CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216185Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 216185
Priority or Standard	Standard
Submit Date(s)	July 7, 2022 (amendment with additional study data March 17, 2023)
Received Date(s)	July 7, 2022 (amendment March 17, 2023)
PDUFA Goal Date	May 5, 2023
Division/Office	Division of Neurology 2 (DN2)
Reviewer Name(s)	Amy Kao, MD
Review Completion Date	May 3, 2023
Established/Proper Name	lacosamide
(Proposed) Trade Name	Motpoly XR
Applicant	Aucta Pharmaceuticals, Inc.
Dosage Form(s)	100 mg, 150 mg, 200 mg extended-release capsules
Applicant Proposed Dosing Regimen(s)	Initial dosage for monotherapy: 200 mg once daily; Initial dosage for adjunctive therapy: 100 mg once daily; Maximum dosage: (b) (4) once daily; (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures in patients 17 years of age and older
Recommendation on Regulatory Action	Approval with changes to label as negotiated and discussed in review (including change in proposed maximum dosage to 400 mg once daily (b) (4)
Recommended Indication(s)/Population(s) (if applicable)	Treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg

Table of Contents

Glossary 6

1. Executive Summary 8
   1.1. Product Introduction 8
   1.2. Conclusions on the Substantial Evidence of Effectiveness 8
   1.3. Benefit-Risk Assessment 9
   1.4. Patient Experience Data 13

2. Therapeutic Context 13
   2.1. Analysis of Condition 13
   2.2. Analysis of Current Treatment Options 14

3. Regulatory Background 20
   3.1. U.S. Regulatory Actions and Marketing History 20
   3.2. Summary of Presubmission/Submission Regulatory Activity 20
   3.3. Foreign Regulatory Actions and Marketing History 21

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 21
   4.1. Study Integrity and Surveillance 21
   4.2. Product Quality 22
   4.3. Nonclinical Pharmacology/Toxicology 22
   4.4. Clinical Pharmacology 22
   4.5. Devices and Companion Diagnostic Issues 22
   4.6. Consumer Study Reviews 22
   4.7. Division of Pediatric and Maternal Health (DPMH) 22

5. Sources of Clinical Data and Review Strategy 23
   5.1. Table of Clinical Studies 23
   5.2. Review Strategy 25
   5.3. Discussion of Individual Studies/Clinical Trials 25

6. Review of Relevant Individual Trials Used to Support Efficacy 38

7. Integrated Review of Effectiveness 39

7.1. Additional Efficacy Considerations....39
7.1.1. Considerations on Benefit in the Postmarket Setting....39
7.1.2. Other Relevant Benefits....39
7.2. Integrated Assessment of Effectiveness....39

8. Review of Safety....39
8.1. Safety Review Approach....39
8.2. Review of the Safety Database....40
8.2.1. Overall Exposure....40
8.2.2. Relevant characteristics of the safety population:....41
8.2.3. Adequacy of the safety database:....41
8.3. Adequacy of Applicant's Clinical Safety Assessments....41
8.3.1. Issues Regarding Data Integrity and Submission Quality....41
8.3.2. Categorization of Adverse Events....41
8.3.3. Routine Clinical Tests....42
8.3.4. Vital Signs....42
8.3.5. Electrocardiograms....42
8.4. Safety Results....42
8.4.1. Deaths....42
8.4.2. Serious Adverse Events....42
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects....42
8.4.4. Treatment Emergent Adverse Events and Adverse Reactions....43
8.4.5. Laboratory Findings....44
8.4.6. Vital Signs....44
8.4.7. Electrocardiograms (ECGs)....45
8.4.8. QT....45
8.4.9. Immunogenicity....45
8.5. Analysis of Submission-Specific Safety Issues....45
8.6. Safety Analyses by Demographic Subgroups....45
8.7. Specific Safety Studies/Clinical Trials....45
8.8. Additional Safety Explorations....45
8.8.1. Human Carcinogenicity or Tumor Development....45

8.8.2. Human Reproduction and Pregnancy 46
8.8.3. Pediatrics and Assessment of Effects on Growth 46
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound 46
8.9. Safety in the Postmarket Setting 46
8.9.1. Safety Concerns Identified Through Postmarket Experience 46
8.9.2. Expectations on Safety in the Postmarket Setting 46
8.9.3. Additional Safety Issues From Other Disciplines 46
8.10. Integrated Assessment of Safety 46
9. Advisory Committee Meeting and Other External Consultations 47
10. Labeling Recommendations 47
10.1. Prescription Drug Labeling 47
10.2. Nonprescription Drug Labeling 48
11. Risk Evaluation and Mitigation Strategies (REMS) 48
12. Postmarketing Requirements and Commitments 48
13. Appendices 49
13.1. References 49
13.2. Financial Disclosure 49

Table of Tables

Table 1: FDA-approved once-daily treatments for partial onset seizures 14
Table 2: Listing of Clinical Studies Submitted in this NDA 24
Table 3: Adverse events during multiple-dose comparative oral bioavailability study based on product received 31
Table 4: Reviewer Table, Safety Population, Size and Denominators (all healthy adult males) 40
Table 5: Reviewer Table, Duration of Exposure to LCM XR 40
Table 6: Adverse Events by System Organ Class and Preferred Term, All Studies 43

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
ASM	antiseizure medication
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
BID	twice daily
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CMC	chemistry, manufacturing, and controls
CNS	Central Nervous System
CRF	case report form
CRT	clinical review template
CSR	clinical study report
DMF	drug master file
DPMH	Division of Pediatric and Maternal Health
DR	delayed release
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	Electrocardiogram
FDA	Food and Drug Administration
GI	Gastrointestinal
GCP	good clinical practice
GRMP	good review management practice
ICD	informed consent document
ICH	International Conference on Harmonization
ILAE	International League Against Epilepsy
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
IR	immediate release
LCM	lacosamide
LD	listed drug
LEV	levetiracetam
LGS	Lennox-Gastaut syndrome
LLN	Lower Limit of Normal
LMG	lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities

NDA	new drug application
OSIS	Office of Study Integrity and Surveillance
OSI	Office of Scientific Investigation
OXC	oxcarbazepine
PI	prescribing information or package insert
PGTCS	primary generalized tonic-clonic seizures
PK	pharmacokinetics
PMR	postmarketing requirement
POS	partial onset seizures
PREA	Pediatric Research Equity Act
PT	Preferred Term
QD	once daily
REMS	risk evaluation and mitigation strategy
RPCT	randomized placebo-controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
TEN	toxic epidermal necrolysis
US	United States (of America)
VPA	valproic acid
WRO	written responses only
XR	extended release

1. Executive Summary

1.1. Product Introduction

Lacosamide (LCM), a slow sodium channel antagonist, is currently approved as Vimpat for the treatment of partial-onset seizures (POS) in patients 1 month of age and older and for adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients 4 years of age and older, across all formulations (tablet, injection for intravenous use, and oral solution). An alternate initial dosage ("loading dose") of all formulations of LCM is labeled for adults and children. 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.

The Applicant has developed this extended-release (XR) product with the intention of providing a once daily dosing alternative to Vimpat, the currently approved LCM immediate release (IR) formulation which is administered twice a day. The LCM XR (proprietary name Motpoly XR) capsule is composed of (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

As a 505(b)(2) submission, the Applicant includes no studies in this NDA to support efficacy. Instead, the NDA relies entirely on the listed drug (LD), Vimpat tablets (NDA 022253), for evidence of effectiveness. With an establishment of bioequivalence of Motpoly XR to Vimpat tablets, the same clinically meaningful effectiveness is assumed for Motpoly XR.

Evidence of effectiveness for relevant, previously approved Vimpat indications is reviewed here. The approval of the tablet and intravenous (IV) formulation in 2008 and of the oral solution in 2010 for the adjunctive treatment of POS in adults 17 years and older was based on demonstration of a significant reduction in partial seizure frequency per 28 days in three adequate and well-controlled trials which administered the tablet formulation and on demonstration of bioequivalence between the tablet and the oral and IV solutions. The approval of LCM as monotherapy for the treatment of POS in adults in 2014 was based on a historical-controlled conversion to monotherapy study, with the endpoint consisting of the percent of patients meeting exit criteria during the maintenance treatment phase. The approval was considered in the context of a then-recent Advisory Committee determination that historical control trials were acceptable in the specific situation in which a drug is already known to be effective as adjunctive treatment based on randomized controlled studies. The 2017 extension of the indication for the treatment of POS in patients 4 years of age and older was based on the extrapolation of efficacy from adult data with supportive clinical pharmacology pediatric pharmacokinetic (PK) data, after a then-recent determination that extrapolation was appropriate based on similar pathophysiology of POS in adults and children 4

years of age and above and on similar exposure-response relationships in adult and pediatric subjects with POS.

The approval in November 2020 of the indication of adjunctive therapy in the treatment of PGTCS in 4 years of age and older was based on positive results from a double-blind, placebo-controlled study in patients 4 years of age and older with idiopathic generalized epilepsy.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

With the approval of Vimpat (lacosamide immediate release) in 2008 for the indication of the treatment of partial onset seizures, the risks and benefits associated with the drug substance, lacosamide (LCM), are well known and established. The studies conducted to establish the pharmacokinetic (PK) characteristics of Motpoly XR (LCM extended release) in relation to Vimpat were not designed to establish an extensive safety profile; however, these studies did not raise any new safety concerns. Motpoly XR offers different administration attributes and therefore provides an alternative option for the treatment of POS. This XR preparation provides an obvious potential benefit over an immediate release formulation of LCM due to the once daily dosing, which will likely enhance compliance and may attenuate adverse events associated with a higher C_{max} or the fluctuation of plasma concentrations throughout a 24-hour period. Given the similarity in safety profile and PK findings to Vimpat, Motpoly XR merits approval for the indication of treatment of POS in adult and pediatric patients weighing at least 50 kg. Although Motpoly XR has the potential to attenuate some C_{max}-associated adverse events, the small safety database provided in this application do not support safety-related labeling changes, and the most serious risks identified in the "Warnings and Precautions" section of the label should remain unchanged.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Despite current approved treatments, many patients with partial-onset seizures (POS) continue to have "breakthrough" and/or refractory seizures. • Refractory seizures are seizures which persist despite adequate trials of two or more antiseizure medications (ASMs). • Breakthrough and refractory seizures increase the risk of life-threatening conditions such as status epilepticus and sudden unexplained death in epilepsy patients (SUDEP).	There is continued need for new, effective medications for patients with POS who have refractory and/or breakthrough seizures.
Current Treatment Options	• Of the many currently available drugs for the treatment of POS, only nine are available as extended-release formulations and/or are dosed once daily. • Noncompliance and fluctuation in ASM plasma levels contribute to some patients' breakthrough seizures.	There is a continued need for new, extended-release formulations of effective medications for patients with POS, especially for patients who may benefit from a particular ASM but have difficulty with compliance, adverse

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Lacosamide (LCM) is approved as Vimpat immediate release tablets, as an oral solution, and as a solution for intravenous use. Vimpat in all currently available formulations is administered twice daily. • For some patients with POS, the benefit-risk profile of a particular ASM may not be favorable due to adverse effects of the drug.	events that are associated with peak plasma concentrations, or breakthrough seizures which are associated with fluctuations in plasma concentrations.
Benefit	• Vimpat has been found to be effective in reducing seizure frequency in adult and pediatric patients as young as one month of age with POS. • This application provides evidence from four studies of pharmacokinetic similarities, including serum concentrations and cumulative AUCs at multiple time points, between Vimpat and Motpoly XR as an adequate basis for the establishment of bioequivalence. • The approved dosing regimen of Vimpat for pediatric patients weighing 50 kg or more is the same as that for adults, except for a lower initial dose of 100 mg/day for pediatrics.	Motpoly XR is bioequivalent to Vimpat, an approved ASM for the treatment of POS in adult and pediatric patients 1 month of age and older. Motpoly XR is expected to have similar benefit on reduction of seizure frequency as its listed drug (LD), Vimpat. Motpoly XR is appropriate for the treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg because Motpoly XR capsules (100 mg, 150 mg, and 200 mg) are effective doses for all patients weighing 50 kg or more.
Risk and Risk Management	• The safety profile of Vimpat is well-characterized in adults and pediatric patients as young as one month of age. • The most common adverse events associated with Vimpat are diplopia, headache, dizziness, nausea, and somnolence. • Warnings and precautions associated with Vimpat include suicidal behavior and ideation; dizziness and ataxia; cardiac rhythm and conduction abnormalities, particularly in patients who receive rapid	With establishment of bioequivalence between Motpoly XR and Vimpat, the safety risks of Motpoly XR are expected to be the same as those noted for the LD, Vimpat. There were no new significant adverse events observed in the trials using Motpoly XR that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infusions, who have underlying cardiac conditions, or who are on concomitant medications that affect cardiac conduction; syncope; withdrawal seizures; and drug reaction with eosinophilia and systemic symptoms. • The safety findings from the studies submitted in this application did not raise concerns of new or increased severity of adverse events with Motpoly XR as compared with the known safety profile of Vimpat.	are not already reported in current approved Vimpat labeling.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Epilepsies affect individuals of all ages and are some of the most common neurologic disorders in all age groups. A large meta-analysis of population-based epilepsy studies found the point prevalence of epilepsy to be 6.38 per 1000, the lifetime prevalence 7.6 per 1000, annual cumulative incidence of 67.77 per 100,000 persons, and an incidence rate of 61.44 per 100,000 person-years.[1] In an analysis based on health insurance claims, the incidence and prevalence estimate of epilepsy in the United States (US) pediatric population in 2012 were 6.8 per 1000 and 104 per 100,000 children, respectively.[2] POS occurred in ~57% of patients with epilepsy assessed over a 50-year period in Rochester, Minnesota[3], and ranges from 12% to 71% in a variety of published epidemiological studies, depending on diagnostic criteria and country being assessed.[4]

Uncontrolled POS are associated with poorer quality of life due to a variety of limitations (e.g., inability to drive, social isolation, difficulty maintaining employment), and can cause significant adverse consequences, including severe trauma, depression, anxiety, and sudden death.[5,6]

Seizures have historically been classified as partial or primary generalized, depending on the

[1] Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017:88; 296-303
[2] Kim H, Thurman DJ, Durgin T, et al. Estimating Epilepsy Incidence and Prevalence in the US Pediatric Population Using Nationwide Health Insurance Claims Data. J Child Neurology 2016, Vol. 31(6) 743-749
[3] Hauser WA, Annegers JF, Rocca WA. descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. 1996 Jun;71(6):576-86.
[4] Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy—a review. Epilepsy Res. 2009 Jul;85(1):31-45.
[5] Baranowski CJ. The quality of life of older adults with epilepsy: A systematic review. Seizure. 2018 Aug; 60:190-197.
[6] Sadr SS, Javanbakht J, Javidan AN, et al. Descriptive epidemiology: prevalence, incidence, sociodemographic factors, socioeconomic domains, and quality of life of epilepsy: an update and systematic review. Arch Med Sci. 2018 Jun;14(4):717-724

location of onset of the seizure.[7] Focal or partial onset seizures involve only a portion of the brain at the onset, originating in one or more localized foci. Seizures that originate focally and spread to involve the majority or entirety of the brain are a subset of focal seizures, clinically called secondarily generalized seizures.[8] A 2017 revised classification of seizure types by the International League Against Epilepsy (ILAE) redefined POS as "focal seizures" with a variety of seizure subtypes: focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic–clonic seizures (to refer to secondarily generalized seizures).[9] The term POS will be used throughout this review. Partial or focal seizures may begin with motor, sensory, autonomic, or psychic symptoms, depending on the location of the electrical discharge.[10]

2.2. Analysis of Current Treatment Options

Approximately 18 drugs are currently approved for an indication of treatment of POS. These include cenobamate, brivaracetam, perampanel, eslicarbazepine, lacosamide, pregabalin, topiramate, lamotrigine, zonisamide, oxcarbazepine, levetiracetam, tiagabine, gabapentin, valproic acid, and phenytoin. Ezogabine, vigabatrin, and felbamate are also approved for the treatment of POS but only for patients who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the potential risks. Of the available drugs for the treatment of POS, nine are available as extended-release formulations and/or are dosed once daily (QD), as displayed in Table 1 below. Carbamazepine extended-release capsules are administered twice daily (BID) so are not discussed in this table.

Table 1: FDA-approved once-daily treatments for partial onset seizures

[7] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for Revised Classification of Epilepsies and Epileptic Syndromes. Epilepsia. 30(4):38%399, 1989
[8] Scheffer IE, Berkovic S, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-521
[9] Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. Curr Neurol Neurosci Rep (2017) 17: 48
[10] Chang BS and Lowenstein DH. Mechanisms of Disease: Epilepsy. NEJM (2003) 349;13

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Admin.	Efficacy Information (pertaining to partial onset seizures)	Important Safety and Tolerability Issues (warnings and precautions)
Phenytoin sodium extended capsules	Treatment of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures and prevention and treatment of seizures during or following neurosurgery	1976	Once daily dosage may be considered in adults if seizure control established with divided doses of three 100 mg daily		Withdrawal seizure/status epilepticus; suicidal behavior and ideation; serious dermatologic reactions; DRESS/multiorgan hypersensitivity; hypersensitivity; cardiac effects (bradycardia, cardiac arrest); angioedema; hepatic injury; hematopoietic complications (thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia); decreased bone mineral density and bone fractures; increased unbound phenytoin with renal or hepatic disease or hypoalbuminemia; exacerbation of porphyria; teratogenicity; hyperglycemia; confusional states or cerebellar dysfunction with levels above therapeutic range.
Zonisamide (capsules)	Adjunctive therapy for the treatment of partial seizures in adults	2000	PO, once or twice daily	Three RPCTs in patients with refractory POS. Primary efficacy endpoint: median percent reduction from baseline in partial seizure frequency.	Serious skin reactions (SJS, TEN); serious hematologic events (aplastic anemia, agranulocytosis); DRESS/multi-organ hypersensitivity; oligohidrosis and hyperthermia in pediatric patients; acute myopia and secondary angle closure glaucoma; suicidal behavior and ideation; metabolic acidosis; withdrawal seizures; teratogenicity; cognitive/neuropsychiatric adverse events (depression and psychosis, psychomotor slowing, difficulty with concentration, speech or language problems, somnolence or fatigue); hyperammonemia and encephalopathy; kidney stones; effect on renal function; status epilepticus
Divalproex sodium (VPA) extended-release tablets	• Monotherapy and adjunctive therapy in the treatment of adults with complex partial seizures that occur in isolation or with other types of seizures • Sole and adjunctive therapy in the	2002	PO, once daily	2002 addition of the same epilepsy indication as Depakote delayed release (DR) in adults was based on demonstration that the conversion scheme was appropriate for most adult on either ASM monotherapy or combination therapy by a BA study of ER vs DR in	Hepatic dysfunction, teratogenicity, pancreatitis, hyperammonemia, thrombocytopenia, hyperammonemic encephalopathy in patients with urea cycle disorders, somnolence in the elderly. Hepatotoxicity (including fatalities) usually occurs in first 6 months of treatment; patients on multiple convulsants, children, patients with congenital metabolic disorders, patients with severe seizure disorders with mental retardation, patients with organic brain disease, and patients under age 2 are at greatest risk.

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Admin.	Efficacy Information (pertaining to partial onset seizures)	Important Safety and Tolerability Issues (warnings and precautions)
	treatment of simple and complex absence seizures in adult patients • Adjunctive treatment in adult patients with multiple seizure types that include absence seizures			adults with epilepsy on an enzyme inducing ASM.	
Levetiracetam (LEV) extended-release tablets	Treatment of partial-onset seizures (POS) in patients 12 years of age and older	2008	PO, once daily	RPCT of add-on 2 x 500 mg once daily in patients 12 to 70 years old with POS. There were inadequate numbers of adolescents in the RPCT so a PK study of ages 12-16 years with POS established dosing in that age group. Primary efficacy endpoint: median percent reduction in POS frequency per week over the 12-week treatment period in the LEV ER vs placebo group	Behavioral abnormalities (psychotic symptoms, suicidal behavior and ideation, irritability, and aggression); somnolence and fatigue; asthenia; anaphylaxis and angioedema; serious dermatological reactions (SJS, TEN); coordination difficulties; withdrawal seizures; hematologic abnormalities (decreases in white blood cells, neutrophil, red blood cells, hemoglobin, hematocrit counts; increases in eosinophil counts); decreased plasma levels of LEV throughout pregnancy
Lamotrigine (LMG) extended-release tablets	• Adjunctive therapy for primary generalized tonic-clonic seizures (PGTCS) and POS with or without secondary generalization in 13 years and older	2009	PO, once daily	RPCT of LMG ER dose dependent on concomitant ASM (VPA, enzyme-inducing, or neutral) in patients 13 years and older with POS. Primary efficacy endpoint: percent reduction in seizure	Serious skin rashes especially with concurrent VPA; hemophagocytic lymphohistiocytosis; multiorgan hypersensitivity/DRESS; cardiac rhythm and conduction abnormalities; hematologic abnormalities (neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, aplastic anemia); suicidal behavior and ideation; aseptic meningitis; potential medication errors; concomitant use with oral contraceptives; withdrawal seizures; status

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Admin.	Efficacy Information (pertaining to partial onset seizures)	Important Safety and Tolerability Issues (warnings and precautions)
	• Conversion to monotherapy in 13 years and older with POS who are receiving treatment with a single antiepileptic drug			frequency from baseline	epilepticus; sudden unexplained death in epilepsy; addition to valproate; binding in eye and other melanin-containing tissues; false-positive drug results, effect on leukocyte tests.
Oxcarbazepine (OXC) extended-release tablets	Treatment of POS in patients 6 years of age and older	2012	PO, once daily	RPCT of OXC ER 1200 mg vs 2400 mg once daily vs placebo in adults 18 to 65 years (plus concentration-response analyses and simulations with pediatric patients) Primary efficacy endpoint: median percent change in 28-day seizure frequency	Hyponatremia; anaphylactic reactions and angioedema; cross hypersensitivity to carbamazepine; serious dermatological reactions (SJS and TEN; increased risk with HLA-B*1502; suicidal behavior and ideation; withdrawal seizures; DRESS; hematologic reactions (pancytopenia, agranulocytosis, leukopenia); risk of seizures in pregnant patient related to decrease in metabolite levels; risk of seizure aggravation (especially PGTC).
Perampanel (tablets, oral suspension)	• Treatment of POS in patients 4 years of age and older • Adjunctive therapy in treatment of PGTCS in 12 years and older	2012	PO, once daily	Three RPCTs in adult and pediatric patients 12 years of age and older. Primary efficacy endpoint: percent change in seizure frequency per 28 days during treatment period as compared to baseline period.	Psychiatric and behavioral adverse reactions (aggression, hostility, irritability, anger, and homicidal ideation and threats), suicidal behavior and ideation; dizziness and gait disturbance; somnolence and fatigue; falls; DRESS/multiorgan hypersensitivity; withdrawal seizure.
Eslicarbazepine (tablets)	Treatment of POS in patients 4 years of age and older	2013	PO, once daily	• Monotherapy use in adults based on two randomized, historical-controlled clinical trials. Primary efficacy	Suicidal behavior and ideation; serious dermatologic reactions (SJS, TEN); DRESS/multiorgan hypersensitivity; anaphylaxis and angioedema; hyponatremia; dizziness, gait/coordination disturbance; somnolence/fatigue; cognitive dysfunction; visual changes (diplopia, blurred

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Admin.	Efficacy Information (pertaining to partial onset seizures)	Important Safety and Tolerability Issues (warnings and precautions)
				endpoint: cumulative 112-day exit rate (due to status epilepticus, emergence of generalized tonic-clonic seizure, doubling of average monthly seizure count, doubling of highest consecutive 2-day seizure frequency, or worsening of seizure severity requiring intervention). • Adjunctive use based on three RPCTs in adults with POS. Primary efficacy endpoint: standardized seizure frequency during the maintenance phase over 28 days. • Use in pediatrics based on extrapolation of efficacy from adult studies using pediatric PK data.	vision, impaired vision); withdrawal seizures; drug induced liver injury; abnormal thyroid function tests; hematologic adverse reactions (pancytopenia, agranulocytosis, leukopenia).
Topiramate extended-release capsules (Trokendi XR)	• Initial monotherapy for the treatment of POS or PGTCS in patients 6 years of age and older • Adjunctive therapy for the treatment of POS, PGTCS, or seizures associated with Lennox-Gastaut syndrome (LGS)	2013	PO, once daily	After thorough discussion with the Applicant, it was determined that BE based on examination of multiple time points of concentrations and cumulative AUCs over a 24-hour period at steady state maintenance using a relative	Acute myopia and secondary angle closure glaucoma; visual field defects; oligohidrosis and hyperthermia; metabolic acidosis; interaction with alcohol; suicidal behavior and ideation; cognitive/neuropsychiatric adverse reactions (cognitive-related dysfunction, psychiatric/behavioral disturbances, e.g., depression or mood problems; somnolence or fatigue); fetal toxicity; withdrawal seizures; decrease in bone mineral density; negative effects on height and weight; serious skin reactions (SJS, TEN);

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Admin.	Efficacy Information (pertaining to partial onset seizures)	Important Safety and Tolerability Issues (warnings and precautions)
	in patients 6 years of age and older			BA study of 200 mg daily vs Topamax 100 mg BID was sufficient.	hyperammonemia and encephalopathy; kidney stones; hypothermia with concomitant VPA use.
Topiramate extended-release capsules (Qudexy XR)	• Initial monotherapy for the treatment of POS or PGTCS in patients 2 years of age and older • Adjunctive therapy for the treatment of POS, PGTCS, or seizures associated with LGS in patients 2 years of age and older	2014	PO, once daily	RPCT in adults with POS was performed and showed a statistically significant percent reduction in frequency of POS in baseline period compared to treatment period (the primary efficacy endpoint). However, approval was based on demonstration of BE to IR topiramate through analysis of concentrations and cumulative AUCs at multiple time points.	Acute myopia and secondary angle closure glaucoma; visual field defects; oligohidrosis and hyperthermia; metabolic acidosis; suicidal behavior and ideation; cognitive/neuropsychiatric adverse reactions (cognitive-related dysfunction, psychiatric/behavioral disturbances, e.g., depression or mood problems; somnolence or fatigue); fetal toxicity; withdrawal seizures; decrease in bone mineral density; negative effects on height and weight; serious skin reactions (SJS, TEN); hyperammonemia and encephalopathy; kidney stones; hypothermia with concomitant VPA use.

Abbreviations: ASM = antiseizure medication; AUC = area under the curve; BA = bioavailability; BE = bioequivalence; DR = delayed release; DRESS = drug reaction with eosinophilia and systemic symptoms; ER = extended release; IR = immediate release; LEV = levetiracetam; LGS = Lennox-Gastaut syndrome; LMG = lamotrigine; OXC = oxcarbazepine; PGTCS = primary generalized tonic-clonic seizures; POS = partial onset seizures; RPCT = randomized placebo controlled trial; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; VPA = valproic acid

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Motpoly XR (lacosamide extended release) is not currently marketed in the United States for any other indication. The United States Food and Drug Administration (FDA) first approved Vimpat (the LD) for the adjunctive treatment of POS in adults in 2008. Section 1.2 above reviews subsequent indications.

3.2. Summary of Presubmission/Submission Regulatory Activity

October 2018: Pre-IND (IND 140785) Written Responses Only (WRO) were issued.

- The Sponsor proposed using the 505(b)(2) regulatory pathway with Vimpat as the LD for its application.
- Feedback from the FDA included the need to adequately justify that the lower $C_{max,ss}$ and higher $C_{min,ss}$ values of the ER capsules as compared to the IR tablets have no significant impact on clinical outcomes.

September 2020: Chemistry Manufacturing and Controls (CMC)-only preIND WRO were issued.

February 2022: The Sponsor submitted an Agreed initial Pediatric Study Plan (iPSP) with revisions from the original submission (June 21, 2021) which included:

(b) (4)

August 2021: pre-NDA WRO were issued.

July 7, 2022: The NDA was submitted. The Applicant submitted letters of authorization to reference Drug Master File (DMF) (b) (4) (lacosamide USP), DMF (b) (4)

March 17, 2023: At the time of the original NDA submission, the Applicant noted that a single dose PK dose proportionality study was being planned. On March 17, 2023, the Applicant submitted an amendment to include the proportionality/linearity and comparative bioavailability study results (Study 22-VIN-0340).

3.3. Foreign Regulatory Actions and Marketing History

Motpoly XR is not approved nor marketed anywhere in the world for any indication.

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

4.1. Study Integrity and Surveillance

All clinical studies submitted in this NDA were conducted outside of the US, at Veeda Clinical Research Pvt Ltd in Gujarat, India. The Division of New Drug Study Integrity within the Office of Study Integrity and Surveillance (OSIS), which conducts inspections of bioavailability/bioequivalence (BA/BE) studies, determined that inspections were not needed. The Office of Regulatory Affairs inspected the clinical site in September 2021 and observed failure to conduct foreign clinical studies in accordance with good clinical practice, e.g., informed consent documents (ICDs) were not written at a level that subjects could comprehend; ICDs translated from English to Gujarati were not directly translated and included explanation and terminology that was not the same for the English to Hindi translation. However, OSIS determined that these issues did not impact data integrity or subject safety. OSIS conducted a Remote Regulatory Assessment for the analytical site in March 2022 and concluded that data from the reviewed studies were reliable.

4.2. Product Quality

The Applicant originally proposed [redacted] (b) (4) See the review by the Chemistry, Manufacturing and Control (CMC) reviewers for details.

4.3. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted.

4.4. Clinical Pharmacology

Per the Applicant's clinical study report of the multiple-dose comparative bioavailability study 20-VIN-0095, peak concentrations occurred later for Motpoly XR (T_{max} of 7 hours) than for Vimpat IR (T_{max} of 2 hours). The arithmetic mean terminal t½ value was longer for Motpoly XR (t½ of 16 hours) than Vimpat IR (t½ of 13 hours). Steady state was achieved after 4 days with Motpoly XR (compared to after 3 days of twice daily administration of Vimpat IR). Our Office of Clinical Pharmacology (OCP) reviewers note that point-to-point comparisons for LCM partial AUC (AUC_{0-t}), plasma concentrations and the partial AUC between time-points (AUC_{t1-t2}) are bioequivalent at steady-state for the majority of the time points throughout the day based on conventional bioequivalence criteria. They also note that high-fat food and sprinkling of the capsule on applesauce had no clinically meaningful impact on the PK. See the OCP review for details.

4.5. Devices and Companion Diagnostic Issues

Not applicable.

4.6. Consumer Study Reviews

Not applicable.

4.7. Division of Pediatric and Maternal Health (DPMH)

DPMH was involved throughout the review cycle and provided expertise relating to pediatric safety, labeling, and PREA PMRs.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Listing of Clinical Studies Submitted in this NDA

Trial Identity	Trial Design	Regimen/ schedule (all administered orally)	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Clinical Pharmacological Studies							
20-VIN-0088	Single-dose, randomized, open-label, four-treatment study to compare bioavailability of lacosamide (LCM) XR capsule and Vimpat tablet under fasting condition	• Two LCM XR 200 mg capsule (three different formulations) • One Vimpat 200 mg tablet BID x 2 doses	PK measures	Single dose	24	Healthy adult males	1 (India)
20-VIN-0095	Multiple-dose, randomized, open-label, two-treatment study to compare bioavailability of LCM XR and Vimpat tablet under fasting condition (pivotal study)	• Two LCM XR 200 mg capsules each morning • One Vimpat 200 mg tablet BID	PK measures	Each treatment period was 7 days	35	Healthy adult males	1 (India)
21-VIN-0184	Single-dose, randomized, three-treatment, crossover study comparing bioavailability of LCM XR under fasting, fed, and fasting sprinkle conditions	• One LCM XR 200 mg capsule fasting • One LCM XR 200 mg capsule after high-fat high calorie meal • Contents of one LCM XR 200 mg capsule over applesauce	PK measures	Single dose	18	Healthy adult males	1 (India)
22-VIN-0340	Single-dose, randomized, five-treatment, crossover study of proportionality/linearity and comparative bioavailability of LCM XR and Vimpat tablet under fasting conditions	• One LCM XR 100 mg capsule • One LCM XR 200 mg capsule • Two LCM XR 150 mg capsules • Two LCM XR 200 mg capsules • One Vimpat 200 mg tablet BID x 2 doses	PK measures	Single dose	25	Healthy adult males	1 (India)

Abbreviations: BID = twice daily; XR = extended release; LCM = lacosamide; PK = pharmacokinetic
Source: Reviewer generated from Summary of Clinical Pharmacology and respective clinical study reports

5.2. Review Strategy

This 505(b)(2) NDA relies on the LD, Vimpat tablets, for clinical and nonclinical data and the FDA's previous findings of efficacy and an acceptable safety profile, with the support of PK studies to bridge between Motpoly XR and Vimpat tablets. Reference is made to the meeting responses as listed in Section 3.2 Summary of Presubmission/Submission Regulatory Activity, which provided the direction for the drug development program and regulatory submission pathway via bridging studies. The focus of my review was on determination of safety to determine whether approval would be supported. I conducted my own analyses of the submitted safety data from the PK studies, and because of the small resulting safety population, considered these within the context of previous safety findings as discussed in the approved Vimpat labeling.

5.3. Discussion of Individual Studies/Clinical Trials

STUDY 20-VIN-0088 "An open label, balanced, randomized, four-treatment, four-sequence, four-period, oral comparative bioavailability study of Lacosamide 200mg extended-release capsule of Aucta Pharmaceuticals, Inc., USA and VIMPAT® (Lacosamide) 200mg film coated tablet of UCB, Inc. Smyrna, GA 30080 in healthy, adult, human subjects at a dose of 400 mg under fasting condition"

Study Center
Veeda Clinical Research Pvt. Ltd., Gujarat, India

Study Periods
Clinical Phase: 24 August 2020 to 18 September 2020
Bioanalytical Phase: 18 September 2020 to 02 October 2020

Study Objective
The objective of this study was to compare the rate and extent of absorption of three different test formulations (two capsules of lacosamide 200mg extended-release capsule; T1, T2, T3) and the reference formulation (one tablet of VIMPAT® 200 mg film coated tablet BID with a 12 hour dosing interval; R) in healthy, adult, human subjects under fasting condition and to monitor the safety and tolerability of the subjects.

Methodology
This study was an open label, balanced, randomized, four-treatment, four-sequence, four-period, oral comparative bioavailability study.

Subjects were randomized to one of four treatment sequences. Washout periods were 7 days between Period 1 and Period 2, 5 days between Period 2 and Period 3, and 9 days between Period 3 and Period 4. Subjects were confined at the study site from at least 10 hours before

dosing (to ensure fasting) to 48 hours post-dose. Blood for PK evaluation was drawn before dosing and at times specified in the protocol up to 48 hours after dosing. Subjects returned to the study site for post-study assessment at 72 hours post-dose, which consisted of clinical examination, electrocardiogram (ECG), assessment of depression and suicidality, AE monitoring, and blood sample for biochemistry and hematology.

Number of Subjects (Planned and Analyzed)

A total of 24 subjects enrolled in the study, and 22 subjects completed the study. One subject withdrew after most recently having received Reference product (R) during Period 3, before Period 4 administration. One subject withdrew consent after receiving T3 during Period 4.

Therefore, all 24 subjects enrolled in the study were included in the safety analysis. Twenty-four subjects were included in the PK and statistical analysis for T2 vs R, and 23 subjects were included in the PK and statistical analysis for T1 vs R and T3 vs R.

Demographics

Per the clinical study report, mean (± standard deviation [SD]) age of the 24 subjects was 31 years (± 4.34), with a range of 24 to 41 years (median 30.5 years). All subjects were male and Asian. Mean (± SD) body mass index (BMI) was 22.6 kg/m^2 (± 2.68), with a range of 18.9 to 27.41 kg/m^2.

Main Criteria for Inclusion

Subjects were judged by the principal investigator to be normal, healthy males between 18 and 45 years with a body weight of at least 45 kg who met all inclusion criteria and no exclusion criteria.

Study Treatments

Test products (T1, T2, T3) were three formulations of lacosamide 200 mg extended-release capsules, manufactured by Catalent Pharma solution for Aucta Pharmaceuticals.

Reference product (R) was Vimpat 200 mg tablets, manufactured for UCB.

Criteria for Evaluation

Pharmacokinetics: Serial blood samples were obtained for the determination of each treatment's PK parameters in plasma, including C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, Kel, AUC_%Extrap_obs, and $t_{1/2}$. Pharmacokinetic parameters were calculated using non-compartmental model using Phoenix WinNonlin® 8.2.

Safety: Safety endpoints included clinical examination including sitting blood pressure, body temperature, radial pulse rate, and respiratory rate; sitting blood pressure and radial pulse rate pre-dose and at times specified in the protocol between 1 hour and 37 hours post-dose; 12-lead electrocardiogram (ECG) at 2 and 14 hours post-dose and post-study; assessment of

depression and suicidality; post-study hematological labs (white blood cell count, differential, hemoglobin, and platelet count); and post-study biochemical labs (liver function tests, bilirubin, creatinine, and urea).

Statistical Methods

Pharmacokinetics: Descriptive statistics (e.g., number of observations [N], mean, standard deviation [SD], minimum, median, maximum, percentage co-efficient of variation (%CV), and geometric mean) were calculated for each time point and pharmacokinetic parameter for each test and reference product. The ln-transformed pharmacokinetic parameters $C_{max,}$ $AUC_{0-t,}$ and $AUC_{0-\infty}$ were analyzed by analysis of variance (ANOVA) using PROC MIXED in SAS Software, Version 9.4. 90% confidence intervals for the difference between least square means of test and reference formulations were calculated using mean square error, obtained in ANOVA, for ln-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ data. 90% confidence intervals for the geometric least squares mean ratio were obtained by taking the exponent of lower and upper limits of 90% confidence interval, obtained for the least square mean difference.

Results

Pharmacokinetic Results: Per the Applicant's CSR, "90% confidence interval for geometric least square mean ratio (T1/R) is within the bioequivalence range of 80.00% to 125.00% for primary pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$."

Safety Results: There were no deaths or serious adverse events (SAEs) during the conduct of this study. There were 3 AEs involving 3 subjects.

One AE occurred in one subject during the post-study assessment (72 hours post-dose) after most recently receiving T2. This consisted of bilirubin conjugated increased (asymptomatic), specifically a high total bilirubin of 2.1 mg/dL (normal range 0-1.3 mg/dL) which was graded as "mild." Review of the listings of laboratory results, as displayed below, showed that conjugated bilirubin was also high at 0.66 (normal range 0-0.3) and unconjugated bilirubin was high at 1.44 (0-1.00). Post-study liver transaminases, complete blood count, creatinine, and urea were normal. No other post-study laboratory tests were performed.

Laboratory test	Screening	Post-study
Total bilirubin	0.3 (0-1.3 mg/dL)	2.1 (0-1.3 mg/dL)
Conjugated bilirubin	0.2 (0-0.3 mg/dL)	0.66 (0-0.3 mg/dL)
Unconjugated bilirubin	0.1 (0-1.00 mg/dL)	1.44 (0-1.00 mg/dL)
SGOT	35 (0-37 U/L)	25 (0-37 U/L)
SGPT	60 (0-63 U/L)	36 (0-36 U/L)
Alkaline phosphatase	115 (46-116 U/L)	Not performed
Albumin	4.0 (3.4-5 g/dL)	Not performed

His screening labs were normal, including a normal total bilirubin (0.3) and normal liver transaminases. At screening, anti-hepatitis C antibodies were nonreactive, hepatitis B surface antigen was nonreactive, and human immunodeficiency virus testing was nonreactive; also

normal at screening were complete blood count, creatinine, urea, cholesterol, uric acid, C-reactive protein, lactate dehydrogenase, and urinalysis. Follow-up information is not available, including repeat labs. The subject was considered as lost to follow-up after reportedly repeat phone calls and requests to return to the facility did not result in the subject's return. This was recorded as a protocol deviation.

Two AEs occurred in two subjects who most recently received the Reference product. One AE of asymptomatic "shortened QT" occurred in the post-study assessment and was graded "mild." Review of the listing of this subject's individual ECG measurements showed the following:

	Screening	Admission for study periods	2 hours post-dose	14 hours post-dose	Post-study (72 hours post-dose)
QTc (msec)	385	390-400	374-395	386-401	380, 378 (on repeat)
QT (msec)	328	326-334	354-368	362-370	298, 322 (on repeat)
Heart rate (bpm)	83	82-91	64-71	67-73	98, 83 (on repeat)

Therefore, although the QT interval was reported as 298 msec at the post-study assessment, the QT corrected for heart rate (QTc) was 380, within the accepted normal range. All QTc measurements in this subject were within the accepted normal range.

The other AE which occurred in a subject who most recently received the Reference product was skin abrasion (right cheek), which occurred after the subject completed Periods 1, 2, and 3 and before the subject received study drug during Period 4. The abrasion was recognized after the washout period, on examination at admission for Period 4. Although the PI determined this AE to not be related to the study drug, this subject was withdrawn.

Reviewer comment: After further review of the submitted data on the subject who was reported to have an AE of shortened QT, it appears that the QTc interval was within the considered normal range. There is no information to suggest that the abrasion in another subject was related to study drug administration. Elevated bilirubin has not been noted with Vimpat and is not included in the approved label; however, the currently approved Vimpat labeling discusses abnormalities in liver function tests in the context of potential hypersensitivity and notes that patients should be instructed to report signs and symptoms of liver toxicity such as fatigue, jaundice, and dark urine, which encompasses signs and symptoms of hyperbilirubinemia. A healthy volunteer in this study had new asymptomatic conjugated hyperbilirubinemia (including elevated unconjugated bilirubin) with normal transaminases on testing at end-of-study, after having received three single doses of LCM XR and two doses of Vimpat separated by 12 hours, with washout periods of 5 to 9 days between study periods/dose administration. An adverse reaction of hyperbilirubinemia in this context would be idiosyncratic, i.e., not in the context of a constant, steady-state exposure. However, the differential diagnosis of asymptomatic conjugated and unconjugated hyperbilirubinemia Without a clear pathogenic mechanism or further information about the course of this subject, the relationship of this event to LCM XR is

unclear, and inclusion in labeling or monitoring beyond routine pharmacovigilance is not warranted.

STUDY 20-VIN-0095 "An open label, balanced, randomized, multiple-dose, two-treatment, two-sequence, two-period, oral comparative bioavailability study of Lacosamide 200mg extended-release capsule of Aucta Pharmaceuticals, Inc., USA and VIMPAT® (Lacosamide) 200mg film coated tablet of UCB, Inc. Smyrna, GA 30080 in healthy, adult, human subjects at a dose of 400 mg under fasting condition"

Study Center
Veeda Clinical Research Pvt. Ltd., Gujarat, India

Study Periods
Clinical Phase: 11 May 2021 to 06 Jun 2021
Bioanalytical Phase: 04 June 2021 to 16 Jun 2021

Study Objectives
The primary objective of this study was to compare the extent of absorption ($AUC_{0-t,ss}$) of the test formulation (two capsules of lacosamide 200mg extended-release capsule; T) and the reference formulation (one tablet of VIMPAT® 200 mg film coated tablet BID with a 12 hour dosing interval; R) under fasting condition. The secondary objectives were to compare the rate of absorption ($C_{min,ss}$ and $C_{max,ss}$) of T and R under fasting condition and to monitor safety and tolerability.

Methodology
This study was an open label, balanced, randomized, two-treatment, two-sequence, two-period, oral comparative bioavailability study.

Subjects were randomized to one of two treatment sequences, with two treatment periods lasting 7 days each. The washout period between the last dose of Period 1 and the first dose of Period 2 was 11 days. Subjects were confined at the study site from at least 10 hours before dosing (to ensure fasting) to 24 hours after the morning dose of T and up to 12 hours after the evening dose or R of Day 7 of each period. Subjects fasted overnight for at least 10 hours before morning doses and for at least 2 hours before the evening dose of R. Blood for PK evaluation was drawn pre-dose on Day 1, pre-dose on Days 5, 6, and 7, and at timepoints specified in the protocol post-dose on Day 7 between 1 and 24 hours for T and between 0.25 and 24 hours for R. Post-study assessment at the end of Period 2 consisted of ECG, AE monitoring, and blood sample for biochemistry and hematology.

Number of Subjects (Planned and Analyzed)
A total of 35 subjects were enrolled in the study. Four subjects withdrew consent before dosing in Period 1; one subject withdrew consent after receiving one dose during Period 1; one subject

withdrew consent after dosing through the evening of Day 2; and two subjects had a positive drug of abuse test at the time of admission for Period 2. Therefore, 31 subjects were dosed in Period 1 and 27 subjects were dosed in period 2. The 27 subjects who completed the study were included in the PK analysis. Thirty-one subjects were included in the safety population.

Demographics

Per the clinical study report, the mean (± standard deviation [SD]) age of the 31 subjects who received at least one dose of study drug was 31.19 (± 7.43) years, with a range of 20 to 44 years (median 32 years). All subjects were male and Asian. Mean (± SD) BMI was 22.61 (±2.48) kg/m^2, with a range of 18.8 to 27.18 kg/m^2 (median 22.86 kg/m^2).

Main Criteria for Inclusion

Subjects were judged by the principal investigator to be normal, healthy males between 18 and 45 years with a body weight of at least 45 kg who met all inclusion criteria and no exclusion criteria.

Study Treatments

Test product (T) was lacosamide 200 mg extended-release capsules, manufactured by Catalent Pharma solution for Aucta Pharmaceuticals.

Reference product (R) was Vimpat 200 mg tablets, manufactured for UCB.

Duration of Treatment

Total duration was 27 days from the day of admission of Period 1 to the end of Period 2.

Criteria for Evaluation

Pharmacokinetics: From the time/concentration values of lacosamide, various pharmacokinetic parameters $C_{max,ss}$, $C_{min,ss}$, $AUC_{0-\tau,ss}$, $T_{max,ss}$, $C_{avg,ss}$, Percent Fluctuation and % Swing were calculated using plasma concentration versus actual time of Day 07 using Phoenix WinNonlin software version 8.2. The primary pharmacokinetic variable was $AUC_{0-\tau,ss}$ with which the bioequivalence of the formulations was assessed.

Safety: Safety endpoints included clinical examination including sitting blood pressure, body temperature, radial pulse rate, and respiratory rate; sitting blood pressure and radial pulse rate on Days 1 to 7 pre-dose and at times specified in the protocol between 1 hour and 13 hours after morning T dose and between 1 hour and 15 hours after morning R dose; ECG at 2 and 14 hours post-dose and post-study; assessment of depression and suicidality; hematological labs (white blood cell count, differential, hemoglobin, and platelet count) and biochemical labs (liver function tests, bilirubin, creatinine, and urea) on admission of Period 2 and at the end of study.

Statistical Methods

Pharmacokinetic: Descriptive statistics (number of observations [N], mean, standard deviation [SD], minimum, median, maximum, percentage co-efficient of variation (%CV), and geometric mean) were calculated for each time point and pharmacokinetic parameter for T and R. ANOVA, least squares means of T and R, their ratios (T/R), intra-subject variability, power, 90% confidence intervals for the geometric least squares mean ratios (T/R) and Two One-Sided Tests for the 90% confidence interval limits were performed for the pharmacokinetic parameters $AUC_{0\text{-}t,ss}$, $C_{max,ss}$ and $C_{min,ss}$.

Results

Pharmacokinetic Results: Per the Applicant's CSR, "the Test Product (T) (Lacosamide 200mg extended-release capsule of Aucta Pharmaceuticals, Inc., USA) when compared with the Reference Product (R) (VIMPAT® (Lacosamide) 200mg film coated tablet of UCB, Inc. Smyrna, GA 30080) meets the bioequivalence criteria in terms of extent of absorption after administration of multiple dose at steady state condition as set in the protocol." The Applicant noted that a partial AUC analysis comparing the two products at multiple time points at steady state demonstrated 90% confidence intervals which fell within the 80-125% standard for bioequivalence at most time points except for those before 4 hours.

Per the Applicant's report, peak concentrations occurred later for a single dose of LCM XR (T_{max} of 7 hours) than the IR treatment (T_{max} of 2 hours). The arithmetic mean terminal $t_{½}$ value was longer for LCM XR ($t_{½}$ of 16 hours) than the IR treatment ($t_{½}$ of 13 hours). Steady state was achieved after 4 days with LCM ER (compared to after 3 days of twice daily administration of the IR formulation).

Safety Results: There were no deaths, SAEs, or study withdrawal due to AE during the conduct of this study. There were six AEs involving six subjects; three AEs occurred in three subjects after administration of T (3/29 = 10.3%) and three AEs occurred in three subjects after administration of R (3/29 = 10.3%).

Table 3: Adverse events during multiple-dose comparative oral bioavailability study based on product received

Adverse event	During Test* product	During Reference+	Total
Pruritis	2	1	3
Heart rate increased	0	1	1
Heart rate decreased	1	0	1
Dizziness	0	1	1

* Test = two capsules of lacosamide 200mg extended-release capsule
+ Reference = one tablet of VIMPAT® 200 mg film coated tablet every 12 hours (BID)
Source: ADAE dataset

All three subjects who had pruritis received cetirizine as treatment. Time from dose administration to onset of pruritis was 8 hours 46 minutes and 8 hours 43 minutes in the two

subjects who had pruritis after Test product and was 8 hours 30 minutes in the subject who had pruritis after Reference product.

Elevated heart rate of 105 beats per minute (bpm) was noted on ECG at 14 hours post-dose (2 hours 12 minutes after administration of Reference product); repeat ECG showed heart rate of 94 bpm. Review of this subject's listings of individual ECG measurements shows that the 14-hour (evening) post-dose heart rate tended to be 20 bpm higher than at 2 hours post-dose. Although the measurement of 105 bpm was >30 points higher than the 2-hour post-dose heart rate (72 bpm), the other 14-hour values often ranged 85-93 bpm, while the 2-hour values ranged 65-79 bpm.

Decreased heart rate of 43 bpm occurred 1 hour 42 minutes after administration of Test product on the first day of Period 1; repeat ECG showed a heart rate of 53 bpm. Review of this subject's listings of individual ECG measurements shows that the subject's heart rate tended to be low, ranging between 45-59 bpm, typically lower at the 2-hour post-dose (morning) time.

Dizziness occurred 8 hours 5 minutes after administration of Reference product.

Reviewer comment: Itching occurred in three of the 31 (9.7%) subjects in this study, making it a common AE in this study. The time between dose administration to onset of itching was similar between Test and Reference product, which would suggest that if caused by LCM, the itching would not be related to Tmax. Itching due to a hypersensitivity-type reaction could be plausible. Pruritis has not been noted with the LD, Vimpat, but rash and hypersensitivity are noted in the Warnings and Precautions section and urticaria is noted in the Postmarketing Experience section of the approved label for Vimpat. At this time, I believe this to be sufficient.

The concern for cardiac conduction abnormalities with LCM is greatest with rapid elevation of exposure. The cases of elevated and decreased heart rate occurred within approximately the first two hours after administration of the Reference and Test products, respectively. This timeframe could be suggestive of an AE which is associated with the T_{max} of the Reference product (immediate-release LCM; Vimpat) but is earlier than expected for the T_{max} of the Test product (reported to be 7 hours by the Applicant based on this study's data). Review of the listings of the ECG individual measurements over the course of the study suggests that the heart rate measurements are more associated with the individual subject's physiological tendencies, rather than with an adverse reaction (AR) to LCM. Regardless, bradycardia and tachyarrhythmia are included in the currently approved label for Vimpat. Dizziness is also a known and common AR to LCM which is included in the currently approved label.

STUDY 21-VIN-0184 "An open label, balanced, randomized, single dose, three-treatment condition, three-sequence, three-period, crossover oral bioavailability study of Lacosamide

Study Center
Veeda Clinical Research Pvt. Ltd., Gujarat, India

Study Period
Clinical Phase: January 26, 2022, to February 15, 2022
Date of last completed: February 21, 2022, to March 4, 2022

Study Objectives
To evaluate bioavailability of one lacosamide 200 mg extended-release capsule (T_{fa}, T_{fe} & $T_{Sprinkle}$) in healthy, adult, human subjects under fasting, fed, and fasting sprinkle conditions and to monitor the safety and tolerability of the subjects.

Methodology
This was a single-dose, randomized, open-label, three-treatment, three-sequence, three-period crossover oral bioavailability study under fasting (10 hours overnight), fed (30 minutes after the start of a high-fat high-calorie breakfast), and fasting sprinkle (entire contents of a capsule sprinkled over 15 grams of applesauce) condition. One LCM ER 200 mg capsule was administered.

Subjects were randomized to one of three treatment sequences. Washout periods were 8 days between Period 1 and Period 2 and 8 days between Period 2 and Period 3. Subjects were confined at the study site from at least 10 hours before dosing (to ensure fasting) to 48 hours post-dose. Blood for PK evaluation was drawn before dosing and at times specified in the protocol up to 48 hours after dosing. Subjects returned to the study site for end-of-study assessment at 72 hours post-dose, which consisted of clinical examination, ECG, assessment of depression and suicidality, AE monitoring, and blood sample for biochemistry and hematology.

Number of Subjects (Planned and Analyzed)
Eighteen subjects were enrolled in the study, and 18 subjects completed the study. A single subject did not report to the facility during Period 2 but reported during Period 1 and Period 3 (and received $T_{sprinkle}$ and T_{fa} but not T_{fe}). Eighteen subjects were included for PK analysis and in the safety population, but 17 subjects were included in the T_{fe} vs T_{fa} statistical analysis and 18 subjects were considered for $T_{Sprinkle}$ vs T_{fa} stat analysis.

Demographics
Per the clinical study report, the mean (± standard deviation [SD]) age of the 18 subjects was 29.22 (± 5.97) years, with a range of 20 to 41 years (median 29 years). All subjects were male and Asian. Mean (± SD) BMI was 22.3 (±2.5) kg/m^2, with a range of 18.85 to 26.13 kg/m^2 (median 22.57 kg/m^2).

Main Criteria for Inclusion
Subjects were judged by the principal investigator to be normal, healthy males between 18 and 45 years with a body weight of at least 45 kg who met all inclusion criteria and no exclusion criteria.

Study Treatment(s)
Lacosamide 200 mg extended-release capsules.

Duration of Treatment
Total duration of the study was 21 days from the day of admission of Period 1 until the end of the study.

Criteria for Evaluation
Pharmacokinetics: Serial blood samples were obtained for the determination of primary variables C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and secondary variables T_{max}, $t_{1/2}$, K_{el}, R^2_adjusted, and AUC_%Extrap_obs.

Safety: Safety endpoints included clinical examination including sitting blood pressure, body temperature, radial pulse rate, and respiratory rate; sitting blood pressure and radial pulse rate pre-dose and at times specified in the protocol between 1 hour and 37 hours after dosing in each study period; ECG at 2 and 14 hours post-dose, on the day of admission of Period 2 and Period 3, and end of study; assessment of depression and suicidality; hematological labs (white blood cell count, differential, hemoglobin, and platelet count) and biochemical labs (liver function tests, bilirubin, creatinine, and urea) on admission of Period 2 and at the end of study.

Statistical Methods
Pharmacokinetics: Descriptive statistics (number of observations [N], mean, standard deviation [SD], minimum, median, maximum, percentage co-efficient of variation (%CV), and geometric mean) were calculated for each time point and pharmacokinetic parameter. ANOVA, least square means for investigational formulation (T_{fa} vs. T_{fe} and T_{fa} vs. $T_{Sprinkle}$), difference between investigational formulation under different condition (T_{fa} vs. T_{fe} and T_{fa} vs. $T_{Sprinkle}$), intra-subject variability and power was calculated for lntransformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} for lacosamide. Geometric least square means of investigational formulation (T_{fa}, T_{fe} & $T_{Sprinkle}$ vs. T_{fe} and T_{fa} vs. $T_{sprinkle}$), 90% confidence interval for geometric least square mean ratio and Two One-Sided Tests for 90% confidence interval limits were calculated for pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} for lacosamide.

Results
Pharmacokinetic Results: Per the Applicant's Summary of Clinical Pharmacology, "Coadministration of Lacosamide XR with a high fat meal has no effect on the overall exposure of Lacosamide. Lacosamide XR capsules can be taken with or without meals."

Safety Results: There were no deaths or SAEs during the conduct of this study. One subject had increased ventricular rate on admission of Period 2, after having received the single dose of the product under fed condition 7 days previously. Review of the listing of this subject's individual ECG measurements and vital sign measurements shows heart rate as follows:

Heart rate (beats per minute) based on ECG

Screening	Period 1		Period 2			Period 3		
	2 hours	14 hours	Admission	2 hours	14 hours	Admission	2 hours	14 hours
89	84	97	102, 98 on repeat	79	95	96	74	94

Heart rate (beats per minute) based on vital sign measurements

	Period 1	Period 2	Period 3
Pre-admission	68	78	86
Pre-dose	66	68	76
Post-dose			
1 hour	74	64	70
3 hours	72	68	62
6 hours	64	72	64
11 hours	74	68	72
13 hours	74	76	68
15 hours	62	64	72
25 hours	66	74	64
37 hours	70	72	70
Before discharge	64	70	70
End of study			96

Reviewer comment: This subject had an AE of "increased ventricular rate" based on measurement on ECG of 102 bpm, consistent on repeat ECG, at approximately 7 days after having received the most recent dose and at a time that exposure levels would have been expected to be negligible. The subject's heart rate measurements by ECG appear to consistently be higher at 14 hours post-dose when compared to heart rate measurements on ECG at 2 hours post-dose and when compared to heart rate based on vital sign measurements at a similar timepoint and throughout testing. Based on the information available, it cannot be determined whether a factor such as anxiety may have contributed to the higher heart rates, but the pattern does not appear to be suggestive of an association with the study product.

Study 22-VIN-0340 "An open label, balanced, randomized, five-treatment, five-sequence, five -period cross-over, single-dose, proportionality/linearity and comparative bioavailability study of Lacosamide Extended-Release Capsule 100 mg (Test T1), Lacosamide Extended-Release Capsule 200 mg (Test T2), Lacosamide Extended-Release Capsule 300 mg (Test T3)

Lacosamide Extended-Release Capsule 400 mg (Test T4) of Aucta Pharmaceuticals, Inc, USA with that of Vimpat® 200mg Film coated tablet (Reference R) of UCB, Inc. Smyrna, GA 30080 in 25 Normal healthy, adult, human subjects under fasting conditions"

Study Center
Veeda Clinical Research Pvt. Ltd., Gujarat, India

Study Period
Clinical phase: January 9, 2023, to February 18, 2023

Study Objectives
Primary:
• To demonstrate the comparative bioavailability between lacosamide extended-release capsule 400 mg (2x 200 mg capsule) (T4), with that of Vimpat® 200mg BID with 12 hours dosing interval under fasting conditions.

Secondary:
• Proportionality/linearity assessment of lacosamide extended-release capsule 100 mg (T1), 200 mg (T2), 300 mg (T3), and 400 mg (T4) under fasting conditions.
• To monitor safety and tolerability.

Methodology
This study was an open label, balanced, randomized, single-dose, five-treatment, five-sequence, five-period, proportionality/linearity and comparative bioavailability study, under fasting conditions.

Subjects were randomized to one of five treatment sequences, with five treatment periods involving administration of a single treatment dose or reference dose (which consisted of two Vimpat 200 mg tablets separated by 12 hours). Subjects were confined at the study site from at least 10 hours before dosing (to ensure fasting) to 72 hours post-dose in each study period. The washout period between Periods 1 and 2 was 10 days; between Periods 2 and 3 was 9 days; between Periods 3 and 4 was 9 days; and between Periods 4 and 5 was 8 days. Blood for PK evaluation was drawn pre-dose and at timepoints specified in the protocol post-dose on Day 7 between 1 and 72 hours for T and between 0.25 and 72 hours for R. Post-study assessment consisted of ECG, AE monitoring, and blood sample for biochemistry and hematology.

Number of Subjects (Planned and Analyzed)
A total of 25 subjects were enrolled in the study, and 20 subjects completed at least two periods with administration of T4 and R. Twenty-five subjects received study drug during Period 1; 22 subjects received study drug during Period 2; and 21 subjects received study drug during Periods 3, 4, and 5. Therefore, 25 subjects were included in the safety population and 20 subjects were included in the PK analysis.

One subject withdrew from the study after having had an AE after dosing during Period 1. Another subject withdrew from the study after having had an AE after dosing during Period 5. Other subjects withdrew consent (1), did not report to the facility for admission for a single period (4), or were withdrawn due to "misbehavior" (1).

Demographics

Per the clinical study report, the mean (± standard deviation [SD]) age of the 25 subjects in the safety population was 34.6 (± 6.75) years, with a range of 21 to 44 years (median 37 years). All subjects were male and Asian. Mean (± SD) BMI was 23.48 (±2.25) kg/m^2, with a range of 19.67 to 27.8 kg/m^2 (median 23.39 kg/m^2).

These characteristics were similar in the population of 20 patients who completed the study and were included in the PK analysis.

Main Criteria for Inclusion

Subjects were judged by the principal investigator to be normal, healthy males between 18 and 45 years with a body weight of at least 45 kg who met all inclusion criteria and no exclusion criteria.

Study Treatment

Test Product (T1): Lacosamide Extended-Release Capsules 100 mg (one capsule)
Test Product (T2): Lacosamide Extended-Release Capsules 200 mg (one capsule)
Test Product (T3): Lacosamide Extended-Release Capsules 150 mg (two capsules)
Test Product (T4): Lacosamide Extended-Release Capsules 200 mg (two capsules)
Reference product (R): VIMPAT® tablet 200 mg (one tablet BID with 12 hours dosing interval)

Duration of Treatment

Total duration of the study was 41 days from the day of admission of Period 1 until the end of the study.

Criteria for Evaluation

Pharmacokinetics: Post-dose blood samples were drawn for PK for Test products (T1, T2, T3, T4) between 1 hour and 72 hours post-dose and for Reference product between 0.25- and 72-hours post-dose. From the time/concentration values, C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{½}$, K_{el}, and AUC_%Extrap_obs were calculated for lacosamide. $C_{max\ D}$, $AUC_{0-t\ D}$ and $AUC_{0-inf\ D}$ were also calculated for Test products (T1, T2, T3 and T4). C_{max}, AUC_{0-t} and AUC_{0-inf} were used in the statistical analysis for to compare the relative bioavailability of the two products. C_{max}, $AUC_{0-t,}$ and AUC_{0-inf} for were estimated to evaluate bioavailability. Dose proportionality was declared if values of β and its 90 % CI lay completely within the acceptance region. Lack of proportionality/linearity was concluded if the calculated 90% CI lay completely outside the acceptance region.

Safety: Safety endpoints included clinical examination including sitting blood pressure, body temperature, radial pulse rate, and respiratory rate on admission day and before discharge in each study period; supine/sitting blood pressure and radial pulse rate pre-dose and at times specified in the protocol between 1 hour and 60 hours after morning dosing in each study period; ECG at 4 and 16 hours post-morning dose, on the day of admission of Periods 2, 3, 4, and 5, and end of study; assessment of depression and suicidality on the day of admission and before discharge in each period; hematological labs (white blood cell count, differential, hemoglobin, and platelet count) and biochemical labs (liver function tests, bilirubin, creatinine, and urea) at the end of study.

Statistical Methods

Pharmacokinetics: ANOVA, least square means for test (T4) and reference (R) formulation, difference between test (T4) and reference (R) formulation, intra-subject variability and power was calculated for lntransformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}.

Results

Pharmacokinetic Results: Per the study report, "The 90 % Confidence interval of slope for $C_{max/D}$, $AUC_{0-t/D}$ and $AUC_{0-inf/D}$ of lacosemide is within the acceptance range of 0.8390-1.1610 with calculated slope of 0.9958, 1.0033 and 1.0017, respectively. Based on calculated slope and 90 % Confidence interval of slope, $C_{max/D}$, $AUC_{0-t/D}$ and $AUC_{0-inf/D}$ of baseline corrected lacosemide are increasing in dose proportional manner after single-dose administration in dose range of 100 mg to 400 mg. Hence, dose proportionality was observed with respect to $C_{max/D}$, $AUC_{0-t/D}$ and $AUC_{0-inf/D}$ for Lacosemide."

Safety Results: There were no deaths or SAEs in this study. Two AEs were reported. One event (in one of 22 subjects [4.55%]) occurred approximately 5 hours after administration of T4 and consisted of vomiting without other complaints. The subject was subsequently withdrawn, so samples were not collected between 6- and 72-hours post-dose. The other event (in one of 22 subjects [4.55%]) occurred 26 hours after administration of R and consisted of gastroenteritis, described as two episodes of vomiting and one episode of loose bowel movement.

> *Reviewer comment: Although the event of vomiting occurred 5 hours after the highest tested dose of LCM XR (400 mg) was administered, which is somewhat close to the reported T_{max} found in Study 0095, no associated exposure levels were available because the subject was withdrawn and blood samples were not collected; definite conclusion of causality cannot be made. Regardless, nausea and vomiting are noted to be common ARs in the currently approved Vimpat label. The event of vomiting and loose stools in the other subject occurred at an interval after dose administration which was long-enough to suggest lack of association.*

6. Review of Relevant Individual Trials Used to Support Efficacy

This NDA was submitted via the 505(b)(2) registration pathway. No clinical efficacy studies were conducted with Motpoly XR. This 505(b)(2) application, supported by PK bridging studies, therefore, relies entirely on the findings of clinical efficacy reported for Vimpat tablets under NDA 22253.

7. Integrated Review of Effectiveness

Not applicable (as discussed above).

7.1. Additional Efficacy Considerations

7.1.1. Considerations on Benefit in the Postmarket Setting

This 505(b)(2) application provides no efficacy data and instead relies on the equivalence of Motpoly XR to Vimpat, the LD, to support a claim of effectiveness. This claim of equivalence appears justified based on the pharmacokinetic data submitted in support of this NDA. However, it remains possible that in a future review of clinical experience that Motpoly XR may demonstrate different efficacy than that of the LD. Reports of lack of effectiveness, increased seizures, or status epilepticus that appear to be more frequent than those reported with the LD should be noted and evaluated further to ascertain whether there are clinically relevant differences in the clinical outcomes of treatment with Motpoly XR compared to Vimpat.

7.1.2. Other Relevant Benefits

Potential benefits of Motpoly XR are improved compliance and decrease in adverse events (AEs).

7.2. Integrated Assessment of Effectiveness

The efficacy of Motpoly XR is expected to be equivalent to that of the LD, Vimpat.

8. Review of Safety

8.1. Safety Review Approach

The Applicant did not conduct Phase 3 studies to support safety, and thus the clinical safety database from the four PK studies conducted by the Applicant are the primary and only sources

of novel data for the clinical safety review. As this is a 505(b)(2) application, the safety conclusions ultimately rely on the safety findings in the LD application. This Applicant performed safety analysis of the data from each of the four PK studies individually but did not provide an integrated summary of safety based on pooling of the data. Therefore, this reviewer combined the safety datasets to perform an independent integrated safety analysis. The tabular listings of raw data including vital signs and ECG measurements were reviewed to better understand clinical context and confirm the classification of AEs.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety Population Exposure

The Applicant defined the Safety Population as all subjects who received a dose of test (Motpoly XR) or reference (Vimpat) product.

Table 4: Reviewer Table, Safety Population, Size and Denominators (all healthy adult males) *

Clinical study	LCM XR (N=96)	Vimpat (N=75)
Study 20-VIN-0088 (three formulations of LCM XR)	24	24
Study 20-VIN-0095 (single LCM XR formulation)	29	29
Study 21-VIN-0184 (single LCM XR formulation fasting, fed, sprinkled)	18	0
Study 22-VIN-0340 (proportionality study)	25	22

Source: reviewer analysis of joined ADSL datasets from all studies
* A subject could have received both LCM XR and Vimpat within the same study. Separate exposures for a single subject are considered independent observations.

Table 5: Reviewer Table, Duration of Exposure to LCM XR

	Number of subjects* exposed to the study drug:	
Dosage	1 dose	7 days
LCM XR 100 mg	N=23	N=0
LCM XR 200 mg	N=40	N=0
LCM XR 300 mg	N=21	N=0
LCM XR 400 mg	N=46	N=29

Source: reviewer analysis of joined ADSL datasets from all studies
* Not all unique subjects. Separate exposures for a single subject are considered independent observations.

Reviewer Comment: The submitted patient exposure numbers do not meet the International Conference on Harmonization (ICH) guidelines for chronically administered medications (i.e.,

n=100 for 1 year). However, this NDA is submitted as a 505(b)(2) application and derives its safety findings from the LD, Vimpat, and as such, the failure to meet ICH guideline criteria is not an issue of review because the studies submitted to support approval of the LD did satisfy the ICH criteria.

8.2.2. Relevant characteristics of the safety population:

The Applicant performed Phase 1 studies in a population of individuals with no significant health issues. The demographic characteristics of the population exposed to Motpoly XR and to the LD, Vimpat, in these studies were homogenous; specifically, the subjects were all Asian and male.

Reviewer Comment: As a 505(b)(2) study, the safety data rely on the safety findings in the approved application for the LD. The population used in the studies which were submitted to support the pharmacological bridging is healthy, young (age range 20 to 44 years), Asian males. Therefore, the data is not as informative as those derived from a study population of subjects with epilepsy on concomitant antiseizure medications (ASMs). However, there is a reasonable expectation that the safety for Motpoly XR will not differ significantly from that of the LD when used in the intended population, and no obvious safety signal emerged in the population evaluated in the studies submitted with this NDA.

8.2.3. Adequacy of the safety database:

The adequacy of the safety database for Motpoly XR is not relevant because this application relies on the previously accepted safety database for the LD, Vimpat.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The application was of sufficient quality to be reviewed.

8.3.2. Categorization of Adverse Events

The Applicant mapped AEs to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 for Study 20-VIN-0088, version 24.1 for Study 20-VIN-0184, and version 25 for Study 22-VIN-0340 by preferred term (PT) and system organ classification (SOC).

For the PT, "bilirubin conjugated increased," this reviewer recoded the associated SOC from "investigations" to "gastrointestinal disorders" to reflect the potential etiology. Similarly, for the PT "electrocardiogram QT shortened," this reviewer recoded the associated SOC from "investigations" to "cardiac disorders" and the SOC for "heart rate increased" from "investigations" to "cardiac disorders."

For the one AE reported in Study 21-VIN-0184, the verbatim term in the AE dataset was "asymthometic increased ventricural rate," and the PT in the AE dataset was "left ventricular end-diastolic pressure increased." This reviewer recoded the PT to "heart rate increased" for accuracy. The verbatim term, "gastroenteritis" in Study 22-VIN-0340 was coded as PT "loose motion." This reviewer recoded it to "gastroenteritis" for precision and accuracy.

8.3.3. Routine Clinical Tests

Standard clinical laboratory profiles for hematology, serum chemistry, and urinalysis were evaluated for all subjects at screening and at timepoints described above within the discussions of each individual study. Urine for drugs of abuse and alcohol were also checked at admission for each study period.

8.3.4. Vital Signs

Vital signs (sitting blood pressure, body temperature, radial pulse rate, and respiratory rate) were captured during clinical examination as described above within the discussions of each individual study. Blood pressure and radial pulse rate were assessed at frequent timepoints pre-dose and post-dose as described above within the discussions of each individual study.

8.3.5. Electrocardiograms

Single 12-lead ECGs were performed at screening, at specified timepoints post-dose, at admission for each study period, and at end-of-study.

8.4. Safety Results

8.4.1. Deaths

There were no deaths reported in the studies included in this application.

8.4.2. Serious Adverse Events

There were no SAEs reported during the studies included in this application.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

One subject in Study 20-VIN-0088 was withdrawn from the study by the investigator due to a facial abrasion which did not appear to be related to the administration of study drug. Two subjects in Study 22-VIN-0340 were withdrawn; one after vomiting and one after vomiting and loose bowel movement which was documented as "gastroenteritis."

Reviewer Comment: The cases of facial abrasion and gastroenteritis are not likely to be

ARs from LCM. Nausea and vomiting are known to occur after administration of LCM, which is established on the approved labeling of the LD. Therefore, nausea and vomiting are expected AEs of Motpoly XR.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

In the four clinical pharmacology studies submitted in this application, conducted in healthy adult male volunteers, 12 total AEs (in 12 subjects) occurred as displayed in Table 6 below. Five subjects (5.2% of the 96 total subjects who received Vimpat) had an AE after most recently having received the LD, Vimpat; seven subjects (9.3% of the 75 total subjects who received LCM XR) had an AE after most recently having received Motpoly XR. Because there was adequate time between exposures to make carryover effects unlikely, separate exposures for a single subject are considered independent observations.

All reported AEs occurred only in a single subject except for pruritus which occurred in one subject who had most recently received Vimpat and in two subjects who had most recently received Motpoly XR.

Table 6: Adverse Events* by System Organ Class and Preferred Term, All Studies

System Organ Class	Preferred Term	Vimpat	LCM XR
CARDIAC DISORDERS	*BRADYCARDIA*	0	*1*
	ELECTROCARDIOGRAM QT SHORTENED	*1*	*0*
	HEART RATE INCREASED		
	fasting	1	0
	fed	*0*	*1*
GASTROINTESTINAL DISORDERS	BILIRUBIN CONJUGATED INCREASED	0	1
	GASTROENTERITIS	*1*	*0*
	VOMITING	0	1
NERVOUS SYSTEM DISORDERS	DIZZINESS	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	PRURITUS	1	2
	SKIN ABRASION	*0*	*1*
TOTAL		5	7

Sources: reviewer analysis of ADAE datasets from all studies
* Events which are italicized are those which, based on independent review by this reviewer, appear to not be an AE (electrocardiogram QT shortened) or is highly unlikely to be an adverse reaction to the treatment due to timing of the AE in relation to dose administration (bradycardia; heart rate increased, fed; gastroenteritis; skin abrasion)

Reviewer Comment: There are significant limitations to these safety findings. The sample size and number of AEs is small, making comparative analysis of AEs following LCM XR and the LD, Vimpat, not necessarily meaningful. In addition, as noted above, the healthy adult male subjects of these studies are not representative of the intended treatment population. These findings were captured after a single dose of LCM XR or a 7-day course; the intended

dosing regimen will be chronic daily administration over periods of months or years. Also, as discussed above within the discussion of the individual studies (Section 5.3 Discussion of Individual Studies/Clinical Trials), in many cases the likelihood of causality is low due to duration between the administered dose and onset of the AE or is difficult to determine due to lack of information. Nevertheless, some of the AEs (bradycardia, increased heart rate, vomiting, and dizziness) are known potential AEs which are discussed in the currently approved Vimpat labeling. Pruritus, which occurred in three subjects, making it the most common AE in this safety population, has not been noted with Vimpat; however, rash, hypersensitivity, and urticaria are noted in the approved label for Vimpat, which I believe would prompt prescribers to take note of a complaint of pruritus as a potential symptom of mild hypersensitivity associated with LCM exposure. Elevated bilirubin has not been noted with Vimpat, but abnormal liver function tests and signs of liver toxicity such as fatigue, jaundice, and dark urine are discussed in the approved label; the asymptomatic conjugated hyperbilirubinemia (including elevated unconjugated bilirubin) reported in this application was detected after multiple single exposures, each separated by 5 to 9 days, with most recent exposure having been 72 hours prior to blood draw. Without a clear pathogenic mechanism or further information including follow-up labs, the relationship of this event to LCM XR is unclear, and routine pharmacovigilance is sufficient at this time.

TEAE Severity

Most AEs (10/12; 83%) reported in these studies were designated as "mild." Those AEs which were designated as "moderate" severity included skin abrasion (recognized by the investigator 7 days after most recent dose administration of Vimpat) and gastroenteritis (occurring 26 hours after Vimpat).

Reviewer Comment: The limitations of the safety findings are as discussed above. Most of the documented AEs in these studies were characterized as mild; no higher severity (moderate) AEs were noted after Motpoly XR administration.

8.4.5. Laboratory Findings

The Applicant performed clinical laboratory tests at screening and after dosing. There were no serious or potentially life-threatening laboratory abnormalities noted in any of the studies included in this NDA.

8.4.6. Vital Signs

An analysis dataset relating to vital signs was not submitted.

Reviewer comment: This reviewer reviewed individual ECG and vital sign measurements as submitted in listing form, when related to reported AEs. This was felt to be adequate, considering the reliance of this application on bioequivalence to the LD, Vimpat, and the

extensive safety experience with Vimpat since its approval in 2008.

8.4.7. Electrocardiograms (ECGs)

See above Reviewer Comment above in Section 8.4.6 Vital Signs.

Reviewer Comment: As discussed within the discussions of the individual studies (5.3 Discussion of Individual Studies/Clinical Trials), the ECG finding of shortened QT did not appear to be accurate. Causality by Motpoly XR of the ECG finding of decreased heart rate cannot be ruled out; based on the subject-specific data, this is confounded by the subject's baseline low heart rate. Regardless, bradycardia is a known potential AE of LCM and is included in the currently approved label for Vimpat.

8.4.8. QT

Not applicable due to reliance on the LD, Vimpat.

8.4.9. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

Not applicable.

8.6. Safety Analyses by Demographic Subgroups

Reviewer Comment: No additional analyses were performed based on demographic subgroups because of the homogeneity of the study subjects (all healthy adult Asian males) and relatively small number of subject exposures.

8.7. Specific Safety Studies/Clinical Trials

Not applicable. As a 505(b)(2) pathway submission, this NDA derives its safety database support from the application for the LD, Vimpat.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric data were provided. However, in consultation with the Division of Pediatric and Maternal Health, this application is appropriate to provide pediatric labeling. The LD, Vimpat, is already approved for pediatric use 1 month to 17 years for the requested indication of POS. See Section 12 Postmarketing Requirements and Commitments for discussion of further pediatric development.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Motpoly XR is not currently marketed anywhere in the world; no postmarketing safety experience is available for review.

8.9.2. Expectations on Safety in the Postmarket Setting

The expectations regarding safety are that the safety profile of Motpoly XR will be identical to that of the LD, Vimpat. It is possible that the safety profile may be less than that of Vimpat, due to the lower C_{max} and less fluctuation of concentration levels.

8.9.3. Additional Safety Issues from Other Disciplines

No other safety issues were communicated at the time of submission of this review.

8.10. Integrated Assessment of Safety

Four studies were designed to establish the PK characteristics of Motpoly XR as compared to the LD, Vimpat, and included the following: a comparative bioavailability study of three different LCM ER formulations with Vimpat, a pivotal comparative bioavailability study of the chosen LCM ER formulation with Vimpat, a comparative bioavailability study of Motpoly XR in different feeding conditions (fasting, fed, sprinkled over applesauce), and a proportionality study of the different strength capsules of Motpoly XR. These studies were conducted in a population different than the intended population, specifically healthy adult (20 to 44 years) Asian males, were small with a relatively low number of exposures (three studies were single-

dose studies; Motpoly XR was administered for seven days in the pivotal study) and did not provide ample clinical details.

However, these studies did not raise concern for new or increased severity of AEs. After analysis, it is this reviewer's opinion that it is possible that AEs of bradycardia (seen in one subject but confounded by the subject's baseline low heart rate), pruritis, and vomiting were adverse reactions to Motpoly XR. These AEs are adequately addressed in the currently approved prescribing information of the LD, Vimpat. The case of isolated asymptomatic hyperbilirubinemia did not have adequate detail to make a determination of association with LCM XR and does not require labeling modification to encourage more than routine pharmacovigilance.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information have been made, but the labeling has not been finalized at the time of this review.

The labeling for Motpoly XR relies on the previous findings of efficacy and safety for the LD, Vimpat; therefore, the approved Vimpat label served as a template for the labeling of Motpoly XR. Notable recommended edits to the Applicant's proposed PI include:

- Addition of pediatric patients weighing at least 50 kg to the indication population, because the available capsule strengths can provide the necessary age-based dosing, and children who weigh at least 50 kg (which is 50th percentile for a 14-year-old) would be able to swallow the capsule formulation whole.
- Deletion of (b) (4)

(b) (4)

- Revision of dosage modifications for renal and hepatic impairment from the percentage of the original recommended dosage to the precise modified maximum dosage.
- Changes to align with the PI for the LD, Vimpat.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required for the safe use of Motpoly XR for the treatment of POS in adult and pediatric patients weighing at least 50 kg. There is no REMS needed for the safe use of the LD, Vimpat. There are no new identified safety issues with Motpoly XR where a REMS would be necessary to mitigate identified risks.

12. Postmarketing Requirements and Commitments

The FDA issued several postmarketing requirements (PMRs) for the LD, Vimpat, at the time of original approval in 2008, at the time of approval of expansion of the indication to include monotherapy treatment of POS and a loading dose in adults in 2014, and at the time of the new indication of adjunctive treatment of PGTCS in ages 4 and older in 2020. A PMR was issued in 2021 to ASMs in the sodium channel inhibitor class to conduct in vitro cardiac ion channel studies and to characterize the antiarrhythmic effects of the ASM. The LD's PMRs have been fulfilled or study reports have been submitted and are in the process of review.

The following is a PMR under the Pediatric Research Equity Act (PREA)for Motpoly XR:

Development and validation by adult bioavailability/bioequivalence study(ies) of appropriate pediatric formulation(s) of Motpoly XR (lacosamide extended-release) to be used in pediatric patients weighing less than 50 kg.

Draft Protocol Submission: 06/2024
Final Protocol Submission: 12/2024
Study Completion: 12/2025
Final Report Submission: 03/2026.

13. Appendices

13.1. References

See footnotes throughout review.

13.2. Financial Disclosure

The Applicant submitted Form 3454 pertaining to the investigators for the below studies.

Covered Clinical Study (Name and/or Number): 20-VIN-0095, 21-VIN-0184, 20-VIN-0088, 22-VIN-0340

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
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): 0		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
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) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

AMY KAO
05/03/2023 04:04:43 PM

PHILIP H SHERIDAN
05/03/2023 09:24:48 PM