A MULTICENTER, OPEN-LABEL, FOLLOW-UP STUDY TO ASSESS THE LONG-TERM USE OF ORAL LACOSAMIDE IN STUDY PARTICIPANTS WHO COMPLETED EP0034 OR SP848 AND RECEIVED LACOSAMIDE TREATMENT

PROTOCOL EP0151 AMENDMENT 1

PHASE 3B

SHORT TITLE:

Long-term use of oral lacosamide in pediatric study participants with epilepsy

Sponsor:
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Regulatory agency identifying numbers:

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Confidential Material

Confidential

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 1	12 Oct 2023	Nonsubstantial
Original Protocol	13 Apr 2020	Not applicable

Amendment 1 (12 Oct 2023)

Overall Rationale for the Amendment

The purpose of this nonsubstantial amendment is to add the European Union Clinical Trial number to the protocol.

Section # and name	Description of change	Brief rationale
Title page	EU CT Number 2022-502639-21-00 was added as a regulatory agency identifying number.	Included for clarity under the new EU Clinical Trials Regulation.

CT=Clinical Trial; EU=European Union

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A multicenter, open-label, follow-up study to assess the long-term use of oral lacosamide in study participants who completed EP0034 or SP848 and received lacosamide treatment

Short Title:

Long-term use of oral lacosamide in pediatric study participants with epilepsy

Rationale:

Epilepsy is the second most prevalent neurological disorder in the world, with more than 70 million people suffering from this disorder. Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy. More than 30% of patients have inadequate seizure control on currently available antiepileptic drugs (AEDs) or experience significant adverse drug effects; therefore, there is a need for AEDs with improved effectiveness and tolerability.

Lacosamide (LCM); (VIMPAT®; SPM 927 [or SPM 929 for neuropathic pain documents]; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, Anticonvulsant Drug Development [ADD] 234037) belongs to a novel class of functionalized amino acids. Lacosamide has proven to be an effective and safe adjunctive treatment for partial-onset seizures (POS), with or without secondary generalization, based on 3 double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in study participants with difficult-to-control POS. Lacosamide is being evaluated in pediatric study participants ≥1 month to <17 years of age with POS in completed and ongoing studies.

EP0151 is an open-label extension study designed to assess the long-term use of LCM (2mg/kg/day to 12mg/kg/day) in pediatric study participants <6 years of age with epilepsy who have completed EP0034 or SP848. EP0151 will allow study participants treated with LCM in EP0034 or SP848 to continue treatment with LCM until either the participant reaches 6 years of age or until marketing application approval is achieved for pediatric patients <4 years of age in the region of participation and LCM oral solution is available (whichever is earliest).

Objectives and Endpoints

Objective	Endpoints
Primary	
• To assess the long-term use of LCM oral solution dosed at 2mg/kg/day to 12mg/kg/day when administered to pediatric study participants with epilepsy who have completed EP0034 or SP848	• TEAEs reported by the study participant or caregiver or observed by the Investigator • Withdrawals from study due to TEAEs • Withdrawals from study due to SAEs • Modal daily dose (mg/kg/day) • Maximum daily dose (mg/kg/day)

LCM=lacosamide; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Overall Design

EP0151 is a multi-center, long-term, open-label, follow-up study to assess the long-term use of LCM oral solution (a formulation suitable for administration to children; also referred to as syrup) for pediatric study participants <6 years of age with epilepsy who have completed either EP0034 or SP848.

Study participants who complete EP0034 or SP848 will be offered participation in EP0151 and will have access to open-label follow-up treatment with LCM.

Lacosamide doses administered in EP0151 must be from 2mg/kg/day to 12mg/kg/day. During EP0151 study visits, Investigators will be allowed to increase or decrease the dose of LCM based on the Investigator's clinical judgement to optimize tolerability and seizure control for each study participant. The Investigator may maintain the study participant's LCM dose, decrease the dose in decrements of 2mg/kg/day per week to a minimum dose of LCM 2mg/kg/day, or increase the dose in increments of 2mg/kg/day per week up to a maximum dose of LCM 12mg/kg/day or 600mg/day, whichever is lower.

This study involves a Treatment Period of approximately up to 205 weeks, depending on the age of the study participant, and an End of Study Period of approximately 8 weeks (including a Taper Period and a Safety Follow-Up Period). Study participants who reach the end of the study and choose to continue treatment with LCM may be immediately prescribed LCM. The Termination Visit at the end of the Treatment Period will be the last study visit completed for study participants who continue treatment with prescribed LCM. Study participants who choose not to continue with LCM treatment and who are taking a dose of 3mg/kg/day or higher will enter an End of Study Period following completion of the Termination Visit or Early Termination Visit, and will gradually taper from LCM treatment during the Taper Period; a Final Visit will be conducted 30 days after the final dose of LCM.

In situations where provision of LCM oral solution in certain participants >6 years of age (eg, developmental delay, need for more precise dosing as afforded by oral solution formulation, etc.) who may need a longer period of treatment with LCM oral solution, the situation will be assessed for approval by UCB on a case-by-case basis following discussions with the participant's physician.

The end of the study is defined as the date of the last visit of the last study participant in the study.

Number of Participants

Approximately 80 to 100 study participants are estimated to be eligible for enrollment.

Treatment Groups and Duration

The maximum total duration of the study per study participant will be approximately 213 weeks, and will include:

- Treatment Period (up to approximately 205 weeks, depending upon the age of the study participant)
- End of Study Period (up to 8 weeks, consisting of a 4-week Taper Period and 30-day Safety Follow-Up Period).

Visit 1 for EP0151 will be the same as Visit 13 in EP0034 or SP848. Clinic visits will be scheduled approximately every 26 weeks relative to the EP0151 Visit 1 date. Dose modifications required for optimization of seizure control or tolerability issues will be addressed in Unscheduled Visits or regularly scheduled visits. A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits.

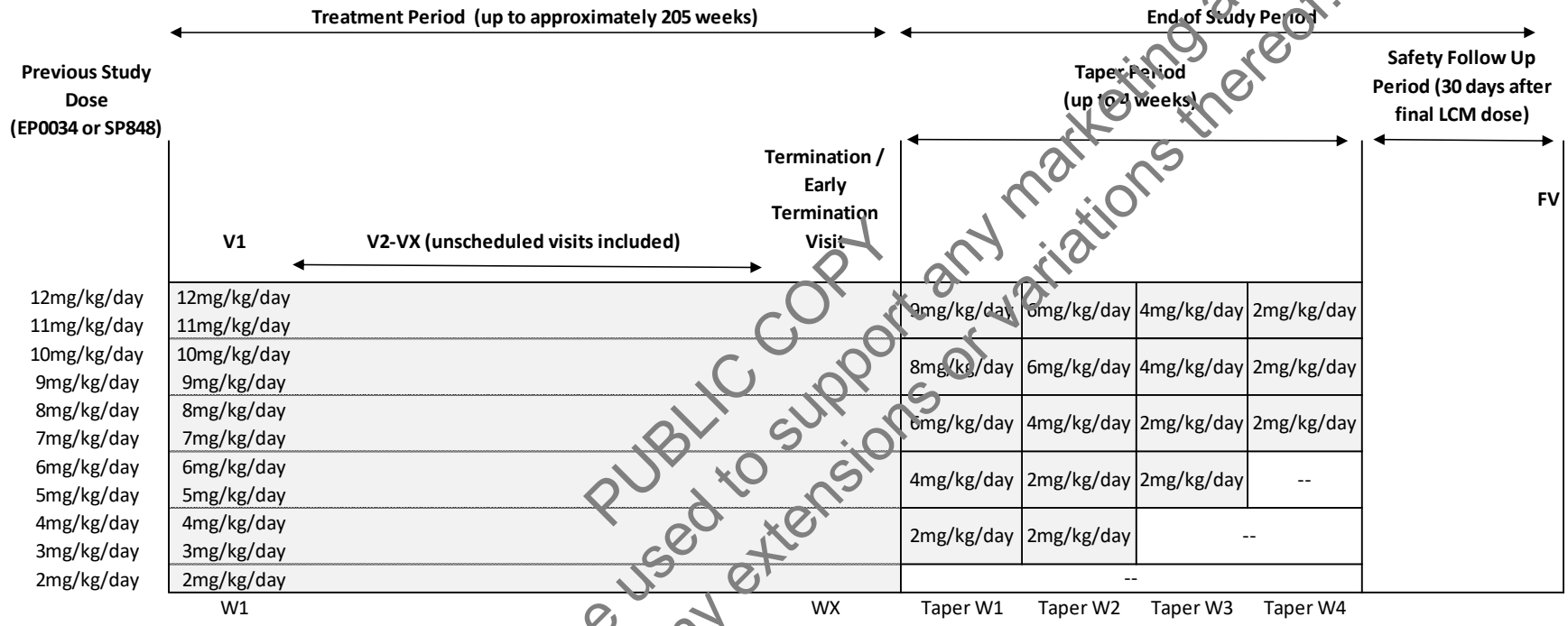
All study participants in EP0151 will receive LCM. The Investigator may maintain the study participant's LCM dose from previous studies EP0034 or SP848, decrease the dose in decrements of 2mg/kg/day per week to a minimum dose of LCM 2mg/kg/day, or increase the dose in increments of 2mg/kg/day per week up to a maximum dose of LCM 12mg/kg/day or 600mg/day, whichever is lower, administered twice per day (BID).

An interactive voice/web response system (IXRS) should be called any time there is a change in LCM dose.

1.2 Schema

A study schematic is presented in Figure 1-1.

Figure 1-1: Study schematic



FV=final visit; LCM=lacosamide; V=visit, W=week
Note: During EP0151 study visits, Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure control.
Note: A slower or faster taper is permitted, if medically necessary; however, the maximum duration of tapering should not exceed 6 weeks.

1.3 Schedule of Activities

A tabular scheme of study activities is presented in Table 1-1.

Table 1-1: Schedule of study activities

	Treatment Period[a]			End of Study Period	
	V1[b]	V2, V3…VX[c]	Termination Visit/Early Termination Visit[d]	Final Visit[e]	Unscheduled Visit[f]
Procedure	**W0**	**W26, W52…WX[g]**	**WX[h]**	**Final dose + 30 days**	**NA**
Informed consent	X				
Verification of inclusion/exclusion criteria	X				
Demography	X[i]				
Medical history update	X				
Concomitant AEDs	X	X	X	X	X
Concomitant non-AED medications	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X
Laboratory assessments[j]	X[k]	X	X	X	
Call IXRS	X	X	X[l]	X[l]	X[l]
Blood pressure and pulse rate[m]	X[k]	X	X	X	
Body weight and height	X[k]	X	X	X	
Dispense LCM	X	X	X[n]		
Review/return LCM		X	X	X	

Table 1-1: Schedule of study activities

	Treatment Period[a]			End of Study Period	
	V1[b]	V2, V3…VX[c]	Termination Visit/Early Termination Visit[d]	Final Visit[e]	Unscheduled Visit[f]
Procedure	W0	W26, W52…WX[g]	WX[h]	Final dose + 30 days	NA
C-SSRS[o]			X		X
Withdrawal criteria		X			
Adverse event review[p]	X	X	X	X	X

AE=Adverse Event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic Case Report Form; IXRS=Interactive Voice Response System; LCM=lacosamide; NA=Not applicable; V=Visit; W=Week

[a] A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits except for the Final Visit. A clinic visit will occur approximately every 26 weeks relative to the EP0151 Visit 1. If necessary, doses may be adjusted during scheduled or unscheduled visits.

[b] Visit 1 for EP0151 will be the same as Visit 13/Termination Visit of EP0034 or SP848. Prior to or at Visit 1 of EP0151, the study participant's informed consent will be signed and eligibility assessed, concomitant medications including AEDs will be recorded, AEs will be assessed, and LCM dispensed (call to IXRS).

[c] The total number of clinic visits will vary between individual study participants, as this study involves a Treatment Period of approximately up to 205 weeks depending upon the age of the study participant. Scheduled clinic visits will occur approximately every 26 weeks relative to EP0151 Visit 1 date.

[d] The Termination Visit will be performed for participants who remain in the Treatment Period and either reach 6 years of age or who participate in a region where marketing application approval is achieved for pediatric patients <4 years of age and LCM oral solution is available (whichever is earliest). An Early Termination Visit must be completed for all participants who prematurely discontinue from the study. Study participants who require taper will complete the End of Study Period which is completed by a Final Visit. The Final Visit will be completed 30 days (-1/+3 days) after the final dose of LCM.

[e] The End of Study Period starts after the Early Termination Visit or Termination Visit. In case of LCM withdrawal and taper, the Investigator may add any other AED during the End of Study Period, following the Investigator's medical judgment. A Final Visit will be completed 30 days (-1/+3 days) after the final dose of LCM.

[f] An Unscheduled Visit may be performed at the discretion of the Investigator. Such visits may be necessary if the dosage of LCM is to be adjusted in between scheduled visits. If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the Investigator's discretion. Please refer to footnote "o" below regarding participants which meet the conditions for administration of the C-SSRS. Participants meeting these conditions will have the C-SSRS administered if the Unscheduled Visit is due to a safety or efficacy reason.

[g] The total number of weeks in the Treatment Period will vary between individual study participants, as this study involves a Treatment Period of approximately up to 205 weeks, depending upon the age of the study participant. Scheduled clinic visits will occur approximately every 26 weeks relative to EP0151 Visit 1 date.

[h] The week of the Termination Visit/Early Termination Visit will vary between individual study participants, depending on study participant age (for Termination Visit) or weeks in study when early termination occurs (for Early Termination Visit).

[i] Demography information will be documented from the parent studies EP0034 or SP848.

[j] Starting from Visit 2, blood specimens for routine assay of hematology and clinical chemistry testing will be analyzed by the local laboratory affiliated with the site. The individual laboratory parameter result data will not be collected in the eCRF; however, the Investigator will report out of range results judged to be clinically significant as an AE.

[k] Designated procedures conducted at Visit 13/Termination Visit of EP0034 or SP848 will serve as the Baseline data for EP0151.

[l] The IXRS should be called for any cases of dose adjustment.

[m] Systolic and diastolic blood pressure and pulse rate will be measured in a semi-supine position after 5 minutes rest.

[n] Dispensing of LCM will be done at the Termination Visit/Early Termination Visit only if tapering of LCM is required.

[o] The "Already Enrolled" version of the C-SSRS should be completed at the Termination Visit or Early Termination Visit if the study participant reaches 6 years of age by the time that visit is conducted. Study participants who are ≥6 years of age who require additional treatment with LCM oral solution and are approved to continue will be administered the "Already Enrolled" version of the C-SSRS at the first visit (scheduled or unscheduled) which occurs upon the study participant reaching 6 years of age. The "Already Enrolled" C-SSRS version will continue to be administered at each subsequent visit (scheduled or unscheduled [see footnote "f" above]) up to and including the Termination Visit or Early Termination Visit.

[p] If the participant reports an AE which could be due to a cardiac condition, an ECG should be performed.

2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy (Ngugi et al, 2011). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and pharmacokinetic (PK) characteristics (Herman and Pedley, 1998). However, more than 30% of patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Beghi and Sander, 2008). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Shorvon, 2009).

Lacosamide belongs to a novel class of functionalized amino acids. Lacosamide has proven to be an effective and safe adjunctive treatment for POS, with or without secondary generalization, based on 3 double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in study participants with difficult-to-control POS. Lacosamide has also been shown to be an effective and safe adjunctive treatment over the long term (up to 9 years) for study participants with POS. Use of a loading dose for initiation of adjunctive LCM treatment (single loading dose of LCM 200mg, followed approximately 12 hours later by LCM 100mg twice daily [200mg/day] maintenance dose regimen) is approved in the EU, US, and other countries.

In the US, oral tablets and oral solution (syrup) of LCM are indicated for the treatment of POS in patients ≥4 years of age. Additionally, LCM has been approved in the EU (oral tablets, oral solution, and solution for intravenous [iv] infusion) as monotherapy and adjunctive therapy in the treatment of POS with or without secondary generalization in patients ≥4 years of age. Lacosamide is being evaluated in pediatric study participants ≥1 month to <17 years of age with POS in completed and ongoing studies; see Section 2.2.1 for further detail.

2.1 Study Rationale

This open-label extension study was designed to assess the long-term use of LCM (2mg/kg/day to 12mg/kg/day) in pediatric study participants <6 years of age with epilepsy, and allow study participants treated with LCM in EP0034 or SP848 to continue treatment with LCM until either the participant is at least 6 years of age or until LCM oral solution is approved in the participating country.

2.2 Background

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. Lacosamide's mode of action is proposed to be mediated by a selective enhancement of slow inactivation of voltage-gated sodium channels which may explain the anticonvulsant effects of LCM (Rogawski et al, 2015; Niespodziany et al, 2012; Errington et al, 2007).

As of 31 Aug 2019, LCM has been approved in over 70 countries. Lacosamide has been approved as monotherapy and adjunctive treatment in patients with POS in the US (4 years and older for film-coated tablets and oral solution; 17 years of age and older for intravenous

[iv] infusion), Canada (18 years and older for film-coated tablets and iv infusion), EU (4 years and older for film-coated tablets, oral solution, and iv infusion), and Japan (4 years and older for film-coated tablets, dry syrup, and iv infusion). Currently, LCM is still under development for use as monotherapy in other regions and also as iv administration in patients with POS, for monotherapy and adjunctive therapy in pediatric patients ≥1 month to <4 years of age with epilepsy, and as adjunctive therapy for primary generalized tonic-clonic seizures in adult and pediatric patients ≥4 years of age with idiopathic generalized epilepsy.

In the clinical development program for LCM, safety and tolerability of multiple doses of up to LCM 400mg given twice daily (LCM 800mg/day) were evaluated in approximately 700 study participants who received LCM in Phase 1 studies. Lacosamide is rapidly and completely absorbed after oral administration and has minimal protein-binding properties, thus a low risk of displacement drug-drug interactions. Lacosamide is neither a strong inhibitor nor a known inducer of the CYP450 enzymes and hence has a low potential for drug-drug interactions. Food does not affect the rate and extent of absorption. Peak plasma concentrations occur between 0.5 and 4 hours after dosing. The PK properties of LCM are proportional to dose, with low intraparticipant and interparticipant variability. The terminal half-life of the unchanged drug in plasma is approximately 13 hours allowing for a twice-daily dose regimen. The O-desmethyl metabolite (referred to as SPM 12809) is excreted in the urine, represents about 30% of the dose, and has no known pharmacological activity. After single-dose administration in healthy study participants, bioequivalence has been shown between the tablet and solution for iv infusion as well as between the tablet and oral solution formulations.

Further information on LCM preclinical results, as well as the PK, efficacy, and safety profiles, can be obtained from the current version of the LCM Investigator's Brochure.

2.2.1 Lacosamide in pediatric studies

Pellock et al (2012) conducted a systematic review of AEDs used in the treatment of POS. The AEDs that were shown to be superior to placebo for the adjunctive treatment of POS in adult clinical studies were also shown to be superior to placebo for adjunctive treatment of POS in the pediatric clinical studies (study participants >2 years of age) in which they were investigated. The efficacy and safety of LCM observed in clinical studies in adults and preclinical data, as well as many additional attributes of LCM, render the drug appropriate to investigate in pediatric study participants. These attributes include predictable and linear PK, lack of drug-drug interactions, easy twice daily dosing, and the availability of 3 different types of formulations in multiple strengths (allowing for flexibility in dose range and individualizing treatment).

Given the demonstrated efficacy and safety of LCM as adjunctive treatment in study participants aged ≥16 years with POS, and the experience with other AEDs in pediatric study participants, the US Food and Drug Administration (FDA) and European Medicines Authority (EMA) determined that it is acceptable to extrapolate the effectiveness of drugs approved for the treatment of POS in adults to pediatrics. UCB chose to utilize extrapolation of efficacy from adults to the pediatric population (≥4 years of age) for the indication of POS in the US and the EU. Based on this extrapolation, the EMA approved this indication on 14 Sep 2017, and the US FDA approved this indication (tablets and oral solution only) on 03 Nov 2017.

Lacosamide is being evaluated in pediatric study participants ≥1 month to ≤17 years of age with seizures in completed and ongoing studies. The completed pediatric studies include SP847

(open-label, safety, tolerability, and PK study) and SP1047 (PK study for study participants prescribed LCM); ongoing pediatric studies include SP848 and EP0034 (open-label, long-term safety studies). In SP847, SP848, and EP0034, study participants with POS have received LCM oral solution at doses up to 12mg/kg/day based on tolerability. In SP1047, study participants with epilepsy received LCM oral tablets (50mg, 100mg, 150mg, or 200mg), or LCM oral solution (LCM 10mg/mL) that they had been prescribed for epilepsy and brought with them to the clinic for dosing. Preliminary data have not demonstrated any clinically relevant changes in vital signs, electrocardiograms (ECGs), or clinical laboratory values; or evidence of cardiac-related treatment-emergent adverse events (TEAEs) or body weight changes. SP0967 is an ongoing Phase 3, multicenter, double-blind, randomized, PBO-controlled, parallel-group study to evaluate the efficacy and safety of LCM oral solution (LCM 8mg/kg/day to 12mg/kg/day, or matching PBO) as adjunctive therapy in study participants ≥1 month to <4 years of age with POS. SP0967 has completed enrollment, and no safety issues have been identified by safety monitoring and an external Data Monitoring Committee. EP0060 is a completed study that evaluated the safety and tolerability of the LCM iv formulation (infusion duration 15 minutes to 60 minutes) in children with epilepsy ≥1 month to <17 years of age. Lacosamide was well tolerated in that study and no safety issues were identified.

2.3 Benefit/Risk Assessment

Epilepsy is a condition for which an improved benefit/risk ratio for medicinal products remains a challenge; this is especially true for pediatric patients.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LCM may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the long-term use of LCM oral solution dosed at 2mg/kg/day to 12mg/kg/day when administered to pediatric study participants with epilepsy who have completed EP0034 or SP848	• TEAEs reported by the study participant or caregiver or observed by the Investigator • Withdrawals from study due to TEAEs • Withdrawals from study due to SAEs • Modal daily dose (mg/kg/day) • Maximum daily dose (mg/kg/day)

LCM=lacosamide; SAE=serious adverse event; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

EP0151 is a long-term, open-label, follow-up study for pediatric study participants <6 years of age with epilepsy who have previously received LCM in either EP0034 or SP848. Study participants who completed EP0034 or SP848 will be offered participation in EP0151 and will have access to open-label follow-up treatment with LCM oral solution.

Treatment Period

Visit 1 for EP0151 will be the same as Visit 13 in EP0034 or SP848. Clinic visits are scheduled approximately every 26 weeks relative to the EP0151 Visit 1 date. Dose modifications required for optimization of seizure control or tolerability issues will be addressed in unscheduled visits or regularly scheduled visits. A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits.

In EP0034 and SP848, study participants received flexible dosing based on the Investigator's clinical judgement, which ranged from a minimum dose of LCM 2mg/kg/day to a maximum dose of 12mg/kg/day or 600mg/day, whichever was lower. During EP0151 study visits, Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure control for each study participant. The Investigator may maintain the study participant's LCM dose, decrease the dose in decrements of 2mg/kg/day per week to a minimum dose of LCM 2mg/kg/day, or increase the dose in increments of 2mg/kg/day per week up to a maximum dose of LCM 12mg/kg/day or 600mg/day, whichever is lower. Lacosamide doses administered in this study must be from 2mg/kg/day to 12mg/kg/day. An IXRS will be used and should be called any time there is a dose increase or dose reduction (Figure 1-1).

Early Termination Visit with tapering of LCM

Study participants who discontinue prematurely from EP0151 and who will not continue further treatment with LCM should gradually taper LCM. These study participants will perform an Early Termination Visit followed by the visits required for the End of Study Period. Study participants should be tapered off LCM at the recommended decrements (Table 6-2). The Taper Period is up to 4 weeks; a slower taper or faster taper is permitted, if medically necessary; however, the maximum duration of tapering should not exceed 6 weeks. All study participants who taper off LCM will attend a Final Visit 30 days after the final dose of LCM. In the case of LCM withdrawal and taper, the Investigator is allowed to add any other antiepileptic drugs (AEDs) during the End of Study Period, following the Investigator's medical judgment.

Termination Visit

Study participants who remain in the Treatment Period and either reach 6 years of age or who participate in a region where marketing application approval is achieved for pediatric patients <4 years of age and LCM oral solution is available (whichever is earliest) will have met the conditions for completing the study. A Termination Visit will be performed for these study participants at the time of the next scheduled visit. Study participants who reach the end of the study and choose to continue treatment with LCM may be immediately prescribed LCM. The Termination Visit will be the last study visit completed for study participants who continue treatment with prescribed LCM. Study participants who choose not to continue with LCM treatment and who are taking a dose of LCM 3mg/kg/day or higher will enter an End of Study Period following completion of the Termination Visit, and will gradually taper from LCM treatment during the Taper Period; a Final Visit will be conducted 30 days after the final dose of LCM.

In situations where provision of LCM oral solution in certain participants >6 years of age (eg, developmental delay, need for more precise dosing as afforded by oral solution formulation, etc.) who may need a longer period of treatment with LCM oral solution, the situation will be

assessed for approval by UCB on a case-by-case basis following discussions with the participant's physician.

The maximum total duration of the study will be approximately 213 weeks, including an approximate 205-week Treatment Period and up to an 8 week End of Study Period (4-week Taper Period and 30-day Safety Follow-up Period). The end of the study is defined as the date of the last visit of the last study participant in the study.

4.2 Scientific rationale for study design

EP0151 is an open-label extension study designed to assess the long-term use of LCM (ranging in dose between LCM 2mg/kg/day to 12mg/kg/day) in pediatric study participants <6 years of age with epilepsy who have previously completed EP0034 or SP848.

EP0151 will allow study participants treated with LCM in EP0034 or SP848 to continue treatment with LCM until either the study participant reaches 6 years of age or until marketing application approval is achieved for pediatric patients <4 years of age in the region of participation and LCM oral solution is available (whichever is earliest). Cases where provision of LCM oral solution that do not meet these set criteria (eg, developmental delay, need for more precise dosing as afforded by LCM oral solution formulation, etc.) will be assessed on a case-by-case basis.

4.3 Justification for dose

Dose selection in EP0151 is based on the doses offered in the previous studies, EP0034 or SP848. During EP0151, Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each study participant (Section 6.6). Lacosamide doses may be adjusted from a minimum dose of LCM 2mg/kg/day up to a maximum of 12mg/kg/day or 600mg/day, whichever is lower. This dose range is anticipated to be clinically safe and effective for monotherapy.

4.4 End of study definition

Study participants who remain in the Treatment Period and either reach 6 years of age or who participate in a region where marketing application approval is achieved for pediatric patients <4 years of age and LCM oral solution is available (whichever is earliest) will have met the conditions for completing the study.

The end of the study is defined as the date of the last visit of the last study participant in the study.

5 STUDY POPULATION

Approximately 80 to100 participants from SP848 and EP0034 may be eligible to enroll in this open-label study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant is male or female, aged <6 years at the time of signing the Informed Consent Form (ICF).

Type of participant and disease characteristics

2. Participant has completed participation in EP0034 or SP848.
3. Participant is expected to benefit from participation, in the opinion of the Investigator.

Informed consent

4. An Independent Ethics Committee (IEC) approved written ICF is signed and dated by the participant or by the parent(s) or legal representative. The ICF or a specific Assent form, where required, will be signed and dated by minors (see Section 10.2.3).

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Participant has a known hypersensitivity to any components of the study medication or comparative drugs as stated in this protocol.

Prior/Concomitant therapy

3. Participant is receiving any investigational drugs or using any experimental devices in addition to LCM.

Prior/Concurrent clinical study experience

4. Participant meets a mandatory withdrawal criterion (ie, MUST withdraw criterion) for EP0034 or SP848, or is experiencing an ongoing serious AE (SAE).

Other exclusions

5. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study.

5.3 Lifestyle restrictions

No restrictions are required.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

A summary of treatments administered is provided in Table 6-1.

Table 6-1: Summary of treatments administered

ARM Name	
Intervention name	Lacosamide
Type	Drug
Dose formulation	Oral solution
Unit dose strength(s)	LCM 10mg/mL
Dosage level(s)	Minimum dose of 2mg/kg/day to maximum dose of 12mg/kg/day or 600mg/day, whichever is lower, administered BID in the morning and evening.
Route of administration	Oral use
Use	Active open-label
IMP and NIMP	IMP
Sourcing	Provided by UCB
Packaging and labeling	Clinical drug supplies will be labeled in accordance with the current ICH guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Primary packaging: bottles with child-resistant closure
Current/former name(s) or alias(es)	Not applicable

BID=twice per day; GCP=Good Clinical Practice; GMP=Good Manufacturing Practice; ICH=International Council for Harmonisation; IMP=investigational medicinal product; LCM=lacosamide; NIMP=non-IMP

Study participants will receive LCM oral solution administered BID from a minimum dose of 2mg/kg/day to a maximum dose of 12mg/kg/day or 600mg/day, whichever is lower, based on optimization of seizure control and tolerability in the judgement of the Investigator.

The Investigator may maintain the LCM dose administered to the study participant in the previous study, decrease the dose to a minimum dose of LCM 2mg/kg/day, or increase the dose to a maximum dose of LCM 12mg/kg/day or 600mg/day, whichever is lower. An IXRS will be used and should be called any time there is a dose increase or dose reduction.

Study participants who are taking a dose of 3mg/kg/day or higher and who either withdraw during the study or complete the study and do not continue treatment with LCM should taper off LCM.

It is recommended that the dose be tapered gradually in weekly decrements according to Table 6-2. A slower taper is permitted, if medically necessary, but should not exceed 6 weeks. In case of an emergency, a faster taper is permitted, after discussion with the Medical Monitor whenever possible.

Table 6-2: Lacosamide doses for Taper Period

LCM dose achieved	LCM doses for Taper Period			
	Week 1	Week 2	Week 3	Week 4
11-12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9-10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7-8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day
5-6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day	----
3-4mg/kg/day	2mg/kg/day	2mg/kg/day	----	----

LCM=lacosamide

6.2 Preparation, handling, storage, and accountability requirements

The Investigator (or designee) must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the investigational medicinal product (IMP) Handling Manual.

The Investigator (or designee) will instruct the participant to store the study medication following the instructions on the label.

Further guidance and information for the final disposition of unused study treatment are provided in the IMP Handling Manual.

6.2.1 Drug accountability

The Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the study medication is used only in accordance with this protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers), partially used, unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label study. Therefore, randomization is not applicable and no blinding is required.

Study participant numbers that were utilized in SP848 and EP0034 will continue to be used in EP0151. The study participant number must be incorporated into the electronic Case Report Form (eCRF).

The IXRS will generate individual assignments for kits of study medication, as appropriate, according to the visit schedule and assigned dose. Participant numbers and kit numbers will be tracked via the IXRS. The IXRS will allocate kit numbers to the participant based on the participant number during the course of the study.

The participant number will be required in all communication between the Investigator or designee and the IXRS regarding a particular participant.

6.4 Treatment compliance

At each visit after study medication is dispensed, participants must return all unused study medication and empty study medication containers. Drug accountability must be done in the participant's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a participant is found to be persistently noncompliant (defined as less than 75% or more than 125% compliant with the dosage schedule), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the participant should be withdrawn from the study.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- If needed to optimize tolerability and seizure reduction in selected participants, concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy. New concomitant AEDs may be introduced as treatment if the medication has been approved by the regulatory authorities in the country in which the participant lives. New concomitant AEDs should be added only when the participant has not optimally or adequately responded to a maximum tolerated dose of LCM.
- Implantation of and/or changes in vagal nerve stimulation settings are permitted.
- The Investigator must contact the Medical Monitor if surgery is planned for any participant. In general, it is not necessary to discontinue LCM for participants undergoing surgery, although each case must be discussed on a case-by-case basis. The Investigator must contact the Medical Monitor before re-starting LCM after a surgery.

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Clozapine
- Monoamine oxidase-A inhibitors
- Cannabidiols (when not approved or indicated for epilepsy by local health authority)

6.5.3 Rescue medication

Therapy that becomes necessary, in the Investigator's opinion, during the course of the study must not be refused to a participant, even if described above as a therapy that is expressly not permitted in the frame of this study. The study participant's participation in this study may be discontinued in such a case.

Any rescue medication is allowed. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded in the eCRF.

6.6 Dose modification

In case a dose modification is necessary, the study treatment will be administered as described in Section 6.1. The IXRS should be called any time there is a dose increase or dose reduction.

6.7 Criteria for study hold or dosing stoppage

Selected data, including SAEs and AEs, from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the study medication and will make recommendations on the continuation or modification of the study as appropriate.

6.8 Treatment after the end of the study

There is no treatment planned after the end of the study.

Study participants who reach the end of the study and choose to continue treatment with LCM may be immediately prescribed LCM following the Termination Visit.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

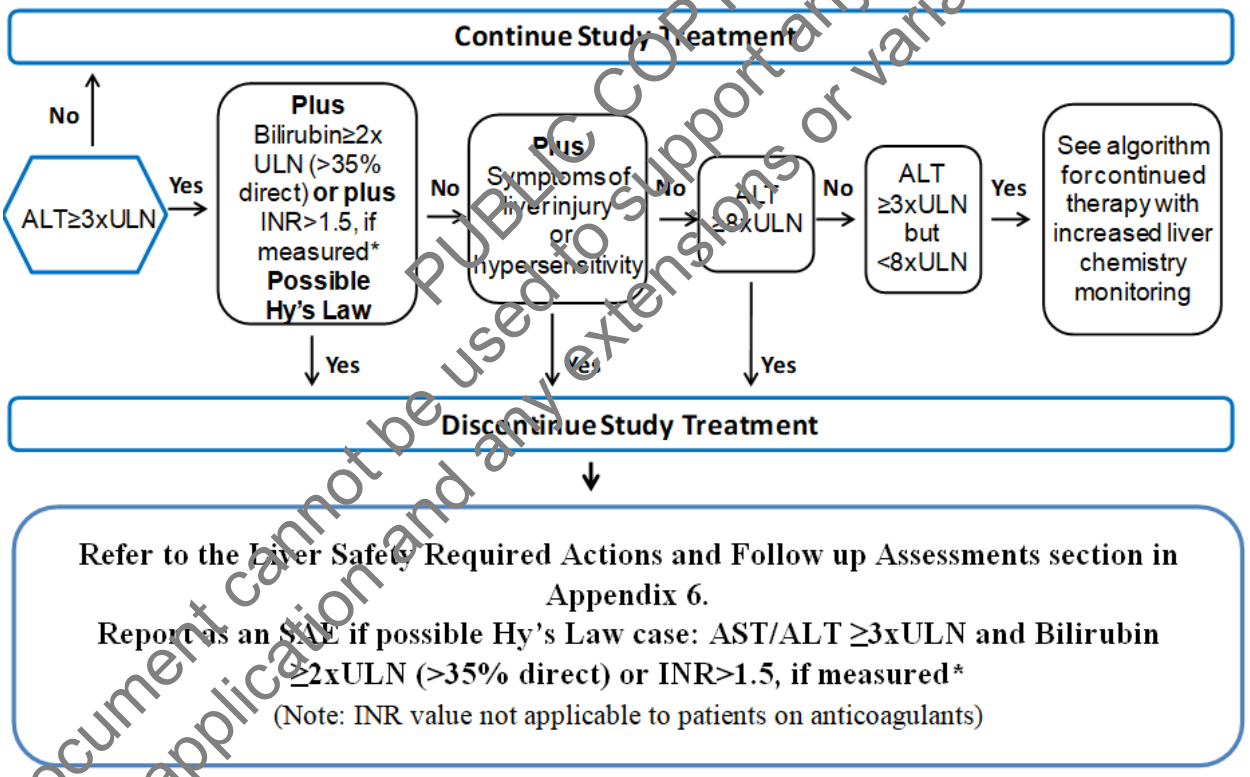
7.1 Discontinuation of study medication

7.1.1 Liver chemistry stopping criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 7-1 or Figure 7-2 or if the Investigator believes that it is in best interest of the participant.

Study medication will be discontinued immediately and permanently for a study participant if liver chemistry stopping criteria are met.

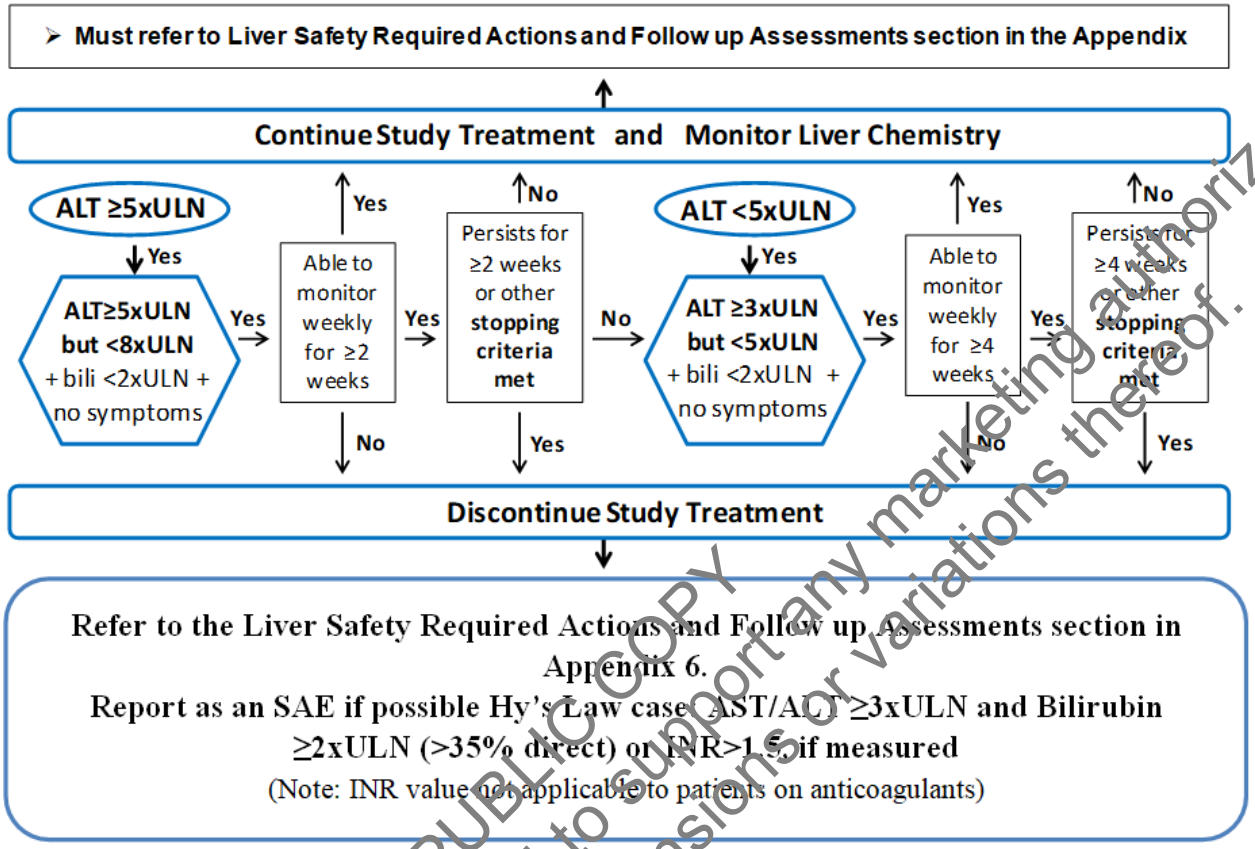
Figure 7-1: Liver chemistry stopping criteria and increased monitoring algorithm



ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Note: Algorithm for continued therapy with increased liver chemistry monitoring can be found in Figure 7-2.

Figure 7-2: Liver chemistry increased monitoring algorithm with continued study intervention for participants with ALT ≥3xULN but <8xULN



ALT=alanine aminotransferase; AST= aspartate aminotransferase; bili=bilirubin; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Specific assessments and follow up actions for potential drug-induced liver injury are provided in Appendix 6 (Section 10.6).

Study participants with potential drug-induced liver injury (PDILI) must be assessed to determine if study medication must be immediately and permanently discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of study medication:

- Participants with either of the following:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5x upper limit of normal (ULN)
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of study medication:

- Participants with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right

upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below allows for participants to continue on study medication at the discretion of the Investigator:

- Participants with ALT or AST ≥3xULN (and ≥2x Baseline), and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

7.1.2 QTc stopping criteria

If the participant reports an AE which could be due to a cardiac condition, an ECG should be performed.

A participant with corrected QT interval (QTc)>500 msec OR Uncorrected QT >600 msec based on the average of triplicate ECG readings will be withdrawn from study medication.

Any new clinically relevant finding should be reported as an AE.

7.2 Participant discontinuation/withdrawal from the study

Participants or the participant's legal representatives are free to withdraw the participant from the study at any time, without prejudice to their continued care.

A participant may withdraw from the study at any time at his/her own request or at the study participant's legal representative's request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of Activities (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants must be withdrawn from this study if any of the following events occur:

1. Participant experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the Investigator, preclude further participation in the study.
2. The Sponsor or a regulatory agency requests withdrawal of the participant.
3. Participant is unwilling or unable to continue or legal representative is unwilling or unable to allow the participant to continue in the study.
4. Investigator decides that withdrawal from further participation would be in the participant's best interest.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant develops an illness that would interfere with his/her continued participation
2. Participant and/or legal representative is noncompliant with study procedures or medication, in the opinion of the Investigator
3. Participant takes prohibited concomitant medications as defined in this protocol (Section 6.5.2)
4. Participant withdraws his/her consent
5. Any clinically relevant change in medical or psychiatric condition (if, in the opinion of the Investigator, the condition warrants discontinuation from the study)

Study Participants discontinuing LCM for any reason should taper off medication as described in Section 4.1. Whenever possible, these cases should be discussed with the Medical Monitor prior to withdrawing the participant from the study

7.3 Lost to follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Table 1-1).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 1-1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Blood collected from each participant over the duration of the study, including any extra assessments, will be done respecting the requirements for collection and volume endorsed for use by the local laboratory. Blood will be collected for laboratory assessments during scheduled visits, which will occur infrequently (approximately every 26 weeks). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Table 1-1).

8.2.1 Vital signs

Pulse rate and blood pressure will be assessed according to the Schedule of Activities (Table 1-1).

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, and pulse rate.

8.2.2 Biometric parameters

Biometric parameters of height and weight will be measured according to the Schedule of Activities Table 1-1).

8.2.3 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency. Starting from Visit 2, blood specimens for routine assay of hematology and clinical chemistry testing will be analyzed by the local laboratory affiliated with the site. The individual laboratory parameter result data will not be collected in the eCRF; however, the Investigator will report any out of range results judged to be clinically significant as an AE.

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study medication should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.4 Suicidal risk monitoring

Lacosamide is considered to be an antiepileptic. There has been some concern that antiepileptics may be associated with an increased risk of suicidal ideation or behavior when given to some participants with epilepsy. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to pediatric participants with epilepsy, UCB considers it important to monitor for such events before and during this clinical study.

Study participants being treated with LCM should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing LCM in study participants who experience signs of suicidal ideation or behavior.

Where appropriate, suicidality will be assessed by trained study personnel using the Columbia-Suicide Severity Rating Scale (C-SSRS; Columbia University Medical Center, 2008). The C-SSRS will be completed at the scheduled timepoints as described in the Schedule of Activities (Table 1-1). The C-SSRS is not validated for study participants <6 years of age and will not be used for this population. Study participants should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The Investigator should be aware of common warning signs that might be a signal for risk of depression. Parents and caregivers should be advised accordingly and effort should be made at clinic visits to specifically assess potential depression. Families and caregivers of study participants being treated with LCM should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

The "Already Enrolled" version of the C-SSRS should be completed at the Termination Visit or Early Termination Visit if the participant reaches 6 years of age by the time that visit is conducted. Participants who are ≥6 years of age who require additional treatment with LCM oral solution (Section 4.1) and are approved to continue will be administered the "Already Enrolled" version of the C-SSRS at the first visit (scheduled or unscheduled) which occurs upon reaching 6 years of age. The "Already Enrolled" C-SSRS version will continue to be administered at each subsequent visit (scheduled or unscheduled) up to and including the Termination or Early Termination Visit.

8.3 Adverse events and serious adverse events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study medication (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the end of the study at the time points specified in the Schedule of Activities (Table 1-1).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no study medication was taken but specific study procedures were conducted. This includes all AEs not present prior to the Visit 1 and all AEs that recurred or worsened after Visit 1.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the study medication), up to 30 days from the end of the study for each study participant, and to also inform study participants of the need to inform the investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports is provided in Appendix 3.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the study participant or caregiver is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest and AEs of special monitoring (as defined in Section 8.3.5 and Section 8.3.6, respectively), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authorities, IECs, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IEC, if appropriate according to local requirements.

8.3.5 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.For LCM, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (2nd degree Type I and II and 3rd degree), and marked bradycardia (<45 beats/min)
- Syncope or loss of consciousness (other than seizure-related)
- Serious suspected multiorgan hypersensitivity reactions

  Serious suspected multiorgan hypersensitivity cases may be identified and reported to the Sponsor by the Investigator using the following algorithm as agreed with the United States Food and Drug Administration:

  An AE or laboratory value (as defined below) suggestive of internal organ involvement (including, but not limited to, hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.

  Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
  - Eosinophils % ≥10%
  - Eosinophils absolute ≥0.5G/L
  - Neutrophils absolute <1.5G/L
  - Platelets ≤100G/L

- ALT ≥2xULN
- AST ≥2xULN

8.3.6 Adverse events of special monitoring

An AE of special monitoring is a product-specific AE, adverse reaction, or safety topic requiring special monitoring by UCB.

For LCM, events of epileptic spasms require immediate reporting (within 24 hours regardless of seriousness) to UCB.**Anticipated serious adverse events**

The following SAEs (Table 8-1) are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including anticipated SAEs) as detailed in Section 8.3.1 and Section 10.3.

Table 8-1: Anticipated SAEs for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administration site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion
	Incontinence
	Status epilepticus
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SAE=serious adverse event

8.4 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the study medication so that Investigators, clinical study participants, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the study medication, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, ECG results) for which data will be periodically reviewed during the course of the study.

8.5 Treatment of overdose

Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

Excessive dosing (beyond that prescribed in the protocol and including overdose [≥14mg/kg/day]) should be recorded in the eCRF. Any SAE or non-serious AE associated with excessive dosing must be followed as any other SAE or non-serious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms.

UCB does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities until return to normal and for at least 3 days.
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Medical resource utilization and health economics

Medical resource utilization and health economics are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan.

9.1 Definition of analysis sets

The primary analysis set will be the Safety Set, which is defined as all participants who sign an ICF, and take at least 1 dose of study medication. This analysis set will be used for summaries of all variables.

9.2 General statistical considerations

Descriptive statistics will be used to provide an overview of the primary variables. For categorical parameters, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of analysis. For continuous variables, descriptive statistics will include number of study participants, mean, standard deviation, median, minimum, and maximum. No statistical hypothesis testing will be performed. Baseline values for primary variables will be determined from Baseline values of the EP0034 or SP848 study, unless otherwise noted.

All computations for the analyses will be performed using SAS® version 9.4 or later (SAS Institute, NC, USA).

9.3 Planned safety analyses

9.3.1 Safety analyses

Treatment-emergent AEs will be defined as those events which started on or after the date of first dose of LCM in EP0151, or events for which severity worsened on or after the date of first dose of LCM in EP0151. Adverse events which occur within 30 days after final dose of LCM in EP0151 will be considered treatment-emergent.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities® (MedDRA). Pretreatment AEs, TEAEs, non-serious TEAEs, withdrawals due to TEAEs, withdrawals due to SAEs, and SAEs will be tabulated by system organ class and preferred term. The incidence of TEAEs will also be summarized by intensity and by relationship to LCM. In addition, all AEs will be listed.

Long-term use of LCM will be assessed by modal daily dose (mg/kg/day) and maximum daily dose (mg/kg/day). These doses will be summarized using descriptive statistics, along with duration of exposure (days).

Actual measurements and changes from Baseline in vital signs, body weight, height, and calculated BMI will be summarized descriptively by visit. In addition, shift tables may be used to evaluate the number and percent of study participants having a different post-Baseline status when compared with their Baseline status.

The endpoints for assessment of long-term use include TEAEs, study participant withdrawals due to TEAEs and SAEs, modal daily dose, and maximum daily dose. Available data related to these measurements will be presented in participant data listings.

Responses to the C-SSRS will be presented in participant data listings.

9.4 Handling of protocol deviations

All data will be used to the maximum possible extent, but without any imputations for missing data for any parameter. Important protocol deviations are deviations from the protocol that could

potentially have a meaningful impact on study conduct or on the key safety outcomes for an individual study participant. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the appropriate protocol-specific document (eg, the Specification of Important Protocol Deviations). To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

9.5 Handling of dropouts or missing data

For evaluation of safety variables, study participants who prematurely discontinue the study will be evaluated based on the data collected at each visit attended.

9.6 Planned interim analysis and data monitoring

No formal interim analysis or Data Monitoring Committee is planned. However, data may be reported prior to the completion of this study to support annual reports, regulatory submissions, and publications.

9.7 Determination of sample size

No formal sample size calculations have been performed for this study, as there are no statistical hypotheses being tested. The sample size will be determined by the number of participants in EP0034 or SP848 who have been treated with LCM that are eligible to enter this open-label follow-up study. It is anticipated that approximately 80 to 100 participants who completed EP0034 or SP848 will participate in this follow-up study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IEC for the protocol.

The Investigator will also promptly report to the IEC all changes in the study, all unanticipated problems involving risks to participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

The Investigator will not make any changes in the study or study conduct without IEC approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IEC as allowed.

As part of the IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IEC (based on IEC requirements), at intervals appropriate to the degree of participant risk involved, but no less than once per year. The Investigator should provide a final report to the IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the Sponsor (or its representative) with evidence of such IEC notification.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

Participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki. When possible or as required according to local IEC, assent also will be obtained from the study participant.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator (or designee). Each participant will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IEC and use of the amended form.

The participant may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.1.5 Data quality assurance

All participant data relating to the study will be recorded on a printed eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

10.1.5.1 Case Report Form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.5.2 Apps

No Apps will be used in this study.

10.1.6 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer-generated and stored electronically must be printed for review by the Monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the study participant's source documents. The Investigator will facilitate the process for enabling the Monitor to compare the content of printouts and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

10.1.7 Study and site Closure

The Sponsor (or designee) reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

- Discontinuation of further study medication development

10.1.8 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of this protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-required safety laboratory assessments

<table>
<tr><th>Laboratory assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet count</td><td rowspan="4">RBC Indices:
MCV
MCH
% reticulocytes</td><td colspan="2" rowspan="4">WBC count with differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>RBC count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="3">Clinical chemistry[a]</td><td>Blood urea nitrogen (BUN)</td><td>Potassium</td><td>AST/SGOT</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT/SGPT</td><td>Total protein</td></tr>
<tr><td>Glucose (fasting)</td><td>Calcium</td><td>Alkaline phosphatase</td><td></td></tr>
</table>

ALT= alanine aminotransferase; AST= aspartate aminotransferase; eCRF=electronic case report form; INR=internal normalized ratio; SAE=serious adverse event; IEC=Independent Ethics Committee; SGOT= serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6. All events of ALT≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT≥3×ULN and INR>1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

Investigators must document their review of each laboratory report.

10.3 Appendix 3: Adverse events – definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency room for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criterion, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but does not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and follow-up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs, but the final intensity grading by the Investigator must be mild, moderate, or severe.
Assessment of Causality
• The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the participant is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest and special monitoring.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB Study Physician by telephone. • Contacts for SAE reporting can be found in the Serious Adverse Event Reporting section.
SAE Reporting to UCB via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the UCB Study Physician. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE eCRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Serious Adverse Event Reporting section.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Not applicable.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Participants with potential drug-induced liver injury must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants with potential drug-induced liver injury should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication and withdrawal from the study.

A specific monitoring plan must be agreed between the UCB Study Physician and the Investigator for study participants who have ALT>5ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values)(see Table 10-1 and Table 10-2).

Phase 3-4 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Table 10-1: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT≥8xULN
ALT increase	ALT≥5xULN but <8xULN persists for ≥2 weeks ALT≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[b]	ALT≥3xULN **and** INR>1.5, if INR measured
Cannot monitor	ALT≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions and Follow up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study medication • Report the event to UCB within **24 hours** • Complete the Liver Event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE[b]	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend

Table 10-1: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
• Perform liver chemistry follow-up assessments • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) • **Do not restart/rechallenge** participant with study medication unless allowed per protocol and UCB approval is granted • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study medication and continue participant in the study for any protocol specified follow up assessmentsConsider the need for a toxicology screening **MONITORING:** **<u>For bilirubin or INR criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline	• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen), quantitative hepatitis B DNA and hepatitis delta antibody[e] • Obtain blood sample for PK analysis[f] • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the Concomitant Medications eCRF. **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]) **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRFs

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; DNA=deoxyribonucleic acid; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM= immunoglobulin M; INR=internal normalized ratio; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal; SAE=serious adverse event

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if

serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT≥3xULN and bilirubin≥2xULN (>35% direct bilirubin) or ALT≥3xULN and INR>1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

[d] Includes: Hepatitis A IgM antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal, 2005).

[f] PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

Table 10-2: Phase 3-4 liver chemistry increased monitoring criteria with continued study medication

Liver Chemistry Increased Monitoring Criteria	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** can be monitored weekly for 2 weeks OR ALT≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** can be monitored weekly for 4 weeks	• Notify the UCB Medical Monitor **within 24 hours** of learning of the abnormality to discuss study participant safety • Participant can continue study medication • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize, or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Table 10-1 • If ALT decreases from ALT≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

10.7 Appendix 7: Medical device adverse events, adverse device effects, serious adverse events and device deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice per day
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
ICF	informed consent form
IEC	Independent Ethics Committee
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IXRS	interactive voice/web response system
LCM	lacosamide
MedDRA	Medical Dictionary for Regulatory Activities®
PK	pharmacokinetic
POS	partial-onset seizures
QTc	corrected QT interval
SAE	serious adverse event
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

10.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

11 REFERENCES

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SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

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