acid and levetiracetam, randomized to LCM, with first dose on [redacted] (74 kg, BMI 24.4 kg/m2). Initially experienced nonserious AE of elevated transaminases on [redacted] prior to first dose that was attributed to valproate. Then she experienced an SAE of increased transaminases on [redacted], 90 days after study drug initiation, moderate in intensity, while on 400 mg/day with AST and ALT at > 3x baseline. She received ademetionine and her valproate dose was reduced. Then LCM was decreased to 300 mg/day on [redacted] and then withdrawn on [redacted] Bilirubin and ALP remained within normal limits, and the LFTs resolved on [redacted] The GGT was also elevated to > 3x upper limit of normal.

  Reviewer's comment: There is a potential role of LCM in the increased transaminases but given the concomitant valproate and the mild elevation in ALT/AST prior to the initiation of the study drug, it is less likely a role for LCM as the main source of drug-induced liver injury. Increased transaminases is already listed as potential adverse event in the prescribing information, and a patient receiving placebo had a similar event of increased transaminases.

In the ISS, there were an additional 36 patients who experienced SAEs in the open-label treatment period of EP0012 or the Phase 2 studies. The SAEs to occur in more than 1 patient each were Convulsion in 10 patients, status epilepticus (3), migraine (2), pneumonia aspiration (2) and vomiting (2). Of the patients with worsening convulsions, none led to discontinuation of the study and may have represented baseline seizures for each patient.

Reviewer's comment: Overall the SAEs did not identify any new safety signals that are not already described in the prescribing information. However, as noted above, there were two SAEs of worsening seizures that occurred shortly after drug initiation that may have been drug-related and should be highlighted as a possible adverse event when treating PGTCS.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were a total of 16 patients in the double-blind Treatment Period who discontinued due to AEs, 11 in LCM arm and 5 in placebo arm. Three of these were SAEs and two are already discussed above (Status epilepticus, increased transaminases), as well as an SAE of a femur fracture in a placebo patient.

The AE terms resulting in discontinuation that occurred in more than one patient on treatment were dizziness (2), suicidal ideation (2) and transaminases increased (2). There was one patient who discontinued due to a rash on LCM, and that patient is included in the narrative discussion below. Of note, there were also two patients on placebo who discontinued due to rash, and one patient on placebo who discontinued due to transaminases increased.

Narratives

- (b) (6), rash
  23-year-old man on concomitant valproic acid and Zonisamide, as well as benzonatate. Enrolled (b) (6) received first dose (b) (6) Experienced nonserious rash on abdomen, back, and slightly behind knees and bilateral arms/thighs, on (b) (6) mild in intensity, 13 days after drug initiation. Received diphenhydramine for the event. Dose was decreased and then withdrawn. The rash resolved on (b) (6)

- (b) (6), transaminases increased
  28-year-old woman on concomitant Ergenyl Chrono (valproate) and topiramate. Enrolled (b) (6), received first dose (b) (6), experienced nonserious increase in ALT and AST on (b) (6) during Titration Period, 15 days after drug initiation. ALT and AST were >4x upper limit of normal (maximum ALT 121, AST 214). The ALP and total bilirubin were normal throughout. The GGT was also elevated (max 165, nl 0-37 U/L) but was also elevated to 77 at baseline. ALT and AST were elevated on the day of first dose (Visit 2) at ALT = 83, AST = 134. Drug was withdrawn and last dose was (b) (6)

.

- [redacted] transaminases increased
  See SAE above

- [redacted] dizziness
  66-year-old woman with complex past medical history on concomitant phenobarbital and phenytoin for AEDs, and concomitant furosemide, venlafaxine, levothyroxine, metoprolol, linaclotide, metformin, rizatriptan, simvastatin, docusate, macrogol, and proctofoam. Enrolled [redacted], received first dose LCM [redacted]. She experienced a nonserious AE of dizziness on [redacted] (resolved in 3 days), [redacted] (resolved in 6 days) and [redacted] all during the Titration period. The third event was considered severe, with no PGTC seizure within 7 days prior to the event. She was on 350 mg/day at the time of the third event and was withdrawn from the study drug at this time, with full resolution 30 days later.

- [redacted], dizziness
  40-year-old woman on concomitant lamotrigine, oral contraceptive, and fluticasone. Enrolled [redacted] and received first dose on [redacted] Had nonserious event of dizziness on 1 [redacted] 84 days after study drug initiation, reported as moderate in intensity. Was on 400 mg/day, and drug was withdrawn due to dizziness. Final dose of study drug was on [redacted]

- [redacted], suicidal ideation
  45-year-old woman on concomitant clonazepam, lamotrigine, and topiramate, as well as budesonide with formoterol, salbutamol, and Spektramox (amoxicillin derivative). She enrolled [redacted], received first dose [redacted] Experienced nonserious AE of diplopia on [redacted] during Titration Period, 30 days after study drug initiation. She was on 400 mg/day for 8 days at time of event. The following day she experienced a nonserious AE of suicidal ideation and had had 2 PGTC seizures within the 7 days prior to the AE. The drug was withdrawn drug do the adverse events of diplopia and SI, with the SI resolving 33 days later, after final dose of the study drug.

- [redacted], suicidal ideation
  55-year-old woman with complex medical history including history of depression, on concomitant phenytoin and valproate. Enrolled on [redacted] and received first dose LCM [redacted] Experienced nonserious AE of suicidal ideation on [redacted] during Titration, 36 days after drug initiation. Considered moderate in intensity, had a single PGTC seizure in 7 days prior to the event. Also reported amnesia and depressed mood at the onset of the SI, study drug was withdrawn with final dose of drug taken [redacted]

- [redacted], suicidal ideation (Transition/Taper)
  20-year-old woman on concomitant clobazam and levetiracetam, folic acid and normensal (hormonal contraceptive). Enrolled [redacted] and received first dose [redacted] Experienced non-serious AE of suicidal ideation on [redacted] during Transition/Taper period, 63 days after drug initiation. The event was reported to be moderate, and there was no PGTC seizure in the 7 days preceding the event. She was on a stable dose of 400 mg/day at the time of the event and had been on that dose for 43 days. The drug was withdrawn due to the AE and last dose was [redacted] The event resolved on [redacted] She was completed a "study completer" because she experienced ≥ 2 PGTC seizures during the Treatment Period.

- [redacted], myoclonic epilepsy
- 25-year-old female patient on concomitant perampanel, initiated LCM on [redacted] and experienced a nonserious adverse event of worsening of myoclonic seizures on [redacted] 15 days after study drug initiation, which was reported as moderate in intensity. At the time of the event, she was on 100 mg/day, and also experienced dizziness and somnolence. The drug was withdrawn due to the worsening of myoclonic seizures as noted above, although the narrative notes the patient continued to increase the dose to 400 mg/day until [redacted] at which point, she tapered off the drug.

  Reviewer's comment: Of note, the patient was also considered a study "completer" because the 125th event occurred, and the patient met the exit criteria for the study. However, the listed reason for discontinuation was the AE. As the patient was actually randomized after the 125th event, she was therefore not included in the efficacy analysis.

- [redacted], vertigo
  23-year-old male on concomitant lamotrigine and levetiracetam. Enrolled [redacted], received first dose [redacted]. Experienced vertigo (nonserious, moderate in intensity) on [redacted] during titration period, 25 days after drug initiation. Was on 400 mg/day for 4 days at time of event. Drug was withdrawn due to the vertigo with final dose taken [redacted]

  Reviewer's comment: Overall, the reported AEs leading to discontinuation are already described in the prescribing information except for myoclonic seizures. (See Section 8.5.1 below for more details).

In the remainder of the ISS, there were an additional 12 patients who discontinued treatment due to AEs during the open-label Phase 2 or open-label extension studies. The AEs leading to discontinuation that occurred in more than one patient were amnesia (2), dizziness (2),

myoclonic seizures (2), petit mal epilepsy (2) and vision blurred (2). Myoclonic seizures are described below in Section 8.5.1.

8.4.4. Significant Adverse Events

During the double-blind Treatment Period (Titration and Maintenance Period), there were 9 patients (6 in LCM treatment arm and 3 in placebo treatment arm) who had a total of 11 TEAEs that were reported as severe. Three of these TEAEs were also SAEs. The only severe TEAE to occur in more than one patient on treatment was dizziness. One of the patients who reported severe dizziness led to withdrawal (patient already outlined above). The other severe TEAEs were Status Epilepticus (also an SAE, described above), facial bones fracture, somnolence, nausea, abdominal pain, and headache.

Including patients who reported severe TEAEs during the Taper/Transition period, there were 5 additional patients who had a total of 6 severe TEAES (3 LCM, 2 placebo). Of the 3 LCM patients, the severe TEAEs included diarrhea, and two episodes of worsening tonic clonic seizures, one of which was an SAE and is described above (patient (b) (6).

In the remainder of the ISS, there were 46 additional patients who recorded severe TEAEs in the open-label Treatment Periods. Those that occurred in more than one patient each were convulsion (3), headache (2), migraine (2), petit mal epilepsy (2), postictal headache (2), and status epilepticus (2). However, only 2 of these led to discontinuation and are mentioned above, one each from petit mal epilepsy and myoclonic epilepsy.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

There were 242 patients in the safety database for Study 0982. There were a total of 551 TEAEs reported by 175 patients during the double-blind Titration and Maintenance Treatment Period. The common TEAEs that occurred in ≥ 2% of patients on LCM and greater than placebo are outlined below in Table 19.

Table 19 Common TEAEs that occurred in **≥** 2% of the patients on LCM and greater than placebo (SS)

Adverse Event	Placebo (N = 121) n (%)	LCM (N = 121) n (%)	Risk Difference %
General disorders and administration site conditions			
Fatigue	6 (5)	8 (7)	2
Infections and infestations			
Nasopharyngitis	4 (3)	8 (7)	4
Nervous System Disorders			
Dizziness	9 (7)	28 (23)	16
Vertigo	2 (2)	8 (7)	5
Headache	12 (10)	17 (14)	4
Somnolence	17 (14)	20 (17)	3
Ataxia	0 (0)	4 (3)	3

Disturbance in Attention	0 (0)	4 (3)	3
Vision blurred	1 (1)	4 (3)	2
Myoclonic seizures	1 (1)	3 (3)	2
Gastrointestinal Disorders			
Nausea	7 (6)	12 (10)	4
Abdominal pain	4 (3)	6 (5)	2
Diarrhea	2 (2))	4 (3)	1
Respiratory, thoracic and mediastinal disorders			
Cough	1 (1)	4 (3)	2
Cardiac Disorders			
Hypertension	1 (1)	3 (3)	2

Source: Reviewer-derived table from SP0982 ADAE dataset, for AEs that occurred during Titration and Maintenance Period only
SS = safety Set; LCM = lacosamide

Reviewer's comment: Overall, the common TEAEs are consistent with those that are already described in the prescribing information and were noted in the controlled studies in partial-onset seizures. Myoclonic seizures is a new adverse event seen in 2.5% of patients receiving LCM that was not previously noted in the POS studies and may be an adverse reaction unique to patients with PGTC seizures receiving LCM. Myoclonus and the narratives of these patients are outlined below in Section 8.5.1. Disturbance in attention is already noted in the prescribing information, but it was not previously listed as one of the common TEAEs in the POS studies. This could be because of the smaller size of these PGTC studies, leading to a greater percentage of patients reporting this as a TEAE. It is unlikely to be unique to the PGTC seizure population, so I do not recommend including it in any more detail in Section 6 other than where it is already noted in the list of "other adverse drug reactions noted".

8.4.6. Laboratory Findings

Laboratory values were reviewed as changes from baseline over time. Hematology, chemistry, and urinalysis parameters remained mostly within the expected ranges in both treatment arms and no clinically relevant treatment-related changes in mean or median values were observed.

The percentage of patients revealing shifts from baseline normal to high maximum or low minimum post-baseline values for hematology and chemistry parameters were relatively similar in the treatment arms or more common in the placebo arm than LCM treatment arm.
The number of patients reporting TEAEs related to abnormal hematology values was low and similar between the treatment arms. There were none that were reported in more than one patient in a treatment arm.
The number of patients reporting TEAEs related to abnormal chemistry values was also generally low and similar between LCM and Placebo treatment arms. The most common TEAEs related to abnormal chemistry values were ALT increased (8, 4 LCM, 4 placebo), AST increased (7, 2 LCM, 5 placebo), GGT increased (4, 3 placebo 1 LCM). The patients who had elevated AST/ALT that resulted in discontinuation were reviewed above. There were no patients who met criteria for Hy's law. No patients in the LCM treatment arm reported the predefined TEAES for potential drug-induced liver injury (PDILI).

Reviewer's comment: No new safety signals were identified in the review of laboratory values.

8.4.7. Vital Signs

The majority of the vital sign changes from Baseline noted throughout the study were mild and not clinically relevant. There were a few patients reporting TEAEs related to abnormal vital signs, including 3 patients receiving LCM (2.5%) who reported a TEAE of hypertension, compared to 1 patient receiving placebo (1%). No vital sign-related TEAEs were reported in patients < 18 years of age, or ≥ 65 years of age.

Reviewer's comment: Overall, there were no new safety signals identified in review of the vital signs. The TEAE of hypertension was reported more frequently in patients receiving LCM compared to placebo; however, the overall incidence was still quite low in both treatment groups.

8.4.8. Electrocardiograms (ECGs)

A review of the summary of 12-lead ECG values and changes from Baseline by age group and visit was conducted. Overall, the mean and median changes from baseline to Last visit were small, except for the mean change in PR interval which was 9.96 ms (SD= 20.48), compared to -0.79 ms (SD = 40.47) for placebo. The prolongation of PR interval is consistent with the safety profile of LCM and is not unexpected.

A summary of TEAEs related to abnormal ECG findings was provided by the Applicant, with 2 patients in the placebo arm reporting sinus bradycardia, and 2 patients receiving LCM reporting right bundle branch block. There was also one patient each on LCM reporting arrhythmia and atrioventricular block first degree, and one patient on placebo who reported tachycardia.

Reviewer's comment: The ECG findings demonstrated a known prolongation of the PR interval which did not result in any clinically relevant findings in the study. Although LCM is also known to result in cardiac conduction abnormalities, these were rare during the study. There were no new safety signals identified.

8.5. Analysis of Submission-Specific Safety Issues

As noted above, the following were considered AEs of special interest for this submission, based on the known safety profile of LCM and the patient population.

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree and third degree) and marked bradycardia (< 45 bpm)

- Syncope or loss of consciousness (non-seizure related)
- Serious suspected multiorgan hypersensitivity reactions
- Emergence of non-preexisting or worsening of any existing epileptic seizure types
- Potential Hy's Law, defined as ≥ 3x ULN ALT or AST with coexisting ≥ 2x ULN total bilirubin in absence of ≥ 2x ULN ALP, with no alternative explanation for the biochemical abnormality

8.5.1. Seizures/Myoclonus

Patients who developed worsening of seizures or new or worsening absence and myoclonic seizures were analyzed. Of note, some patients reported myoclonus, and others reported myoclonic seizures. However, given the patient population with known IGE, the two conditions were lumped together for this review and the terms were used interchangeably.

There were 4 patients who developed worsening myoclonic seizures during the Titration and Maintenance double-blind Treatment Periods. Of these patients, 3 patients were receiving LCM and 1 patient was receiving placebo. One additional patient reported worsening myoclonus during the Taper/Transition Period. None of these events were serious or severe; however, one of the events led to drug discontinuation and is described above in Section 8.4.3. The remaining narratives are outlined below.

- (b) (6) *Myoclonic epilepsy*
  35-year-old male patient on concomitant clonazepam, levetiracetam, and topiramate. He was also on cycanobalamin, fish oil, herbal preparation, citalopram, cholecalciferol, multivitamin, zolpidem, naproxen, buspirone, and sumatriptan prn. He initiated LCM on (b) (6) He experienced myoclonic epilepsy on (b) (6) 35 days after initiation of the drug, which was reported as nonserious and moderate in intensity. He was on 400 mg/day at the time of the event and had been on that dose for 14 days. Also experienced speech disorder and sedation on the same day which resolved 2 days later. The final dose in Study SP0982 was taken on (b) (6) Of note, the patient completed the study as he had 2 PGTC seizures in the Titration Period and then entered the Transition Period. He did continue into the OLE study (EP0012) but was lost to follow-up after 43 days in that study.

- (b) (6), *Myoclonic epilepsy*
  See Dropouts and Discontinuations, Section 8.4.3 above.

- (b) (6), *Myoclonic epilepsy*
  27-year-old female patient, on concomitant lamotrigine and retigabine, initiated treatment with LCM on (b) (6) and experienced nonserious event of myoclonic epilepsy on (b) (6) 11 days after drug initiation, which was reported as mild in intensity. There were

no PGTC seizures in the 7 days prior to the event. She was on 200 mg/day at the time of the event and had been on that dose for 4 days. She also experienced vertigo which self-resolved. The dose was not changed, and the myoclonic seizures continued. Patient completed study. She entered Transition/Taper period after 2nd PGTC occurred during the Maintenance Treatment Period (107 days). She subsequently entered the OLE (EP0012) and continued in that study for an additional 870 days (> 30 months) and is still ongoing.

- (b) (6), *Myoclonic seizures*

26-year-old male patient on concomitant levetiracetam, as well as concomitant ibuprofen, paracetamol, and omeprazole. He initiated LCM 100 mg/day on (b) (6) He experienced nonserious adverse event of worsening myoclonic seizures on (b) (6) during the Transition/Taper Period, 69 days after initiation of treatment, and 8 days after increasing the dose to 400 mg/day. The event was considered mild in intensity, and the dose was unchanged. The final dose of Study 0982 was taken on (b) (6) Of note, the patient was already in the Transition Period because he had 2 PGTC seizures in the Titration Period but remained on LCM. He continued into the OLE study (EP0012) and continued for 323 days and then was discontinued for protocol violation.

- (b) (6), *Myoclonic seizures (Placebo)*

30-year-old female patient on concomitant valproate and femodene, was randomized to Placebo and received first dose on (b) (6) She experienced a mild adverse event of myoclonus on (b) (6) 62 days after drug initiation and had a few episodes of myoclonic seizures during the Maintenance Treatment Period. Of note, she experienced her 2nd PGTC seizure on Day 59, just prior to the development of the myoclonus, and completed the study and transitioned to the open-label extension study (EP0012). Her last day in Study SP0982 was (b) (6) but she continued on LCM in the OLE for > 15 months prior to withdrawing from the study.

In the total ISS, there was also a patient in the open-label Phase 2 studies who developed worsening myoclonic seizures. There were also an additional 6 patients who experienced myoclonus or worsening myoclonic seizures during the open-label extension study EP0012. Of these 6 patients, two discontinued from the open-label study due to the AE of myoclonic seizures. I also noted that 4 of the 6 patients who reported an AE of myoclonic seizures during the open-label extension had received placebo during SP0982 and were new to treatment when the myoclonus developed.

The Applicant also looked at total increase in days with absence seizures and myoclonic seizures during the Treatment Period compared to Prospective Baseline in the Safety Set population of Study SP0982. Overall, the number of patients reporting an increase in days with absence seizures was greater in the placebo arm (7%) than the LCM arm (2.5%).

However, the number of patients reporting an increase in days with myoclonic seizures was greater in the LCM arm (5%) compared with the placebo arm (2.5%).

Reviewer's comment: In total, there were 12 patients in the ISS who reported AEs of worsening myoclonus or myoclonic seizures. As noted above, both terms were considered the same for the purpose of this safety review. One patient each in the LCM and placebo treatment groups reported new seizure type of myoclonic seizures. Eleven of the patients reporting an AE of myoclonic seizures were receiving LCM when the myoclonus was noted, either during the double-blind or open-label treatment periods. Although many of these patients did have myoclonic seizures at baseline, it appears likely that there is a potential for worsening of myoclonus with treatment of LCM. However, the majority of these patients reported the myoclonus as mild and continued in the study despite the myoclonus. For this reason, I believe the potential for worsened myoclonic epilepsy should be noted as a noted adverse reaction; however, it is not a safety signal that would preclude approval or rise to the level of a warning. Although there were a few TEAEs of worsening absence seizures, there was no overall trend of worsening and in fact, it appeared that LCM may have had some trend towards efficacy in number of days with absence seizures.

8.5.2. Cardiac Events

There were no significant TEAEs that occurred in the Cardiac Disorders SOC; no cardiac TEAEs were serious, severe, and none led to discontinuation. In the whole ISS there were a few TEAEs of cardiac events in patients receiving LCM, including a total of 4 patients with palpitations, 3 patients with Right bundle branch block, and 2 patients each with tachycardia, bradycardia, AV block, and one patient with arrhythmia. The patients in SP0982 are already described above in Section 8.4.8.

Reviewer's Comment: Cardiac conduction abnormalities are well described with the use of LCM but no serious or severe cardiac TEAEs occurred in this development program. The decreased use of concomitant sodium channel blockers may have benefited the patient population, and they may be at less risk for conduction abnormalities. No new cardiac safety signals were identified.

8.5.3. Syncope/Loss of Consciousness

A single patient reported a TEAE of loss of consciousness during the Maintenance Period. The patient was on 400 mg/day of LCM and was stable on this dose for 27 days prior to the event, which began on Day 56, was mild in intensity and did not lead to discontinuation. The TEAE resolved in one day. The patient was also on concomitant lamotrigine.

Reviewer's comment: The single isolated episode of syncope does not raise any new safety signals in this patient population.

8.5.4. Serious suspected multiorgan hypersensitivity reactions

There were no cases of DRESS or multi-organ hypersensitivity in Study SP0982 or in the total ISS, including the open-label study populations.

8.5.5. Hepatotoxicity

In the total ISS population, there were 14 patients who reported 21 events of liver related TEAEs including ALT increased, AST increased, hepatitis A, hepatic steatosis, and transaminases increased. There were no cases of Hy's law, and no patients met the criteria for PDILI.

Reviewer's comment: No new safety signal for hepatoxicity or PDILI was identified.

8.5.6. Suicidal Ideation

There were a few reported TEAEs of suicidal ideation that are already described above in Section 8.4.3, as they all led to patient discontinuation from the study. One additional patient in the Open-Label Extensions study reported a mild TEAE of "non-specific suicidal thoughts".

Reviewer's comment: Suicidal ideation and risk is already outlined in the Warnings and Precautions section of the prescribing label given the association between patients with epilepsy and suicidal behavior. There is no new safety signal identified in this study.

8.5.7. Pediatrics, Growth, Neurodevelopment

There were no clinically significant differences between treatment arms noted in the mean T-scores at Baseline or change from baseline in either the Achenbach Child Behavior Checklist or the BRIEF-P and BRIEF questionnaires.

There was a patient who reported a TEAE of decreased appetite during the Titration period on Day 41, 20 days after titrating to 400 mg/day. The event was mild, did not lead to discontinuation of study drug, but was not resolved at the end of the study. Of note, the patient was on concomitant topiramate, which is known to decrease appetite.

Of note, there was also a report of decreased appetite in a placebo patient, which was mild, did not lead to discontinuation and resolved after 4 days.

Reviewer's comment: The reported TEAEs of decreased appetite occurred in one patient each on LCM and placebo. Although identified by the Applicant as a significant TEAE of interest,

there are no new safety signals identified. No safety signals related to pediatric behavior was identified.

8.6. Safety Analyses by Demographic Subgroups

Table 20 Incidence of TEAEs by Age, Sex, and Race (SP0982 SS)

	Sex		Age			Race			
	M N = 100 n (%)	F N =142 n (%)	≥ 4 to < 12 years N= 17 n (%)	≥ 12 to < 18 years N = 32 n (%)	≥ 18 years N =193 n (%)	White N = 186 n (%)	Black N =4 n (%)	Asian N = 43 n (%)	Other* N = 9 n (%)
TEAEs	68 (68)	107 (75)	9 (53)	28 (88)	138 (72)	131 (70)	3 (75)	32 (74)	9 (100)
SAEs	4 (4)	8 (6)	0	2 (6)	10 (5)	10 (5)	0	2 (5)	0

**Other races = American Indian, Alaska Native, Other, or Not Reported*
Source: Reviewer analysis of SP0982 ADSL and ADAE datasets of Safety Set, Double-blind treatment period only

Reviewer's comment: Overall, in Study SP0982, there were no significant differences in the incidence of TEAEs or SAEs by age, sex, or race. There was slightly decreased incidence of TEAEs in the youngest patients, and higher incidence among the "Other" race group, but given the small numbers in these categories, no significant conclusions can be drawn.

8.7. Additional Safety Explorations

8.7.1. Human Reproduction and Pregnancy

One patient had a positive urine pregnancy test during the Transition Period and reported an SAE of an induced abortion. No other pregnancies and no partner pregnancies were reported throughout this development program.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The Applicant reviewed all postmarketing data with LCM since approval in 2008, and analyzed for patients with potential PGTCS. The Applicant identified 578 safety case reports in the UCB Global Safety Database, and determined that 281 case reports were considered relevant to PGTCS. A review of all fatal cases and any cases related to the product-specific significant adverse events were analyzed including AES related to cardiac conduction, syncope, suicidality, hepatotoxicity, DRESS, and dizziness/ataxia, among others. There were no specific concerns identified in the postmarketing data that appeared unique or specific to patients with PGTCs. The adverse events that were described in the postmarketing setting are already clearly

outlined in the prescribing information.

8.8.2. Expectations on Safety in the Postmarket Setting

Postmarket safety is expected to be in alignment with the established use of LCM in the treatment of previously approved indications in partial-onset seizures. Routine pharmacovigilance is recommended.

8.8.3. Additional Safety Issues From Other Disciplines

None.

8.9. Integrated Assessment of Safety

Overall, the most frequently reported TEAEs in Study SP0982 were consistent with the known safety profile of LCM in the previously approved indication of treatment of partial-onset seizures. The most commonly reported adverse reactions seen with LCM (≥ 10% and greater than placebo) were dizziness, somnolence, headache, and nausea. There was a newly reported adverse drug reaction of worsening myoclonic seizures which may be unique to patients being treated for PGTCS and is a known risk for patients with PGTCs being treated with sodium-channel blocking treatments. There were also a few serious adverse events of acute worsening of seizures, including status epilepticus, shortly after treatment initiation with LCM. Although worsening of seizures had previously been reported in the post-marketing space, providers should be aware that some patients with PGTCS may indeed have seizure worsening while titrating onto LCM.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The label has not been finalized at the time of completion of this review. See final approved labeling.

9.2. Nonprescription Drug Labeling

Not applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

None required.

11. Postmarketing Requirements and Commitments

PREA is triggered by the new indication of the adjunctive treatment of PGTC seizures in patients with idiopathic generalized epilepsy. The Applicant has requested a waiver for patients under 4 years of age because studies in this age group are highly impracticable as idiopathic generalized epilepsy rarely presents in this age group or becomes refractory, and the Division agrees with the waiver. The oral formulations (NDA 022253 and NDA 022255) will be approved for ages 4 years and older as that is the population studied in Study SP0982.

The intravenous formulation is also approvable for ages 4 years to < 17 years of age based on the interim study results of Study EP0060 (as covered in the review of NDA 02254-S36).

The use of a loading dose of either intravenous or oral LCM is recommended as an option for treatment initiation in adults. Therefore, a PREA requirement to study the use of a loading dose for treatment initiation for PGTCs in pediatric patients with IGE is triggered by this approval. The safety and tolerability of such a loading dose in patients ≥ 4 to < 17 years of age has not yet been studied, but is currently under evaluation through a study aimed at addressing the following PREA requirements (NDA 022543/S-027, NDA 022254/S-029, NDA 022255/S-012):

#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 ≥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 ≥ 1 month to < 17 years of age.

See the Final Approval Letter for the exact language of the new proposed PMRs. The Applicant has requested a deferral of such requirements with plans to align with the ongoing study above, which has a proposed Study Completion Date of 09/2020 and Final Report Submission 03/2021.

Routine postmarket surveillance will continue.

12. Appendices

12.1. References

See footnotes throughout.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): SP0982

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 497		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

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