CLINICAL STUDY PROTOCOL

STUDY NUMBER: SP848

PHASE OF STUDY: 2

AN OPEN-LABEL STUDY TO DETERMINE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM ORAL LACOSAMIDE (LCM) AS ADJUNCTIVE THERAPY IN CHILDREN WITH EPILEPSY

EudraCT Number: 2011-001559-35

Sponsor:

UCB BIOSCIENCES, Inc

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United States

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SERIOUS ADVERSE EVENT REPORTING

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AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
Bid	twice daily
BMI	body mass index
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
CBCL	Child Behavior Checklist
CDMS	clinical data management system
COVID-19	coronavirus disease 2019
C_{max}	maximum plasma concentration
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IEC	Independent Ethic Committee
IRB	Institutional Review Board
iv	intravenous
LCM	lacosamide
LFT	liver function test
MAOI	monoamine oxidase inhibitor
MedDRA®	Medical Dictionary for Regulatory Activities
n	number of subjects
PDILI	potential drug-induced liver injury
PedsQL™	Pediatric Quality of Life Inventory
PET	polyethylene terephthalate
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PS	Patient Safety
PT	preferred term
QTc	corrected QT interval
QTcB	corrected QT interval using the Bazett method
RDC	remote data capture

SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SPM 12809	O-desmethyl-LCM
SS	Safety Set
TEAE	treatment-emergent adverse event
TV	Titration Visit
ULN	upper limit of normal

1 SUMMARY

SP848 is an open-label study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with epilepsy (partial-onset seizures and other pediatric epilepsy syndromes) treated with lacosamide (LCM) oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes. SP848 includes subjects ≥1 month to ≤18 years of age since subjects who complete SP847 or another applicable LCM pediatric epilepsy study in subjects <18 years of age may have aged to 18 years old by the time they complete that study and enroll in SP848.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy.

Protocol Amendment 6 allows up to approximately 75 additional eligible pediatric subjects with epilepsy who participated in EP0060 to enroll into SP848. Protocol Amendment 8 allows an enrollment increase from 75 to 100 eligible pediatric subjects ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of subjects down to 1 month of age. In addition, subjects already enrolled in SP848 may participate in EP0060, if eligible, and then resume participation in SP848. These subjects may either voluntarily choose to have an iv LCM infusion even though they are capable of taking oral LCM or require iv LCM infusion due to a medical reason or procedure (ie, unable to take oral LCM).

Approximately 200 subjects who may participate in other LCM pediatric clinical studies in epilepsy will be eligible to participate in SP848. In total, up to approximately 400 subjects may be eligible to participate in SP848.

Subjects who complete SP847 or another applicable LCM pediatric epilepsy study and choose to enter this open-label study will begin on the LCM dose they achieved in SP847 or their previous pediatric LCM study. Subjects who discontinued from SP847 due to a dose reduction or status

epilepticus, but for whom it is determined medically appropriate to enter this open-label study, will also begin on the LCM dose they achieved in SP847. Subjects who enroll from EP0060 will begin SP848 with an equivalent LCM dose as they last received in EP0060; however, the LCM dose may be further titrated/adjusted to a level to optimize tolerability and seizure control (up to a maximum level as described below). Subjects who meet eligibility requirements and enroll directly into SP848 without previous participation in a LCM clinical study will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (up to a maximum level as described below).

Subjects will be able to receive LCM oral solution (syrup) or LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

The study variables to be assessed are defined in Section 4.2.

2 BACKGROUND INFORMATION

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 classification of epilepsies in children was described in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (1989; Aicardi, 1994). Seizures are categorized based on whether the onset is focal or generalized and whether the disorder is idiopathic, symptomatic, or cryptogenic. Specific syndromes are further classified according to a number of criteria including seizure type, cause, anatomy, precipitating factors, age of onset, and sometimes prognosis.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and 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 (CHMP/EWP/566/98, 2010). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander, 1998).

Among the newer AEDs, only 6 (gabapentin, lamotrigine, oxcarbazepine, topiramate, levetiracetam, and perampanel) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Rheims and Ryvlin, 2013; Glauser et al, 2006; Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide (LCM, Vimpat®, SPM 927, [R]-2-acetamido-N-benzyl-3-methoxypropionamide) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide (200mg/day to 400mg/day) is approved and indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16 to 18 years of age) patients with epilepsy and was first approved in Aug 2008 by the European Commission. Lacosamide is available in tablet (50mg, 100mg, 150mg, and 200mg) and syrup (10mg/mL) oral formulations as well as solution for infusion (10mg/mL) formulation for use as temporary iv replacement when oral administration is not feasible. Lacosamide (200mg/day to 400mg/day) was approved in the US in Oct 2008 as adjunctive therapy and in Aug 2014 as monotherapy in the treatment of partial-onset seizures in patients 17 years of age and older. Initiation of adjunctive LCM treatment with a single loading dose of LCM 200mg (oral tablets, syrup, or iv infusion) followed 12 hours later by a LCM 100mg twice daily (200mg/day) maintenance dose regimen was also approved by the European Commission in Nov 2012. Use of a LCM 200mg loading dose for initiation of initial LCM monotherapy, conversion to LCM monotherapy, or adjunctive therapy was approved in the US in Aug 2014.

The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in 1308 adult subjects, aged 16 to 70 years, established the efficacy of oral LCM as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with difficult to control partial-onset seizures. In these studies, LCM was initiated at a dose of 100mg/day (in 2 divided doses) and escalated to the randomized dose (200mg/day, 400mg/day, or 600mg/day) in 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent adverse events (TEAEs) were central nervous

system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, nausea, and diplopia. The nature and frequency of adverse events (AEs) were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

SP847 was an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. The study completed on 26 Aug 2014. Forty-seven subjects (aged 1 month to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs were enrolled and treated during the study. The study consisted of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject was up to approximately 13 weeks.

SP848 is an open-label study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with epilepsy (partial-onset seizures and other pediatric epilepsy syndromes) treated with LCM oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures.

3 STUDY OBJECTIVES

The objectives of this study are:

- To obtain information about the safety, tolerability, and PK of LCM during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long-term exposure
- To allow subjects who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM

- To allow subjects who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM

4 STUDY DESIGN

4.1 Study description

4.1.1 Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy

Subjects who complete SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or subjects from another applicable LCM pediatric clinical study in epilepsy and who choose to enter the open-label study, will begin with an equivalent LCM dose as they last received in the primary study. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may titrate/adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

4.1.2 Subjects enrolling directly into SP848

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years

to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (see Section 4.4.1). Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator.

SP848 includes subjects ≥1 month to ≤18 years of age since subjects who complete SP847 or another applicable LCM pediatric epilepsy study in subjects <18 years of age may have aged to 18 years old by the time they complete that study and enroll in SP848.

The same study conditions described in Section 4.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and study medication taper) also apply.

4.2 Variables to be assessed

4.2.1 Safety variables

4.2.1.1 Primary safety variables

The primary safety variables are:

- Incidence of TEAEs
- Incidence of serious AEs (SAEs)
- Subject withdrawal from the study due to TEAEs

4.2.1.2 Other safety variables

The other safety variables are:

- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner Stage (if applicable)
- Achenbach Child Behavior Checklist (CBCL) at Baseline for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales at Baseline for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)
- Cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]/BRIEF®-Preschool Version [BRIEF®-P]) (if applicable)
- LCM palatability and ease of use questionnaire

4.2.2 PK variables

4.2.2.1 Primary PK variables

No primary PK variables are defined for this study.

4.2.2.2 Other PK variables

The other PK variables are:

- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs

4.2.3 Efficacy variables

4.2.3.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

4.2.3.2 Secondary efficacy variables

The secondary efficacy variables, based on daily seizure diaries, are:

- Percent change from Baseline in 28-day partial-onset seizure frequency
- ≥50% reduction in 28-day partial-onset seizure frequency
- ≥75% reduction in 28-day partial-onset seizure frequency
- Seizure days per 28 days (subjects with generalized seizures only)
- Seizure-free status

4.2.3.3 Other efficacy variables

The other efficacy variables are:

- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)
- All seizure frequency analyses as described in the secondary efficacy variables (presented for the overall Treatment Period only) may be additionally presented by modal daily dose group, by seizure type, by seizure classification subgroup, by time interval, by visit or time period, or by completer cohort

4.3 Selection and withdrawal of subjects

4.3.1 Inclusion criteria

All subjects in SP848 must fulfill the following inclusion criteria:

1. A signed informed consent form has been obtained from the parent/legal guardian and assent has been obtained from the subject (when possible or as required according to local Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).

4. Subject and caregiver (which may be a parent, legal guardian, or other delegated caregiver) are willing and able to comply with all study requirements, including maintaining a daily seizure diary.

Subjects who have participated in SP847 or other LCM pediatric clinical studies in epilepsy must fulfill the following inclusion criteria:

2. Subject has completed SP847 (or the subject discontinued SP847 due to a dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures, or subject has participated in other LCM pediatric clinical studies in epilepsy.
3. Subject is expected to benefit from participation, in the opinion of the investigator.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study must fulfill the following inclusion criteria:

5. Subject is male or female and ≥4 years to ≤17 years of age.
6. Subject has a diagnosis of epilepsy with partial-onset seizures.
    - The results of at least 1 prior electroencephalogram (EEG) AND 1 prior magnetic resonance imaging/computerized tomography scan should be consistent with the above diagnosis.
7. Subject has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with at least 2 AEDs (concurrently or sequentially).
8. Subject has been observed to have at least 2 countable seizures in the 4-week period prior to Screening.
    - In the case of simple partial seizures, only those with motor signs will be counted towards meeting the inclusion criteria (only partial seizures with a recognizable and countable manifestation).
9. Subject is on a stable dosage regimen of 1 to 3 AEDs. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of at least 1 week prior to Screening. Vagal nerve stimulation is not counted as medical therapy; however, VNS settings must be kept constant for a period of at least 1 week prior to Screening.
10. Subject is an acceptable candidate for venipuncture.

4.3.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria are met:

1. Subject is receiving any investigational drugs or using any experimental devices in addition to LCM.
3. Subject ≥6 years of age has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Subjects who have participated in SP847 or other LCM pediatric clinical studies in epilepsy are not permitted to enroll in the study if any of the following criteria are met:

2. Subject meets either of the following:

a. Withdrawal criteria for the primary study (with the exception of subjects who discontinued due to a dose reduction or status epilepticus). For subjects entering from EP0060, if the subject (or legal guardian) withdraws consent solely due to route of LCM administration (iv) or if the subject requires more than 10 iv LCM infusions, the subject may be allowed to participant in SP848 after discussion with and agreement from the Medical Monitor.

b. Ongoing serious AE (SAE).

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study are not permitted to enroll in the study if any of the following criteria are met:

4. Subject has ever received LCM.
5. Subject has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate in this study.
6. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
7. Subject has a known hypersensitivity to any component of the investigational medicinal product.
8. Subject is a female of childbearing potential and does not practice an acceptable method of contraception for the duration of the study.
    - Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone, oxcarbazepine]) which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.
    - The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit.
9. Subject has a creatinine clearance less than 30mL/min.
10. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a QT prolongation greater than 450ms).
11. Subject has hemodynamically significant heart disease (eg, heart failure).
12. Subject has an arrhythmic heart condition requiring medical therapy.
13. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.

14. Subject has nonepileptic events, including psychogenic seizures, that could be confused with seizures. If both epileptic and nonepileptic events are present, epileptic events must be distinguished from nonepileptic phenomena.
15. Subject has a history of primary generalized epilepsy.
17. Subject is taking monoamine oxidase inhibitors-A (MAOI-A) or narcotic analgesics.
18. Subject has epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen syndrome.
19. Subject has a known sodium channelopathy, such as Brugada syndrome.
20. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.

Subjects who were directly enrolled in EP0060 for iv LCM replacement therapy or to initiate LCM treatment are not permitted to enroll in the study if any of the following criteria are met:

21. Subjects have previously participated in a long-term, open-label LCM study.

4.3.3 Criteria for withdrawal

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable. The following criteria for subject withdrawal from SP848 are outlined below. Additional discontinuation criteria for potential drug-induced liver injury (PDILI) are presented in Section 4.3.3.1.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency

3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
9. Subject experiences convulsive status epilepticus (if none had occurred prior to study entry) and is compliant with study treatment
11. For subject who did not complete a C-SSRS at Screening, subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) of the screening version of the C-SSRS. The investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
12. For all subjects ≥6 years of age, regardless of whether or not a C-SSRS was completed at Screening, subject has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "since last visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
5. For subject who did not complete a C-SSRS at Screening, subject had actual suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the screening version of the C-SSRS. The investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the patient from the study.

If a subject from SP848 enrolls in EP0060 and either withdraws consent solely due to route of LCM administration (iv) or if the subject requires more than 10 iv LCM infusions, the subject may be allowed to return to SP848 after discussion with and agreement from the Medical Monitor. If a subject from SP848 is advised to withdraw from the SP848 after participation in EP0060, the subject will be required to return to the SP848 to complete the required ETV and Safety Follow-up assessments.

Investigators should attempt to obtain information on subjects in the case of withdrawal. For subjects considered as lost to follow up, the investigator should make efforts (at least 1 phone call and 1 written message to the subject), and document his/her efforts (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 subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

4.3.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP 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 IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN
- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below requires discussion with the Medical Monitor to decide whether the subject is allowed to continue on IMP.

- Subjects 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).

Evaluation of PDILI must be initiated as described in Section 8.3.2. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI 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 IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

4.4 Study treatments

4.4.1 Treatments to be administered

4.4.1.1 Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy

Subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), who are eligible to participate in the open-label study SP848, and who choose to enter SP848, will begin SP848 on the LCM dose they achieved in the primary study.

Subjects who enroll from EP0060 will begin SP848 with an equivalent dose to the last dose they received in EP0060; however, the LCM dose may be further titrated/adjusted to a level to optimize tolerability and seizure control (up to a maximum level as described in Section 4.4.1.3). For those subjects who initiated adjunctive LCM treatment in EP0060, the recommended LCM dose titration approach is outlined in Section 4.4.1.2.

4.4.1.2 Subjects enrolling directly into SP848

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. After Screening, eligible subjects will initiate treatment with LCM (oral solution or tablet, as chosen by the investigator and subject/caregiver), and the LCM dose will be titrated to a level to optimize tolerability and seizure control.

At the first Titration Visit (TV) (see Section 5.2), subjects who have enrolled directly into SP848 will receive a single dose of LCM (1mg/kg [oral solution] or 50mg [tablet]) during the clinic visit. Over the following days, subjects will be administered LCM 1mg/kg bid (oral solution) or LCM 50mg bid (tablet), and will begin titrating in weekly increments of 2mg/kg/day (oral solution) or 100mg/day (tablet) up to a level to optimize tolerability and seizure control (not to exceed 12mg/kg/day [or 600mg/day based on body weight, whichever is lower]). Subjects must be on each LCM dose for at least 5 days before titrating up to the next dose.

A total of up to 6 Titration Visits may be required (eg, for a subject whose dose is titrated to the maximum permitted dose of LCM 12mg/kg/day). However, based on tolerability and seizure control, a subject's LCM dose may be titrated to a lower dose level; in such a case, fewer than 6 Titration Visits would be required.

The following table summarizes the recommended titration steps for the oral solution and tablet formulations:

Recommended LCM dose titration for subjects enrolling directly into SP848

Formulation	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Oral solution (syrup)	2mg/kg/day (1mg/kg bid)	4mg/kg/day (2mg/kg bid)	6mg/kg/day (3mg/kg bid)	8mg/kg/day (4mg/kg bid)	10mg/kg/day (5mg/kg bid)	12mg/kg/day (6mg/kg bid)
Tablet	100mg/day (50mg bid)	200mg/day (100mg bid)	300mg/day (150mg bid)	400mg/day (200mg bid)	500mg/day (250mg bid)	600mg/day (300mg bid)

bid=twice daily; LCM=lacosamide

4.4.1.3 All subjects

The investigator, together with the subject/caregiver (including parent/legal guardian), will be able to choose either the oral solution (syrup) formulation or the tablet formulation of LCM in this study. The study medication will be orally administered bid (at 12-hour intervals, once in the morning and once in the evening) in equally divided doses. The oral solution (syrup) formulation will be measured and orally administered via a dosing syringe. The selection of doses, titration scheme, and rate of taper in SP847 were based on adult studies and were adjusted to a mg/kg basis plus 40% (ie, 600mg/day adult dose of LCM corresponds to [600mg/70kg] x 1.4 = approximately 12mg/kg/day for a child). The selection of doses in this trial is based on the maximum recommended dose in SP847.

The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower.

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup] or the corresponding dose level for the tablet formulation). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Subjects enrolling from SP847 will have the option of remaining on the oral solution formulation of LCM or switching to the commercial tablet formulation, if feasible. Consideration of the current LCM milligram dose in the oral solution (syrup) should occur if/when transitioning to the tablet formulation. In cases where the LCM dose received with the oral solution (syrup) is not supported by the tablet strengths available in SP848 (50mg and 100mg), a clinical decision must

be made by the investigator or other study physician to either increase or decrease the LCM dose to the next multiple of 100mg with a maximum permitted dose of 600mg/day.

Subjects achieving a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet) who withdraw during the study should taper off study medication. It is recommended that the dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (see tables below). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Recommended LCM dose reduction (taper) for oral solution (syrup) formulation

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
12mg/kg/day (6mg/kg bid)	8mg/kg/day (4mg/kg bid)	4mg/kg/day (2mg/kg bid)	0
10mg/kg/day (5mg/kg bid)	6mg/kg/day (3mg/kg bid)	2mg/kg/day (1mg/kg bid)	0
8mg/kg/day (4mg/kg bid)	4mg/kg/day (2mg/kg bid)	0	–
6mg/kg/day (3mg/kg bid)	2mg/kg/day (1mg/kg bid)	0	–
4mg/kg/day (2mg/kg bid)	0	–	–

bid=twice daily; LCM=lacosamide

[a] Maximum LCM dose achieved is based upon the maximum recommended dose in SP847.

Recommended LCM dose reduction (taper) for tablet formulation

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
600mg/day (300mg bid)	400mg/day (200mg bid)	200mg/day (100mg bid)	0
500mg/day (250mg bid)	300mg/day (150mg bid)	100mg/day (50mg bid)	0
400mg/day (200mg bid)	200mg/day (100mg bid)	0	–
300mg/day (150mg bid)	100mg/day (50mg bid)	0	–
200mg/day (100mg bid)	0	–	–

bid=twice daily; LCM=lacosamide

[a] Maximum LCM dose achieved is based upon the maximum recommended dose in SP847.

4.4.1.4 Study completion

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up telephone contact are not required for subjects who participate in EP0151 or EP0152.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or parent/legal guardian) should taper LCM gradually as described in Section 4.4.1.3. These subjects should complete Visit 13/Termination Visit, followed by the Final Visit which occurs 2 weeks after the final dose of study medication, and then the Safety Follow-Up telephone contact which occurs 28 to 35 days after the last dose of LCM.

4.4.2 Description of investigational medicinal product

Beginning with protocol Amendment 3, the oral solution formulation contains 10mg/mL of drug substance (formerly containing 15mg/mL of drug substance) and is colorless to pale yellow in appearance. The oral solution (syrup) will be packaged in amber polyethylene terephthalate (PET) bottles with a white, child-proof, polypropylene screw cap.

The tablet formulation will be supplied in doses of 50mg and 100mg. The 50mg tablets are light pink, oval, film-coated tablets debossed with "SP" on 1 side and "50" on the other. The 100mg tablets are dark yellow, oval, film-coated tablets debossed with "SP" on one side and "100" on the other. The tablets will be packaged in high-density polyethylene bottles with a child-proof, polypropylene screw cap.

4.4.3 Randomization

This is an open-label study; subjects will not be randomized. Subjects who participated in SP847 or other LCM pediatric clinical studies in epilepsy will keep the unique number assigned in the primary study.

Subjects enrolling directly into SP848 without participation in a previous LCM clinical study will be assigned unique numbers for the purpose of study and subject identification, as well as for subject confidentiality. At the Screening Visit, each subject will be assigned the unique identifying number for this study.

4.5 Expected duration of the study

The maximum duration of LCM administration for an individual subject will be approximately 2 years or until approval of the marketing application (for Japan only), whichever comes first.

The start of the study is defined as the first visit of the first subject entering the study. The end of the study is defined as the date of the last visit of the last subject in the study.

4.6 Concomitant medication(s)/treatment(s)

The following medications/therapies are prohibited during the course of this study:

- Monoamine oxidase inhibitor-A compounds
- Narcotic analgesics
- Cannabidiols not approved or indicated for epilepsy by a local health authority

All concomitant medications and treatments must be recorded in the appropriate study documents (eCRF and source document).

Stable use of amphetamines and sedative antihistamines is allowed during the study. Also, stable, low doses of anxiolytics or hypnotics (ie, diazepam 5mg/day) are allowed for nonepilepsy indications only.

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

4.7 Procedures for monitoring subject compliance

Subjects' caregivers (including parent/legal guardian) will be instructed to return unused medication at each study visit. Returned medication will be reconciled by the investigator (or designee) in order to monitor the subject's compliance with the medication schedule. Drug accountability must be done in the subject's caregiver's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen.

All findings will be documented on forms provided by UCB BIOSCIENCES. Subject's noncompliance with regards to intake of LCM is defined as being less than 75% or more than 125% compliant with the dosage schedule.

If a subject is found to be noncompliant, a decision will be made by the investigator, in conjunction with UCB BIOSCIENCES, as to whether the subject should be withdrawn from the study.

5 TREATMENT PROCEDURES BY VISIT

For all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact), a visit window of ±7 days relative to Visit 1 is applicable. The Safety Follow-Up telephone contact will be performed 28-35 days after the last dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up telephone contact are not required for subjects who participate in EP0151 or EP0152.

Assessments will be done during monthly visits for the first 3 months, every 2 months for the remainder of Year 1, and every 3 months for Year 2. A detailed tabular schedule of study procedures is provided in Section 16.1. For further details of the assessments and the required procedures and methods, please refer to Section 6, Section 7, and Section 8.

5.1 Screening Visit

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848.

At the Screening Visit, subjects entering directly into SP848 (ie, subjects who have not participated in SP847 or another applicable LCM pediatric clinical study in epilepsy) will be evaluated for their suitability for enrollment in SP848. The Screening Visit is not applicable for subjects who have participated in SP847 or another applicable LCM pediatric clinical study in epilepsy; the first visit in SP848 for these subjects is Visit 1 (see Section 5.3).

The Screening assessments will be conducted up to 14 days prior to the first administration of LCM. It is acceptable for the Screening assessments to be conducted on more than 1 day, although it should not be done over longer than 1 week. Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by the local IRB/IEC, the subject will be requested to give assent to participate in the study. Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria and the results of the following pretreatment assessments (for further details of the assessments and the required procedures and methods, please refer to Section 6, Section 7, and Section 8 of this protocol).

- Concomitant medications assessment
- Concomitant AEDs assessment
- Medical history assessment
- Seizure history over the past 4 weeks (historical Baseline)
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight assessment
- Height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- C-SSRS

- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries
- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Adverse event reporting
- Health care resource use
- Dispense subject diary

The subject will be scheduled to return for a clinic visit (TV) less than 14 days from the last Screening Visit assessment(s).

5.2 Titration Visit(s) (TV1, TV2, TV3, TV4, TV5, TV6)

Eligible subjects who enter directly into SP848 (without prior participation in SP847 or another applicable LCM primary study) will initiate treatment with LCM at TV1, and the LCM dose will be titrated over the following week(s). Titration Visits are not applicable for subjects who have participated in SP847 or another LCM primary study; the first visit in SP848 for these subjects is Visit 1 (see Section 5.3).

At TV1, subjects who have enrolled directly into SP848 will receive a single dose of LCM (1mg/kg [oral solution] or 50mg [tablet]) during the clinic visit. Over the following days, subjects will be administered LCM 1mg/kg bid (oral solution) or LCM 50mg bid (tablet), and will begin titrating in weekly increments of 2mg/kg/day (oral solution) or 100mg/day (tablet) up to a level to optimize tolerability and seizure control (not to exceed 12mg/kg/day [or 600mg/day based on body weight, whichever is lower]). Subjects must be on each LCM dose for at least 5 days before titrating up to the next dose. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these cases would not be considered dose reductions. The LCM dose titration steps are summarized in Section 4.4.1.2.

A total of up to 6 Titration Visits may be required (eg, for a subject whose dose is titrated to the maximum permitted dose of LCM 12mg/kg/day). However, based on tolerability and seizure control, a subject's LCM dose may be titrated to a lower dose level; in such a case, fewer than 6 Titration Visits would be required.

The following assessments are required for each TV:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)

- Vital signs assessment (blood pressure and pulse)
- Body weight
- Blood sample for clinical chemistry, hematology, and endocrinology (TV4 only)
- Urine sample for urinalysis (TV4 only)
- LCM return/compliance (as applicable)
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Health care resource use
- Dispense subject diary
- Dispense LCM (as applicable)

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM maximum plasma concentration (C_{max}) 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. Subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

5.3 Visit 1 (Week 0)

For subjects who completed SP847, Visit 1 for SP848 was the same as Day 2 of the second PK collection time period (which may include an overnight stay at a hospital or medical facility) in SP847 (Day 28 for Cohorts 1, 2, 3, and 5 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 5 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 5 with maximum recommended dose of 12mg/kg/day). For subjects who discontinued SP847 due to a dose reduction or status epilepticus, Visit 1 was the Early Termination Visit in SP847. For subjects in SP847 who were titrated up to the maximum permitted dose of 600mg/day sooner than the study schedule would ordinarily indicate (based on body weight) and who enroll in SP848, the Early Termination Visit of SP847 also served as Visit 1 for SP848.

For subjects who enroll in SP848 after participation in other LCM pediatric clinical studies besides SP847 (ie, SP0966 and EP0060) in epilepsy, SP848 Visit 1 will be specified in the respective primary study protocol.

For subjects who enter directly into SP848 (without prior participation in SP847 or other LCM pediatric clinic studies in epilepsy), the LCM dose will be titrated at weekly intervals as described in Section 4.4.1.2 and Section 5.2. These subjects will reach Visit 1 either (1) when the LCM dose is titrated to a level that, in the opinion of the investigator, optimizes tolerability and seizure control, or (2) when the maximum permitted LCM dose is reached (12mg/kg/day [or 600mg/day based on body weight, whichever is lower]). In the case of a subject who requires a dose reduction during the Titration Visits, the subject's LCM dose will be returned to the

previous dose level and the next clinic visit will be Visit 1 at the reduced level. Visit 1 should occur at least 5 days after the final TV. At Visit 1, the progress in SP848 for subjects who entered directly into SP848 and for subjects who have enrolled from SP847 or other LCM pediatric clinical studies in epilepsy will be aligned; subsequent regularly scheduled clinic visits for all subjects will be at 4-week intervals as outlined in the following sections.

The informed consent process for SP848 will be conducted at Visit 1 for subjects who have not previously been through the informed consent process at the Screening Visit (ie, subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy for whom Visit 1 is the first study visit in SP848). Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by local IRB/IEC, the subject will be requested to give assent to participate in the study.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments (applicable only for subjects for whom Visit 1 is the first clinic visit for SP848), and a complete medical history update will be obtained. If available, the data for the following assessments will be taken from the last assessment during SP847 (or other primary study, as applicable):

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment but 30 minutes to 1 hour after the administration of LCM)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- C-SSRS

- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older) (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Adverse event reporting
- Health care resource use
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

5.4 Telephone contacts (Weeks 2, 6, 10, 16, 24, 32, 40, 48, 66, and 78)

Between scheduled clinic visits, the investigator (or designee) should contact the subject's caregiver (including parent/legal guardian) by telephone. The investigator (or designee) should remind the subject's caregiver (including parent/legal guardian) to ensure the diary is completed and to bring unused LCM to the next clinic visit. The following should be performed via telephone:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Adverse event reporting

If an AE necessitates the subject's withdrawal from the study, the subject should return for an Early Termination Visit (Section 5.17) as soon as possible.

Lacosamide is supplied so that the subject or caregiver (including parent/legal guardian) can immediately decrease their dose, if needed, in consultation over the telephone with the investigator or subinvestigator. Thus, LCM can be continued at a decreased dose until a clinic visit can be scheduled.

5.5 Visit 2 (Week 4)

During Visit 2 (Week 4), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination

- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry and hematology
- Blood samples for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine pregnancy test for female subjects of childbearing potential
- LCM return/compliance. Subject's caregivers will be instructed to return unused LCM at each study visit. Returned medication will be reconciled by the investigator (or designee) in order to monitor the subject's compliance with the medication schedule. If a subject is found to be noncompliant, a decision will be made by the investigator, in conjunction with UCB BIOSCIENCES, as to whether the subject should be withdrawn from the study.
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Health care resource use
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).
- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

5.6 Visit 3 (Week 8)

During Visit 3 (Week 8), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Urine pregnancy test for female subjects of childbearing potential
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Health care resource use
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parents/legal guardians) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).
- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased to a LCM level dose that is ≥8mg/kg/day or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).
- All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day. This ECG can be conducted at an Unscheduled Visit if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

5.7 Visit 4 (Week 12)

Assessments for Visit 4 (Week 12) are the same as those described for Visit 3 (Week 8), in Section 5.6.

5.8 Visit 5 (Week 20)

During Visit 5 (Week 20), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine sample for urinalysis
- Urine pregnancy test for female subjects of childbearing potential
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older) (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Adverse event reporting
- Health care resource use
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parents/legal guardians) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

5.9 Visit 6 (Week 28)

Assessments for Visit 6 (Week 28) are the same as those described for Visit 3 (Week 8) in Section 5.6, with the following exception: completion of the palatability and ease of use questionnaire and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) are conducted at Visit 6.

5.10 Visit 7 (Week 36)

Assessments for Visit 7 (Week 36) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exception: a 12-lead ECG is not conducted at Visit 7.

5.11 Visit 8 (Week 44)

Assessments for Visit 8 (Week 44) are the same as those described for Visit 3 (Week 8), in Section 5.6, with the following exception: a Tanner Stage assessment is conducted at Visit 8 (if applicable).

5.12 Visit 9 (Week 52)

Assessments for Visit 9 (Week 52) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exception: completion of the palatability and ease of use questionnaire and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) are conducted at Visit 9.

5.13 Visit 10 (Week 60)

Assessments for Visit 10 (Week 60) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exceptions: a 12-lead ECG is not conducted at Visit 10 (all sites) and a PK sample is routinely drawn at sites in Japan (removed for all other sites).

5.14 Visit 11 (Week 72)

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions for all sites: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no

endocrinology), the palatability and ease of use questionnaire is completed, and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted. In addition to the noted differences, a PK sample is routinely drawn at sites in Japan (removed for all other sites).

5.15 Visit 12 (Week 84)

Assessments for Visit 12 (Week 84) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exceptions for all sites: the laboratory blood sample is collected for endocrinology as well as clinical chemistry and hematology and a 12-lead ECG is not conducted. In addition to the noted differences, a PK sample is routinely drawn at sites in Japan (removed for all other sites).

5.16 Visit 13/Termination Visit (Week 96)

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up telephone contact are not required for subjects who participate in EP0151 or EP0152.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or parent/legal guardian) should taper LCM gradually as described in Section 4.4.1.3. These subjects should complete Visit 13/Termination Visit, followed by the Final Visit which occurs 2 weeks after the final dose of study medication, and then the Safety Follow-Up telephone contact which occurs 28 to 35 days after the last dose of LCM.

Assessments for Visit 13/Termination Visit (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions for all sites: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, a Tanner Stage assessment is conducted (if applicable), an Achenbach CBCL is conducted, Bayley-III scales are conducted, BRIEF-P/BRIEF and PedsQL scores are obtained, and the palatability and ease of use questionnaire is completed. In addition to the noted differences, a PK sample is routinely drawn at sites in Japan (removed for all other sites).

Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible. Taper of LCM may not

be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian.

5.17 Early Termination Visit

Subjects who withdraw from the study prematurely must complete an Early Termination Visit.

At the time of withdrawal from the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete the Early Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after the Early Termination Visit. The Final Visit is not required for subjects who withdraw from the study prematurely and who do not undergo taper of LCM.

Subjects who withdraw from the study prematurely and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or parent/legal guardian) should taper LCM gradually as described in Section 4.4.1.3. These subjects should complete the Early Termination Visit, followed by the Final Visit which occurs 2 weeks after the final dose of study medication, and then the Safety Follow-Up telephone contact.

The following will be performed at the Early Termination Visit:

- Concomitant medication assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
  - Under any circumstance for an ETV during Year 1
  - If possible, if the early termination during Year 2 is due to a SAE and the event is ongoing
- Urine sample for urinalysis
- Serum pregnancy test for females of childbearing potential
- Tanner Stage assessment (if applicable)
- Clinical Global Impression of Change

- Caregiver Global Impression of Change
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries
- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Palatability and ease of use questionnaire
- Adverse event reporting
- Health care resource use
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs)
- Dispense LCM. Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian.

5.18 Unscheduled Visit(s)

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, if an LCM dose increase is required at any time, or if a new concomitant AED is introduced, the subject must return for an Unscheduled Visit. If an AE prompts a dose reduction, the reduction can be implemented immediately at the investigator's discretion. However, the subject should return to the clinic as soon as possible for an Unscheduled Visit.

The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination

- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- LCM return/compliance (as applicable)
- Subject diary assessment
- C-SSRS (only if Unscheduled Visit is conducted due to an AE)
- Adverse event reporting
- Health care resource use
- Dispense LCM (as applicable)
- If possible, a blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM) if the unscheduled visit is due to a SAE

Additional assessments can be performed at the investigator's discretion.

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or after a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

5.19 Final Visit

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication. The Final Visit is not required for subjects who participate in EP0151 or EP0152.

During the Final Visit, the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology

- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Health care resource use

5.20 Safety Follow-Up telephone contact

The Safety Follow-Up telephone contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study) who do not participate in EP0151 or EP0152. For subjects who complete the study, this telephone contact will occur 28 to 35 days after Visit 13/Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]). For subjects who withdraw prematurely from the study, this telephone contact will occur 28 to 35 days after the Early Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]). The Safety Follow-Up telephone contact is not required for subjects who participate in EP0151 or EP0152.

The following should be performed via telephone:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Adverse event reporting. If an AE is reported at this telephone contact, the investigator will follow the AE until a definite outcome is achieved (Section 8.1.2).

5.21 Study conduct due to coronavirus disease 2019 pandemic

The protocol-mandated visit schedule should be followed to the extent possible, considering the individual benefit-risk assessment by the investigator. If necessary, remote visits may be conducted and the subjects or caregivers will be contacted by telephone or videoconference. Remote follow-up, at minimum with a telephone call after 3 months, must be done (preferably more frequently and as needed to follow-up on participant safety assessments).

Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the coronavirus disease 2019 (COVID-19) pandemic (eg, any measures that may limit access to the site or may require additional actions by the study participant prior to entry to the site).

If a subject needs to be discontinued and cannot come into the clinic, then appropriate tapering instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible.

In situations where a subject is unable to return to the study site, investigators will assess and document the subject's safety via telephone contact. Based on information gathered from the

telephone contact, investigators will confirm whether the subject could continue the current study treatment based upon the outcome of the safety assessment. Subjects' agreement to implement this procedure should be obtained and documented prior to implementing any changes. Changes in the study treatment supply in this situation are described in Section 9.5.

If a subject visits another facility for a medical issue (or has to switch sites for a COVID-19-related reason), the investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the clinical study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

Deviations to data collection including inability to perform some assessments, such as ECG, blood collection for safety laboratory assessments and PK, or alternative methods of assessment, such as phone calls, should be recorded in the source documentation and notated as "not done" in the eCRF.

In cases where subjects cannot return to the clinic, and it will not be possible to dispense a new seizure diary, subjects will be instructed to continue recording of seizures in a manner that is mutually agreed with the investigator (eg, hand-written notes, recording on a smart device). Any recording of seizures in a manner outside of the study seizure diary must be carefully documented in the source medical records (copies/print-screen printouts of these recordings will be brought to and retained at the site).

6 ASSESSMENT OF EFFICACY

6.1 Seizure counts

At Screening of SP847 (or other primary study as applicable) or at the Screening Visit of SP848 (for subjects who entered directly into SP848) subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous 4 weeks; this will serve as a historical Baseline. After the subject is enrolled in the SP848 study, seizure data will be collected in diaries provided to subjects/caregivers (including parents/legal guardians). Each subject/caregiver (including parent/legal guardian) will keep a diary to note daily seizure activity throughout the current study. The subject/caregiver (including parent/legal guardian) should be reminded to bring the diary with them at each clinic visit. The following information will be recorded:

- Seizure type
- Seizure frequency

6.2 Global Impression of Change

6.2.1 Clinical Global Impression of Change

The Clinical Global Impression of Change will be assessed at least once per year and be completed according to the tabular schedule of study procedures, Section 16.1.

For the assessment of the Clinical Global Impression of Change, the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1

of SP847 (or other primary study as applicable) will serve as Baseline; the Screening Visit of SP848 will serve as Baseline for those subjects entering directly into SP848.

The investigator will be asked to check the number that best describes the subject's condition over the past 4 weeks compared to Baseline:

1. Very much improved
2. Much improved
3. Minimally improved
4. No Change
5. Minimally worse
6. Much worse
7. Very much worse

6.2.2 Caregiver Global Impression of Change

The Caregiver Global Impression of Change will be assessed at least once per year and be completed according to the tabular schedule of study procedures, Section 16.1.

For the assessment of the Clinical Global Impression of Change, the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline; the Screening Visit of SP848 will serve as Baseline for those subjects entering directly into SP848.

The caregiver will be asked to check the number that best describes the subject's condition over the past 4 weeks compared to Baseline:

1. Very much improved
2. Much improved
3. Minimally improved
4. No Change
5. Minimally worse
6. Much worse
7. Very much worse

6.3 Pediatric Quality of Life Inventory

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001; Varni et al, 2011). The PedsQL will be completed up to two times per year and will be administered according to the tabular schedule of study procedures, Section 16.1.

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects ≥1 month to ≤12 months; ≥13 months to ≤24 months; >2 years to ≤4 years, ≥5 years to

≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≥1 month to ≤18 years of age.

The multidimensional PedsQL scale encompasses the essential core domains for pediatric HRQoL measurement: 1) Physical Functioning/Symptoms, 2) Emotional Functioning, 3) Social Functioning, and 4) Cognitive/School Functioning. The PedsQL assessment is retrospective to the prior month, and individual items are scored using a 5-point Likert scale (never, almost never, sometimes, often, or always). A total health summary score is calculated from the sum of the raw scores of the individual items, with higher scores indicating higher HRQoL.

6.4 Health care resource use

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations not related to study, and hospitalizations not related to study. Health care resource use parameters will be collected according to the tabular schedule of study procedures, Section 16.1.

7 ASSESSMENT OF PHARMACOKINETICS

Blood samples will be collected at selected visits for the assessment of LCM and concomitant AED plasma concentrations (for population PK analysis). These blood samples will be collected along with the clinical chemistry/hematology samples at any time after intake of study medication according to the tabular schedule of study procedures, Section 16.1. In each case, the exact time and dose (in mg) when the subject took the most recent doses of LCM and concomitant AED(s), and the exact time of blood sampling must be recorded.

Each blood sample drawn will be split into 2 duplicate samples. The samples will be centrifuged and stored at ≤-20ºC until shipped to a central laboratory. The central laboratory will store the plasma samples at -20ºC until analysis. Details of plasma sample collection and processing, sample labeling, and shipment will be provided in the laboratory manual.

8 ASSESSMENT OF SAFETY

8.1 Adverse events

8.1.1 Definition of AE

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after signature of the Informed Consent), including any Pretreatment and Posttreatment Periods required by the protocol, must be reported in the eCRF even if no investigational product was taken but specific study procedures were conducted. These include all AEs not present prior to the initial visit and all AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline Period.

8.1.2 Procedures for reporting and recording AEs

The study participant will be given the opportunity to report AEs spontaneously. A general prompt will also be given to detect AEs, for example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

8.1.3 Description of AEs

When recording an AE, the investigator should use overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE eCRF page (including judgment of relationship to trial medication) are described in the AE Completion Guideline in the eCRF.

8.1.4 Follow up on adverse events

If an AE is still ongoing at the end of the study for a subject, a follow-up report should be provided until resolution/stable level of sequelae, the investigator no longer deems that it is clinically significant, or until the subject is lost to follow-up. If no follow-up report is provided, the investigator must provide a justification. The follow-up will be usually continued for 30 days after the subject has completed the study.

UCB BIOSCIENCES may request that the investigator perform or arrange for the conduct of supplementary measurements and/or evaluations.

8.1.5 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- the outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening",
- the AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one.

8.1.6 Pregnancy

Should a subject become pregnant after the first intake of any investigational medicinal product, UCB BIOSCIENCES should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known and the following should be completed:

- The subject should return for an early discontinuation visit

- The subject should immediately stop the intake of the investigational medicinal product or be down-titrated as instructed at the early discontinuation visit
- A Safety Follow-up visit should be scheduled 28 to 35 days after the subject has discontinued the investigational medicinal product.

The investigator must inform the subject of information currently known about potential risks and about the available alternatives, eg, voluntary termination with medication (to be proposed on a study-specific basis).

In cases where the partner of a male subject enrolled in a clinical trial becomes pregnant, UCB BIOSCIENCES will ask the investigator or designee to contact the subject and his partner to request consent via the Partner Pregnancy Consent Form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome Form will be forwarded to the subject's partner for completion.

The pregnancy will be documented on the Pregnancy Report and Outcome Form. The progression of the pregnancy and the eventual birth (if applicable) must be followed-up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.

In certain circumstances, UCB BIOSCIENCES may request that follow-up is continued for a period longer than 30 days.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those serious events must be additionally reported using the Investigator SAE Report Form.

8.1.7 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

8.1.8 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed per the protocol and including overdose) should be recorded in the source documents and eCRF module. Any SAE or non-serious AE associated with excessive dosing must be followed as any other serious or non-serious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

8.1.9 Safety signal detection in ongoing clinical studies and Data Monitoring Committees

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the investigational medicinal product so that investigators, clinical

study subjects, regulatory authorities, and IRBs/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 (PS) representative.

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

8.1.10 Occurrence of COVID-19

Occurrence of COVID-19 in subjects should be reported as either "suspected COVID-19" or "confirmed COVID-19" along with all available relevant data including diagnostic and laboratory data. For subjects where COVID-19 is still suspected despite a negative viral test, please report as "suspected COVID-19" and provide relevant data to support the diagnosis as well as the test results.

8.2 Serious adverse events

8.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. A SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious

  (Important medical events include, but are not limited to, potential Hy's Law [see Section 8.2.2], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  A patient admitted to a hospital, even if released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for

this criteria and, instead, should be evaluated for one of the other criteria in the definition of serious (eg, life-threatening adverse experience, important medical event).

Hospitalizations for reasons not associated with the occurrence of an AE (eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE since there is no AE upon which to assess the serious criterion. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

8.2.2 AEs of special interest

An AE of special interest is any AE that a regulatory authority has mandated to be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

The following are the LCM AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree Type I and II and third degree), and marked bradycardia (<45beats/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 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 one 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 ≥2x ULN
  - AST ≥2x ULN

- 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, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

8.2.3 Immediate reporting of AEs

The following AEs must be reported immediately:

- SAE: AEs that the investigator classifies as serious by the above definitions, regardless of causality.
- Suspected transmission of an infectious agent via a medicinal product.
- AEs of special interest (as defined in Section 8.2.2).

8.2.4 Procedures for reporting serious adverse events

If an SAE is reported, UCB BIOSCIENCES must be informed within 24 hours of receipt of this information by the site (see contact details for SAE reporting listed in the Study Contact Information section). The investigator must forward to UCB BIOSCIENCES (or its representative) a duly completed Investigator SAE Report form provided by UCB BIOSCIENCES, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

A copy of the Investigator SAE Report form will be provided to the investigator. The Investigator SAE Report form must be completed in English.

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The reference document for the assessment of the expectedness of the SAEs is the Investigator Brochure.

8.2.5 Follow up of serious adverse events

A SAE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events are provided in Section 8.3.2.4.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety database without limitation of time.

8.2.6 Anticipated serious adverse events

The following list of anticipated SAEs is 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 8.2.4.

Anticipated SAEs for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administrative site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion
	Incontinence
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder
Reproductive system and breast disorders	Menstrual disorder

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

8.3 Laboratory measurements

Blood and urine specimens (approximately 5 to 15mL each) for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedule of study procedures, Section 16.1. For subjects aged 5 to 17 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine samples. The procedures for handling and shipping these specimens will be provided to the sites.

The following laboratory tests will be performed:

Urinalysis	Hematology	Clinical chemistry		Endocrinology
Specific gravity	RBC	Total serum protein	Cholesterol	FSH
pH	WBC	Albumin	Triglycerides	LH
Protein	Differential count	Calcium	Total bilirubin	Testosterone
Glucose	Platelet count	Phosphorus	Alkaline phosphatase	TSH
Ketone	Hemoglobin	Glucose	Creatinine	T3 (total and serum-free)

Urinalysis	Hematology	Clinical chemistry		Endocrinology
Microscopic exam for blood cells for casts/hpf	Hematocrit	Serum electrolytes (sodium, potassium, chloride, bicarbonate) Uric acid	AST ALT GGT BUN	T4 (total and serum-free)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; GGT=gamma glutamyl transferase; hpf=high power field; LH=luteinizing hormone; RBC=red blood cells; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cells

8.3.1 Pregnancy testing

Females of childbearing potential will have serum and urine pregnancy tests performed during the study according to the tabular schedule of study procedures, Section 16.1.

8.3.2 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 4.3.3.1 with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 8.2.2), and, if applicable, also reported as an SAE (see Section 8.2.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 8–1 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 8.3.2.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 8.3.2.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 4.3.3.1), IMP must be permanently discontinued.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 8–1: Required investigations and follow up of PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 8.3.2.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥5xULN	NA	NA				
≥3xULN	NA	Yes				
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 8.3.2.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Table 8–1: Required investigations and follow up of PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 8.3.2.3)	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 8.3.2.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

8.3.2.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 8.3.2.3) and SAE report (if applicable).

8.3.2.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 4.3.3.1 and Table 8–1 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

8.3.2.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 8–2 (laboratory measurements) and Table 8–3 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 8–2: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Hematocrit
	Hemoglobin
	Platelet count
	RBC count
	WBC count
	WBC differential count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
	ALT
	AST
	ALP
	GGT
	Albumin
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma-glutamyltransferase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RBC=red blood cell; RNA=ribonucleic acid; ULN=upper limit of normal; WBC=white blood cell

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 8–3: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

8.3.2.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 8–1. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

8.4 Other measurements

8.4.1 Physical examination

Physical examinations will be performed by medically qualified clinicians licensed to perform the examination according to the tabular schedule of study procedures, Section 16.1. Height will be measured without shoes according to the tabular schedule of study procedures, Section 16.1.

8.4.1.1 Complete physical examination

The complete physical examination will include cardiac and respiratory function via auscultation, temperature, and review of all body systems.

8.4.1.2 Brief physical examination

The brief physical examination will includes a review of the following body systems:

- Cardiovascular
- Pulmonary
- Abdominal (hepato-gastrointestinal)
- Dermatologic

8.4.2 Neurological examination

The neurological examination will be performed according to the tabular schedule of study procedures, Section 16.1. The neurological examination should be conducted by a medically qualified clinician with documented training in the conduct of neurological examinations. If possible, the same clinician should conduct all neurological examinations for the same subject during the study. The investigator or subinvestigator is responsible for confirming the diagnosis of partial-onset seizures or other epilepsy syndrome.

8.4.2.1 Complete neurological examination

The complete neurological examination will include selected assessment of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.

8.4.2.2 Brief neurological examination

The brief neurological examination will include selected assessment of mental status, cranial nerves, and coordination/cerebellar function.

8.4.3 Vital signs and body weight

Noninvasive blood pressure (systolic and diastolic) and pulse rate will be measured at all visits in a sitting position after at least 3 minutes at rest. Body weight will be determined without shoes and wearing light clothing, according to the tabular schedule of study procedures, Section 16.1.

8.4.4 12-lead ECG

Standard 12-lead ECGs will be performed according to the tabular schedule of study procedures, Section 16.1, and as described in Section 5.

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a

LCM dose level that is ≥8mg/kg/day or when a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Care should be taken to assure proper lead placement and quality of ECG recording. Subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording.

8.4.4.1 Overall ECG interpretation

An immediate initial review of the ECGs will be conducted locally by the investigator, subinvestigator, or qualified designated reader. If this reading identifies abnormal ECG findings that are assessed by the investigator or subinvestigator to be clinically significant, then the ECG should be repeated in 1 hour, unless circumstances require a more rapid assessment. If the clinically significant abnormality is confirmed by the repeat ECG or if the investigator feels it is medically necessary, then the subject must be withdrawn from the study (see Section 4.3.3). The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

8.4.4.2 Specific QTcB criteria

The ECG recorder provides a corrected QT interval using the Bazett method (QTcB) for each QT interval measurement. The value of the QTcB is used to determine subject eligibility to enter and to continue in the study (as noted in Section 4.3.2 and Section 4.3.3).

8.4.5 Tanner Stage

At selected visits for applicable subjects, the investigator or qualified designee will evaluate the subject's sexual development using the 3-item scale. The investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at screening or those subjects who become pubescent during the course of the study).

The evaluation of Tanner Stage for applicable subjects will be completed according to the tabular schedule of study procedures, Section 16.1.

8.4.6 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures, Section 16.1.

Subjects enrolling directly who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent

visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version used at subsequent visits.

The C-SSRS is not validated and will not be used for subjects <6 years of age. Subjects 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. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Parents and caregivers should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

8.4.7 Achenbach CBCL

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. Behavioral problems will be scored by the parent(s)/legal representative(s). Depending on the subject's age, 2 versions of the CBCL will be used. The CBCL/1½-5 checklist is intended for use in children 18 months to 5 years and 11 months of age. For subjects ≥6 years to ≤17 years of age, the CBCL/6-18 version will be used.

The Achenbach CBCL will be completed according to the tabular schedule of study procedures, Section 16.1.

In both questionnaires, the occurrence of certain problems and behaviors (in the past 2 months for the CBCL/1½-5 version and in the past 6 months for the CBCL/6-18 version) will be scored on the following scale:

- 0=not true (as far as known)
- 1=somewhat or sometimes true
- 2=very true or often true

Syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each syndrome and composite scores, categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

In addition, the Achenbach CBCL/6-18 includes ratings related to performance in school, activities in leisure time, and special interests.

8.4.8 Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley-III scales are recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) are a standardized individually administered adaptive assessment that measures the developmental functioning of infants and young children from 1 month to 42 months of age (Bayley, 2006). The Bayley-III scales measure cognitive, language, motor, social-emotional, and adaptive development and are a revision of the predecessor, the Bayley Scales of Infant Development, Second Edition (BSID-II) (Bayley, 1993). The Bayley-III

scales are a technically sound instrument, with strong internal consistency, as well as test-retest stability. The Bayley-III scales are validated only in English.

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for SP848.

The Bayley-III scales are an individually administered adaptive assessment that presents children with situations and tasks designed to produce an observable set of behavioral responses. They consist of a cognitive scale, a language composite scale with receptive and expressive language subscales, and a motor composite scale with fine and gross motor subscales to be completed by the Investigator or designee, and of a social-emotional scale, comprising social emotional competence, and sensory processing, and an adaptive behavior scale, which assesses the attainment of skills necessary for the development of independence, to be completed by the child's parent or caregiver.

The completion of the Bayley-III scales will require approximately 50 minutes for children who are 12 months old or younger and 90 minutes for children aged 13 months and older.

The Bayley-III scales will be completed according to the tabular schedule of study procedures, Section 16.1.

8.4.9 Palatability and ease of use questionnaire for LCM

UCB BIOSCIENCES has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg, taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

The questionnaire will be completed according to the tabular schedule of study procedures, Section 16.1.

8.4.10 Behavior Rating Inventory of Executive Function

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P/BRIEF will be administered according to the tabular schedule of study procedures, Section 16.1.

The BRIEF-P and BRIEF include rating forms used by parents to assess subjects' executive functioning. Executive functions broadly encompass a set of cognitive skills that are responsible for the planning, initiation, sequencing, and monitoring of complex goal-directed behavior.

The BRIEF-P rating form consists of items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The clinical scales form 3 broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition) and 1 composite score (Global Executive Composite).

The BRIEF rating form consists of items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of materials, and Monitor. These clinical scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

Both the BRIEF-P and the BRIEF include validity scales to measure negativity and inconsistency of responses.

9 MANUFACTURING, HANDLING, AND ACCOUNTABILITY OF STUDY MEDICATION

9.1 Manufacturing, packaging, and labeling

Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws and regulations. It is suitably packaged, in such a way as to protect the product from deterioration during transport and storage.

Description of packaging:

Lacosamide oral solution (syrup) will be packaged in 200mL amber PET bottles with a white, child-proof, polypropylene screw cap. Different volumes of LCM syrup will be taken to obtain the appropriate dose.

Lacosamide tablets will be packaged in high-density polyethylene bottles with a child-proof, polypropylene screw cap.

Contents of the labels:

The labels for LCM will include the following information (not all information will appear on all labels):

- Sponsor name, address, and telephone number
- Statement "Caution: New drug – Limited by federal law to investigational use"
- Statement "For clinical trial use only"
- Study number
- Kit number
- Pharmaceutical dosage form
- Name of drug
- Route of administration
- Directions for use
- Date bottle opened
- Do not use after (date)
- Strength per unit
- Quantity of dosage units
- Batch number
- Statement "Keep out of reach of children"
- Storage conditions
- Expiry date

- Subject number
- Visit number
- Date dispensed
- Name of investigator and telephone number
- Statement “Return all empty, partially used, and unused product”
- Statement “Class scheduling as a controlled substance”

9.2 Supply, handling, and storage

Lacosamide (oral solution [syrup] and tablet) is stable at room temperature and is to be stored at temperatures not exceeding 25.4°C (77.7°F) or below 14.5°C (58.1°F). Lacosamide should not be frozen or refrigerated.

The investigator (or designee) is responsible for safe and proper storage of LCM at the site. Lacosamide stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature and by completion of a temperature log in accordance with local requirements on a regular basis, showing minimum and maximum temperatures reached over the time interval.

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

The investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

9.3 Drug accountability procedures

A Drug Accountability form will be used to record LCM dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any LCM 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 LCM until returned or destroyed by a UCB representative.

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 LCM is used only in accordance with the 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 LCM must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs 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.

9.4 Retrieval/recall of study medication

Lacosamide being returned following study completion or due to product expiration or defect should be returned to UCB BIOSCIENCES or designee for final inventory using the provided forms. UCB BIOSCIENCES or designee will oversee destruction of returned drug after the clinical study report is completed.

9.5 Alternative study treatment supply due to COVID-19 pandemic

When a subject can no longer return to the study site due to general circumstances but will continue in the study, the following methods may be used to provide study treatment:

- Site to subject: In instances where site staff can ship study treatment dispensed from the site pharmacy supply directly to the subject.
- Depot to subject: In instances where it is not possible for the site staff to access study treatment in the site pharmacy and/or ship study treatment dispensed from the site pharmacy supply directly to the subject.

10 DATA QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Site qualification

A site visit will be performed by UCB BIOSCIENCES or designee to discuss the protocol, to ensure the availability of appropriate study personnel, adequate resources, and to assess their ability to properly conduct the study according to International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and local requirements. These procedures do not need to be repeated for this extension study (if a site needs to be added to SP848 that did not participate in SP847, an assessment will be made to determine whether a site visit is required).

10.2 Monitoring

UCB BIOSCIENCES or designee will monitor the study to meet the Sponsor's monitoring standard operating procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB BIOSCIENCES to a CRO or a contract monitor.

The investigator and his/her staff will be expected to cooperate with UCB BIOSCIENCES personnel or agents of UCB BIOSCIENCES and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information.

The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspections.

10.2.1 Definition of source data

All source documents must be accurate, legible, 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 correcting fluid or have temporary attachments (such as removable self-stick notes). Photocopies of CRF forms are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/physician records, charts, diaries, x-rays, laboratory results, printouts, pharmacy

records, care records, ECG or other printouts, completed scales, or Quality of Life Questionnaires, 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 subject's source documents. The investigator will authorize the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

10.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents.

10.3 Auditing

The investigator will permit study-related audits mandated by UCB, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

11 DATA HANDLING AND RECORD KEEPING

The parent/legal guardian's consent, subject's assent, and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.1 Case Report form completion

This study is performed using remote data capture (RDC); 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.

11.2 Database entry and reconciliation

Electronic Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. This study is performed using RDC; the data are entered into the eCRFs once and are subsequently verified. An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

11.4 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). 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.

11.5 Data management

Details regarding data management will be elaborated in the study-specific Data Management Manual.

12 STATISTICS

This study has an explorative, descriptive aim and does not intend to prove or disprove any statistical hypotheses. Hence, inferential statistical tests are not planned for the primary and secondary variables described below.

12.1 Description of statistical methods

Descriptive statistics will be used to provide an overview of the study results. For categorical parameters, these will consist of the number and percentage of subjects in each category. The

denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.

Visit 1 of SP847 (or other primary study as applicable) or the Screening Visit of SP848 (for subjects who enter directly into SP848) will serve as Baseline values for safety and efficacy variables unless otherwise noted.

Further statistical methods are presented below, and will be described in more detail in the Statistical Analysis Plan.

12.1.1 Definition of analysis sets

The Safety Set (SS), which is defined as all enrolled subjects who take at least 1 dose of LCM in this study. All safety analyses will be performed on the SS.

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects from the SS having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) on at least 1 visit with documented LCM intake times.

The Full Analysis Set (FAS) will be used for the analysis of seizure data and will consist of all subjects in the SS, who have at least 1 completed post-Baseline seizure diary.

12.1.2 Statistical analysis of safety variables

12.1.2.1 Primary safety variables

The primary variables, for assessment of safety and tolerability, are the incidence of TEAEs and the incidence of SAEs.

12.1.2.1.1 AEs

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), and tabulated by system organ class and preferred term.

Treatment-emergent AEs will be defined as those events which started on or after the date of first SP848 LCM administration, or whose severity worsened on or after the date of first SP848 LCM administration. Adverse events occurring within 30 days after last dose of LCM will be considered treatment-emergent. The incidence of TEAEs will be presented by system organ class and preferred term. Serious AEs will also be tabulated and listed.

12.1.2.2 Other safety variables

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, endocrinology, and urinalysis), 12-lead ECG measurements, vital sign measurements (blood pressure and pulse rate), physical and neurological exam findings, body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 [or other primary study as applicable] Visit 1) or the Screening Visit (for subjects who entered directly into SP848) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

The shift from Baseline to the subject's last visit at which a physical and/or neurological examination was performed post-Baseline will be summarized by category.

Laboratory, ECG, and vital signs data outside of the respective reference ranges will be listed and highlighted.

Changes in behavior and development from Baseline as measured using the Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) and Bayley-III scales for children <18 months of age will be summarized descriptively and presented by visit. Changes in cognitive function as measured using the BRIEF-P/BRIEF will be summarized by descriptive statistics at each visit. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

12.1.2.2.1 Palatability and ease of use questionnaire

Data from the palatability and ease of use questionnaire will be summarized descriptively at each visit where it is assessed.

12.1.3 Statistical analysis of PK variables

12.1.3.1 Descriptive statistics

Descriptive summaries (n, mean, SD, coefficient of variation (CV), median, minimum, and maximum) for the LCM plasma concentration and the plasma concentrations for selected concomitant AEDs will be presented by visit and actual dose.

12.1.3.2 Population PK analysis

The plasma concentration data of SP848 will be included in a population PK model of LCM, using the LCM plasma concentrations and dosing records, as well as demographic covariates and the presence of concomitant AEDs.

Further details will be described in the Statistical Analysis Plan or in a separate Population PK analysis plan.

12.1.4 Statistical analysis of efficacy variables

12.1.4.1 Secondary efficacy variables

12.1.4.1.1 Percent change from Baseline in 28-day partial-onset seizure frequency

Seizure frequency will be assessed using seizure diaries in order to evaluate the preliminary efficacy of LCM in this population. Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval]) divided by [number of days in the interval]) multiplied by 28 and summarized descriptively for the overall Treatment Period.

12.1.4.1.2 ≥50% reduction in 28-day partial-onset seizure frequency

For subjects with POS, the number and percentage with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders) will be summarized for the overall Treatment Period.

12.1.4.1.3 ≥75% reduction in 28-day partial-onset seizure frequency

For subjects with POS, the number and percentage with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders) will be summarized for the overall Treatment Period.

12.1.4.1.4 Seizure days per 28 days (subjects with generalized seizures only)

For subjects with generalized seizures, the number of seizure days per 28 days will be summarized descriptively for the overall Treatment Period.

12.1.4.1.5 Seizure-free status

The number and percentage of subjects achieving a seizure-free status for the overall Treatment Period will be presented.

12.1.4.2 Other efficacy variables

12.1.4.2.1 Clinical Global Impression of Change and Caregiver Global Impression of Change

The number and percentage of subjects with each Clinical Global Impression of Change and Caregiver Global Impression of Change value will be summarized at each visit in which they are assessed and grouped by dose.

12.1.4.2.2 PedsQL

The PedsQL score and change from Baseline scores will be analyzed in a descriptive manner. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

12.1.4.2.3 Health care resource use

Descriptive statistics will be presented for the number of medical resources used (medications, consultations, procedures, hospitalizations, and length of hospital stays).

12.1.4.2.4 Seizure frequency analyses

All seizure frequency analyses as described in the secondary efficacy variables (Section 12.1.4.1) may be additionally presented by modal daily dose group, by seizure type, by seizure classification subgroup, by time interval, by visit or time period, or by completer cohort. Additional details will be provided in the Statistical Analysis Plan.

12.1.5 Handling of protocol violators, drop-outs, and missing values

All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

Subjects who discontinue from the study prematurely will be evaluated based on the data collected at each visit attended.

Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.

12.1.6 Interim analysis

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

12.2 Determination of sample size

Approximately 42 subjects from the SP847 study will be eligible to enroll in this open-label study. Other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848. Protocol Amendment 8 allows an enrollment increase from 75 to 100 eligible pediatric subjects ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of subjects down to 1 month of age.

In total, up to approximately 400 subjects may be eligible to participate in SP848.

13 ETHICS AND REGULATORY

13.1 Informed consent

Informed consent has to be obtained from the subject's parent/legal guardian 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 IRB/IEC, assent also has to be obtained from the subject.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject and/or the subject's parent/legal guardian in both oral and written form by the investigator (or designee). Each subject and/or subject's parent/legal guardian will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the written informed consent form should be signed and personally dated by the subject's parent/legal guardian and by the person who conducted the informed consent discussion (investigator or designee). The subject's parent/legal guardian must receive a copy of the signed and dated informed consent form. As part of the consent process, each subject's parent/legal guardian must consent to direct access to the subject's medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

The informed consent form should be updated or amended whenever new information becomes available that may be relevant to the subject. The subject's parent/legal guardian should then sign the revised informed consent form.

13.2 Notification/submission to relevant regulatory authority(ies)

UCB BIOSCIENCES in conjunction with the CRO is responsible for fulfilling all regulatory aspects of the study with regard to regulatory submissions/filings.

13.3 Institutional Review Board/Independent Ethics Committee

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB BIOSCIENCES will ensure that an appropriately constituted IRB/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 BIOSCIENCES will forward copies of the protocol, informed consent form, investigator's brochure, investigator's curriculum vitae, advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written, signed, and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. 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 IRB/IEC as allowed.

The investigator is specifically requested to collect and report to UCB BIOSCIENCES (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the investigational product), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any AE within this period. Adverse events that the investigator thinks may be associated with the investigational product must be reported to UCB BIOSCIENCES regardless of the time between the event and the end of the study.

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

13.3.1 Reporting to ethics committee

The investigator is responsible for reporting to the IRB/IEC (eg, reporting of SAEs) in accordance with national or local requirements.

13.4 Basic principles and appropriate national guidelines

This protocol will be conducted under the current ICH E6 guideline commonly known as GCP, the applicable national requirements, and ethical principles that have their origins in the Declaration of Helsinki.

13.5 Subject privacy

UCB BIOSCIENCES staff or any designees affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB BIOSCIENCES will be identified only by an identification number.

The investigator agrees that representatives of UCB BIOSCIENCES, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject'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 subject's study participation, and autopsy reports for deaths occurring during the study).

13.6 Protocol amendments and emergency deviations

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Other than in an emergency, all items in the protocol and amendment(s) are to be followed exactly. If an amendment is required, this must be made in written form and receive approval according to the appropriate SOP. Protocol amendment(s) will be distributed to investigator(s) with instructions. All protocol amendments, except those with only logistical/administrative implications will be submitted to the IRB/IEC for review and approval prior to implementation and to regulatory authorities for approval/notification, as applicable.

In the event that an emergency or other medical event occurs that requires a protocol deviation, the investigator (or designee) must contact UCB BIOSCIENCES as soon as possible to decide whether the subject should continue with the study. The protocol deviation will be documented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in separate agreements as appropriate.

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16 SUPPLEMENTS

16.1 Tabular schedule of study procedures

Table 16–1: Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h, j]		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h, j]					X				X	X		X	
Blood sample for LCM PK[k]	X[h, j]		X			X		X		X	X			
Blood sample for concomitant AEDs[k]	X[h, j]		X			X		X		X	X			
Urinalysis (subjects aged 5 to 17 years)	X[h, j]					X				X	X		X	
Pregnancy test[l]	X[h, j, S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[m]	X[h, j]								X		X			
Clinical GIC	X[h, j]					X				X	X			
Caregiver GIC	X[h, j]					X				X	X			
Palatability and ease of use questionnaire							X			X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[n]	X[o]		
LCM return/compliance			X	X	X	X	X	X	X	X	X	X[o]	X	

Table 16–1: Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[p]	X[h]		X	X	X	X	X	X	X	X	X	X[q]	X	
Achenbach CBCL	X					X				X	X			
Bayley-III scales	X					X				X	X			
BRIEF-P/BRIEF	X					X				X	X			
PedsQL	X					X				X	X			
AE reporting[r]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; SAE= serious adverse event; U=urine; Unsch=Unscheduled; V=Visit

Note: All subjects who directly enrolled into SP848 should follow the titration schedule in Table 16–3.

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] For subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication. The Final Visit is not required for subjects who participate in EP0151 or EP0152.

[g] This TC occurs 28 to 35 days after the last dose of LCM. The Safety Follow-Up TC is not required for subjects who participate in EP0151 or EP0152.

[h] For subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy, assessments may have been done as part of the last visit of the primary study. For subjects enrolling directly into SP848, these assessments should be completed at Visit 1.

[i] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[j] For subjects enrolling from EP0060, these assessments should be completed at Visit 1.

[k] Blood samples may be drawn at any time post-dosing with LCM.

[l] For female subjects of childbearing potential, serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[m] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[n] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[o] As applicable.

[p] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[q] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[r] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Table 16–2: Schedule of study procedures for SP848 (Year 2)

Study SP848	Year 2								Safety Follow-Up
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/ TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK	X[h]		X[h]	X[h]	X[h]	X[i]	X[i]		
Blood sample for concomitant AEDs						X[i]	X[i]		
Urinalysis (subjects aged 5 to 17 years)			X		X	X		X	
Pregnancy test[j]	X[U]		X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[k]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Palatability and ease of use questionnaire			X		X	X			
Dispense LCM	X		X	X	X[l]	X[l]	X[m]		
LCM return/compliance	X		X	X	X	X	X[m]	X	

Table 16–2: Schedule of study procedures for SP848 (Year 2)

Study SP848	Year 2								Safety Follow-Up
Visit[a]	V10	TC[b]	V11	V12	V13/ TermV	ETV[c]	Unsch Visit[d]	Final Visit[e]	TC[f]
Weeks in study	**60**		**72**	**84**	**96**				
Dispense diary	X		X	X	X	X			
Diary assessment	X		X	X	X	X	X	X	
C-SSRS[n]	X		X	X	X	X	X[o]	X	
Achenbach CBCL			X		X	X			
Bayley-III scales			X		X	X			
BRIEF-P/BRIEF			X		X	X			
PedsQL			X		X	X			
AE reporting	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; TermV=Termination Visit; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication. The Final Visit is not required for subjects who participate in EP0151 or EP0152.

[f] This TC occurs 28-35 days after the last dose of LCM. The Safety Follow-Up TC is not required for subjects who participate in EP0151 or EP0152.

[g] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their

morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[h] Blood sample for LCM PK will be routinely collected for subjects enrolled at sites in Japan. Blood samples may be drawn at any time post-dosing with LCM.

[i] Blood samples for LCM and concomitant other AEDs may be collected at an Unscheduled Visit or Early Termination Visit if the visit is related to an ongoing SAE.

[j] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[k] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[l] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[m] As applicable.

[n] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[o] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Table 16–3: Schedule of study procedures for SP848 (Screening Visit and Titration Visits, subjects enrolling directly into SP848)

Study SP848	Screening	Titration Visits					
Visit	**Screening Visit**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**
Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Seizure history	X						
Concomitant medications	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X
Physical exam (complete)	X						
Physical exam (brief)		X	X	X	X	X	X
Neurological exam (complete)	X						
Neurological exam (brief)		X	X	X	X	X	X
12-lead ECG[a]	X	X	X	X	X	X	X
Blood pressure and pulse	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X
Height	X						
Clinical chemistry and hematology blood sample	X				X		
Endocrinology blood sample	X				X		
Urinalysis (subjects aged 5 to 17 years)	X				X		
Pregnancy test[b]	X						
Tanner Stage	X						
Clinical GIC							
Caregiver GIC							
Dispense LCM		X	X	X	X	X	X
LCM return/compliance		X	X	X	X	X	X
Dispense diary	X	X	X	X	X	X	X
Diary assessment		X	X	X	X	X	X

Table 16–3: Schedule of study procedures for SP848 (Screening Visit and Titration Visits, subjects enrolling directly into SP848)

Study SP848	**Screening**	**Titration Visits**					
Visit	**Screening Visit**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**
C-SSRS[c]	X	X	X	X	X	X	X
Achenbach CBCL	X						
Bayley-III scales	X						
BRIEF-P/BRIEF	X						
PedsQL	X						
AE reporting	X	X	X	X	X	X	X
Health care resource use	X	X	X	X	X	X	X

AE=adverse event; AEDs=antiepileptic drugs; C_{max}=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; GIC=Global Impression of Change; LCM=lacosamide

[a] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[b] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Screening Visit.

[c] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

16.2 International Classification of Epileptic Seizures (1981)

Adapted from the International Classification of Epileptic Seizures (1981)

I. Partial seizures (focal, local)

A. Simple partial seizures (consciousness not impaired)

1. With motor signs
2. With somatosensory or special sensory symptoms (simple hallucinations, eg, tingling, light flashes, buzzing)
3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation)
4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures.

B. ***Complex partial seizures (with impairment of consciousness: may sometimes begin with simple symptomatology)***

C. Partial seizures evolving to secondarily generalized seizures (this may be generalized tonic-clonic, tonic, or clonic)

II. Generalized seizures (convulsive or non-convulsive)

A. Absence seizures

B. ***Myoclonic seizures - Myoclonic jerks (single or multiple)***

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures - (Astatic)

Unclassified epileptic seizures

Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, eg, rhythmic eye movements, chewing, and swimming movements.

Status epilepticus (prolonged partial or generalized seizures without recovery between attacks)

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981; 22:489-501.

17 APPENDICES

17.1 PROTOCOL AMENDMENT 1

Rationale for the Amendment

The AEs of special interest were revised to reflect the Sponsor's current understanding of the potential risks of LCM based on a comprehensive review of the data from clinical trials and commitments to regulatory agencies.

The LFT withdrawal criteria were revised to reflect the Sponsor's current understanding of the safety profile of LCM based on a comprehensive review of the data from clinical trials.

The remainder of the changes in this amendment are administrative and are described in detail below.

MODIFICATIONS/CHANGES

- The title and contact information of the Medical Director (Medical Therapeutics) and Associate Medical Director (Drug Safety) were updated.
- For clarification, updated dose reduction wording as follows: the investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet).
- For clarification, text was added indicating that incomplete doses should not be readministered (Section 4.4.1 Treatments to be administered).
- For Unscheduled Visits (Section 5.16) added text to discuss LCM dose increase between scheduled visits.
- For Unscheduled Visits (Section 5.16 Unscheduled Visit(s) and Section 16.1 [Tables 1 to 2]) in regards to dispensing LCM and LCM return/compliance, "as applicable" was added.
- Revised text regarding safety signal detection (Section 8.1.8 Safety signal detection in ongoing clinical studies and Data Monitoring Committees).
- Revised text regarding AEs of special interest (Section 8.2.2 AEs of Special Interest) and immediate reporting of AEs (Section 8.2.3 Immediate reporting of AEs).
- Revised text on ability to collect and provide urine samples (Section 8.3 Laboratory measurements).
- Revised text regarding liver function tests (Section 8.3.1 Liver function tests).
- Text was revised to indicate that Tanner staging is performed for applicable subjects at scheduled visits (Section 8.4.5 Tanner Stage).
- The tabular schedules of trial procedures were updated to reflect the changes to the protocol.

REFERENCE

Clinical Trial Protocol, Contact information for the Senior Medical Director (Medical Therapeutics) and Associate Medical Director (Drug Safety). Page 3. Original text:

Senior Medical Director (Medical Therapeutics):

Name: [redacted] MD, PhD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Associate Medical Director (Drug Safety):

Name: [redacted] MD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Was revised as follows:

Medical Director (Medical Therapeutics):

Name: [redacted], MD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Associate Medical Director (Drug Safety):

Name: [redacted], MD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Trial Protocol, Section 1 (Summary). Page 10; paragraph 1 (third sentence) and paragraph 2 (second sentence). Original text:

Paragraph 1:

The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a second dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

Paragraph 2:

Subjects who discontinued from SP847 due to a second dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847.

Was revised as follows:

Paragraph 1:

The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

Paragraph 2:

Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847.

Clinical Trial Protocol, Section 2 (Background Information). Page 12; paragraph 5 (second sentence) and paragraph 6 (last sentence). Original text:

Paragraph 5:

A total of 30 children (aged 2 to 17 years) with uncontrolled partial-onset seizures after an adequate course of treatment with at least 2 AEDs (concurrently or sequentially) will be enrolled.

Paragraph 6:

The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study (or discontinued SP847 due to a second dose reduction or status epilepticus), and who, in the investigator's opinion, would benefit from long-term administration of LCM.

Was revised as follows:

Paragraph 5:

Approximately 30 children (aged 2 to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs will be enrolled.

Paragraph 6:

The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study (or discontinued SP847 due to a dose reduction or status epilepticus), and who, in the investigator's opinion, would benefit from long-term administration of LCM.

Clinical Trial Protocol, Section 3 (Study Objectives). Page 13; last bullet point. Original text:

- To allow subjects who have completed the SP847 study (or discontinued SP847 due to a second dose reduction or status epilepticus) to continue receiving LCM

Was revised as follows:

- To allow subjects who have completed the SP847 study (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM

Clinical Trial Protocol, Section 4.1 (Study description). Page 13; paragraph 1 (first sentence)
Original text:

Subjects who complete the SP847 study (or discontinue SP847 due to a second dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose they achieved in SP847.

Was revised as follows:

Subjects who complete the SP847 study (or discontinue SP847 due to a dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose they achieved in SP847.

Clinical Trial Protocol, Section 4.3.1 (Inclusion criteria). Page 14; second bullet point.
Original text:

2. Subject has completed SP847 (or the subject discontinued SP847 due to a second dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures.

Was revised as follows:

2. Subject has completed SP847 (or the subject discontinued SP847 due to a dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures.

Clinical Trial Protocol, Section 4.3.2 (Exclusion criteria). Page 14; second bullet point.
Original text:

2. Subject meets the withdrawal criteria for the primary study (SP847) (with the exception of subjects who discontinued due to a second dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).

Was revised as follows:

2. Subject meets the withdrawal criteria for the primary study (SP847) (with the exception of subjects who discontinued due to a dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).

Clinical Trial Protocol, Section 4.3.3 (Criteria for withdrawal). Page 15; 10th bullet point.
Original text:

10th bullet point:

10. Liver function test (LFT) results are above the upper limit of normal (ULN), to the extent specified in the table below. Subjects with abnormal LFTs are to be followed as specified below.

Abnormal liver function test results requiring discontinuation from the study

Liver function test result	Action
Transaminases (AST and/or ALT): ≥3x to <5x ULN And Total bilirubin ≥2x ULN	**Lacosamide to be discontinued immediately** Liver function tests to be repeated as soon as possible (within 7 days) and thereafter as clinically indicated.
Transaminases (AST and/or ALT): ≥5x ULN	**Lacosamide to be discontinued immediately.** Liver function tests to be repeated as soon as possible (within 7 days). Liver function test monitoring should continue until resolved.

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

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Liver function test results are above the ULN, to the extent specified in the table below. Subjects with abnormal LFTs are to be followed as specified below.

Abnormal liver function test results that may require discontinuation from the study

Liver function test result	Action
Transaminases (AST and/or ALT): ≥3x to <5x ULN And Total bilirubin within normal range	**Lacosamide discontinuation at investigator discretion**. Confirm results within a few days. If the repeat test confirms the abnormality, twice weekly LFT monitoring should continue until resolved.
Transaminases (AST and/or ALT): ≥3x ULN	Test subject for hepatitis A, B, and C.

ALT=alanine aminostransferase; AST=aspartate aminotransferase; LFT=liver function test; ULN=upper limit of normal

Was revised as follows:

10th bullet point:

10. In the case of liver function test (LFT) results of transaminases (AST and/or ALT) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST and/or ALT) ≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.

Clinical Trial Protocol, Section 4.4.1 (Treatments to be administered). Pages 16; paragraph 1 (first sentence) and paragraph 2. Original text:

Paragraph 1:

Subjects who complete the SP847 study (or discontinue SP847 due to a second dose reduction or status epilepticus) and choose to enter the open-label extension study will begin on the LCM dose they achieved in SP847.

Paragraph 2:

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 8, 10, or 12mg/kg/day (oral solution [syrup]) or 400, 500, or 600mg/day (tablet), depending on the maximum recommended dose in SP847. The investigator may decrease the dose of LCM by 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet). Increases in the LCM dose must occur only during office visits.

Was revised as follows:

Paragraph 1:

Subjects who complete the SP847 study (or discontinue SP847 due to a dose reduction or status epilepticus) and choose to enter the open-label extension study will begin on the LCM dose they achieved in SP847.

Paragraph 2:

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 8, 10, or 12mg/kg/day (oral solution [syrup]) or 400, 500, or 600mg/day (tablet), depending on the maximum recommended dose in SP847. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Clinical Trial Protocol, Section 4.5 (Expected duration of study). Page 18; paragraph 1. Original text:

The maximum duration of LCM administration will be approximately 2 years. The trial can be terminated by the Sponsor once LCM is commercially available. If LCM is not commercially available in a subject's country at the time the Sponsor closes the trial, access to LCM will be provided according to local laws.

Was revised as follows:

The maximum duration of LCM administration will be approximately 2 years.

Clinical Trial Protocol, Section 4.7 (Procedures for monitoring subject compliance). Page 19; paragraph 2 (removal of last sentence). Original text:

All findings will be documented on forms provided by SCHWARZ BIOSCIENCES. Subject's noncompliance with regards to intake of LCM is defined as being less than 75% or more than 125% compliant with the dosage schedule. Compliance will be determined by assessment of the remaining volume of LCM using a graduated cylinder (oral solution [syrup]) or pill count (tablet).

Was revised as follows:

All findings will be documented on forms provided by SCHWARZ BIOSCIENCES. Subject's noncompliance with regards to intake of LCM is defined as being less than 75% or more than 125% compliant with the dosage schedule.

Clinical Trial Protocol, Section 5.1 (Visit 1[Week 0]). Page 19; paragraph 1. Original text:

For subjects who complete the SP847 study, Visit 1 is the second day of the second inpatient hospitalization in SP847 (Day 28 for Cohorts 1 to 3 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 4 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 4 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue the SP847 study due to a second dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847.

Was revised as follows:

For subjects who complete the SP847 study, Visit 1 is Day 2 of the second overnight stay at a hospital or medical facility in SP847 (Day 28 for Cohorts 1 to 3 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 4 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 4 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue the SP847 study due to a dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847.

Clinical Trial Protocol, Section 5.2 (Telephone contacts [Week 2, 6, 10, 16, 24, 32, 40, 48, 66, and 78]); Page 20; last paragraph. Original text:

Lacosamide is supplied so that the subject or caregiver (including parent/legal guardian) can immediately decrease their dose by a step of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet), if needed, in consultation over the telephone with the investigator or subinvestigator. Thus, LCM can be continued at a decreased dose until a clinic visit can be scheduled.

Was revised as follows:

Lacosamide is supplied so that the subject or caregiver (including parent/legal guardian) can immediately decrease their dose, if needed, in consultation over the telephone with the investigator or subinvestigator. Thus, LCM can be continued at a decreased dose until a clinic visit can be scheduled.

Clinical Trial Protocol, Section 5.16 (Unscheduled visit[s]); Page 25; first sentence and added bullet points 7 and 10. Original text:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, the subject must return for an Unscheduled Visit. The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Subject diary assessment
- Adverse event reporting

Additional assessments can be performed at the investigator's discretion.

Was revised as follows:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- LCM return/compliance (as applicable)
- Subject diary assessment

- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

Clinical Trial Protocol, Section 8.1.7 (Overdose of investigational medicinal product); Page 30; first sentence. Original text:

Excessive dosing (beyond that prescribed per the protocol and including overdose) should be recorded in the Drug Accountability or Drug Dosing module.

Was revised as follows:

Excessive dosing (beyond that prescribed per the protocol and including overdose) should be recorded in the source documents and Drug Accountability or Drug Dosing Log CRF module.

Clinical Trial Protocol, Section 8.1.8 (Safety Signal detection in ongoing clinical studies and Data Monitoring Committees)); Page 30; replaced entire text. Original text:

A regular monitoring of safety data collected during clinical studies will be performed as described in the Safety Signal Detection in Ongoing Clinical Trials Charter for lacosamide.

This ongoing monitoring of safety data will be performed at the product level, possibly by an independent Data Monitoring Committee in some studies.

Safety data, including SAEs, AEs, vital signs, laboratory results and ECG data (as applicable) will be periodically reviewed by SCHWARZ BIOSCIENCES.

The data from all studies with the same investigational medicinal product will be scrutinized to detect as early as possible any safety concern related to the investigational medicinal product so that the investigators, the clinical study subjects, the regulatory authorities, and the ethics committees will be informed in the most appropriate manner.

Was replaced as follows:

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the investigational medicinal product so that investigators, clinical study subjects, regulatory authorities, and IRBs/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 GCSP representative.

As appropriate for the stage of development and accumulated experience with the investigational medicinal product, medically qualified personnel at UCB may identify additional safety measures (examples: AEs, vital signs, laboratory or electrocardiogram results) for which data will be periodically reviewed during the course of the study.

Clinical Trial Protocol, Section 8.2.2 (AEs of Special Interest); Page 31; replaced entire text. Original text:

The following are AEs of special interest:

- Any case of torsade de points
- Any ECG abnormality accompanied by related clinical symptoms
- Any case of discontinuation due to any ECG abnormality or QTc prolongation

Was replaced as follows:

The following are AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (2nd degree Type I and II and 3rd degree), and marked bradycardia (<45beats/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 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 one 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 ≥2x ULN
  - AST ≥2x ULN

Clinical Trial Protocol, Section 8.2.3 (Immediate reporting of AEs); Page 31; replaced entire text. Original text:

The following AEs must be reported immediately:

- SAE: AEs that the investigator classifies as serious by the above definitions regardless of causality.
- Suspected transmission via a medicinal product of an infectious agent.

- AEs of special interest:
  - Any case of torsade de points
  - Any ECG abnormality accompanied by related clinical symptoms
  - Any case of discontinuation due to any ECG abnormality or QTc prolongation

Was replaced as follows:

The following AEs must be reported immediately:

- SAE: AEs that the investigator classifies as serious by the above definitions, regardless of causality.
- Suspected transmission of an infectious agent via a medicinal product.
- AEs of special interest (as defined in Section 8.2.2).

Clinical Trial Protocol, Section 8.3 (Laboratory measurement); Page 32; first paragraph.
Original text:

Blood and urine specimens (approximately 5 to 15mL each) for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedule of study procedures, Section 16.1. A central laboratory will perform the routine analysis of blood and urine samples. The procedures for handling and shipping these specimens will be provided to the sites.

Was revised as follows:

Blood and urine specimens (approximately 5 to 15mL each) for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedule of study procedures, Section 16.1. For subjects aged 5 to 17 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine samples. The procedures for handling and shipping these specimens will be provided to the sites.

Clinical Trial Protocol, Section 8.3.1 (Liver function tests); Page 32, 33; replaced entire text.
Original text:

Transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or both) greater than or equal to 3 times but less than 5 times the ULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat test confirms the abnormality (ie, transaminases are greater than or equal to 3 times but less than 5 times the ULN with normal bilirubin) twice weekly monitoring of LFTs should continue until resolved. The investigator is to decide whether or not to stop the study medication.

Transaminases (AST, ALT, or both) greater than or equal to 3 times but less than 5 times the ULN, in the presence of total bilirubin greater than or equal to 2 times the ULN, will result in immediate discontinuation of the study medication and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 7 days later and thereafter as clinically indicated.

Transaminases (AST, ALT, or both) greater than or equal to 5 times the ULN will result in immediate discontinuation of the study medication and withdrawal of the subject from the study, regardless of the total bilirubin level. The LFTs will be repeated as soon as possible, and in no case more than 7 days later. Liver function test monitoring should continue until resolved.

In all cases of transaminases (AST, ALT, or both) greater than or equal to 3 times the ULN, testing for hepatitis A, B, and C will be done.

All LFTs that meet the criteria above will be followed until resolution (ie, Baseline or stable condition).

Referral to a specialist (ie, hepatologist or gastroenterologist) is at the discretion of the investigator. This is recommended especially if the transaminase abnormalities greater than 3 times the ULN persist after discontinuation of the study medication.

Was replaced as follows:

Transaminases (AST, ALT, or both) ≥3x ULN but <5x ULN, in the presence of total bilirubin ≥2x ULN, or transaminases (AST, ALT, or both) ≥5x ULN will result in immediate discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later (see Section 4.3.3).

Clinical Trial Protocol, Section 8.4.5 (Tanner Stage); Page 35; first paragraph (first sentence). Original text:

At each scheduled visit for selected patients, the investigator will evaluate the subject's sexual development using the 3-item scale.

Was replaced as follows:

At selected visits for applicable subjects, the investigator or qualified designee will evaluate the subject's sexual development using the 3-item scale.

Clinical Trial Protocol, Section 12.1.2.2 (Other safety variables); Page 40; first paragraph (second sentence). Original text:

The actual measurement and its change from Baseline (SP847 Visit 1) will be analyzed descriptively and presented by visit and day of collection.

Was revised as follows:

The actual measurement and its change from Baseline (SP847 Visit 1) will be analyzed descriptively and presented by visit.

Clinical Trial Protocol, Section 16.1 (Table 1 and 2); Pages 46 to 51). Original table:

Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X		X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X		X	
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X		X	
Urinalysis	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X					
Clinical GIC						X				X	X			
Caregiver GIC						X				X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]			
LCM return/ compliance			X	X	X	X	X	X	X	X	X		X	
Dispense diary	X		X	X	X	X	X	X	X	X	X			

Study SP848	Year 1													Safety Follow-Up
Visit[a]	V1[b]	TC[c]	V2	V3	V4	V5	V6	V7	V8	V9	ETV[d]	Unsch Visit[e]	Final Visit[f]	TC[g]
Weeks in study	0		4	8	12	20	28	36	44	52				
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
AE reporting[n]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Visit 1 is also the last visit of the primary study (SP847). At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between visits due to an AE, the subject must return for an Unscheduled Visit.

[f] A Final Visit should be performed 2 weeks after a subject has tapered off LCM.

[g] This TC occurs 28-35 days after the last dose of LCM.

[h] Assessments should have been done as part of the last visit of the previous SP847 study.

[l] An ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 ECGs will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

[j] Blood samples may be drawn at any time post-dosing with LCM.

[k] For female subjects of childbearing potential (ie, females who have begun menstruating), serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[n] Ongoing aEs from the primary study (SP847) will be followed, as well as recording of new aEs during the current study.

Schedule of study procedures for SP848 (Year 2)

Study SP848	Year 2								Safety Follow-Up
Visit[a]	V10	TC[b]	V11	V12	V13	ETV[c]	Unsch Visit[d]	Final Visit[e]	TC[f]
Weeks in study	60		72	84	96				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X		X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X		X	

Study SP848	Year 2								Safety Follow-Up
Visit[a]	V10	TC[b]	V11	V12	V13	ETV[c]	Unsch Visit[d]	Final Visit[e]	TC[f]
Weeks in study	60		72	84	96				
Blood sample for concomitant AEDs[h]	X		X	X	X	X		X	
Urinalysis			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Dispense LCM	X		X	X	X^k	X^k			
LCM return/compliance	X		X	X	X	X		X	
Dispense diary	X		X	X	X	X			
Diary assessment	X		X	X	X	X	X	X	
AE reporting	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between visits due to an AE, the subject must return for an Unscheduled Visit.

[e] A Final Visit should be performed 2 weeks after a subject has tapered off LCM.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] An ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 ECGs will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential (ie, females who have begun menstruating), serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X		X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X		X	
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X		X	
Urinalysis	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X		X			
Clinical GIC						X				X	X			
Caregiver GIC						X				X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]	X[n]		
LCM return/ compliance			X	X	X	X	X	X	X	X	X	X[n]	X	

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	V1[b]	TC[c]	V2	V3	V4	V5	V6	V7	V8	V9	ETV[d]	Unsch Visit[e]	Final Visit[f]	TC[g]
Weeks in study	0		4	8	12	20	28	36	44	52				
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
AE reporting[o]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Visit 1 is also the last visit of the primary study (SP847). At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit.

[f] A Final Visit should be performed 2 weeks after a subject has tapered off LCM

[g] This TC occurs 28-35 days after the last dose of LCM.

[h] Assessments should have been done as part of the last visit of the previous SP847 study.

[i] An ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 ECGs will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

[j] Blood samples may be drawn at any time post-dosing with LCM.

[k] For female subjects of childbearing potential (ie, females who have begun menstruating), serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[n] As applicable

[o] Ongoing AEs from the primary study (SP847) will be followed, as well as recording of new AEs during the current study.

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	Year 2								Safety Follow-Up
Visit[a]	V10	TC[b]	V11	V12	V13	ETV[c]	Unsch Visit[d]	Final Visit[e]	TC[f]
Weeks in study	60		72	84	96				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X		X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X		X	
Blood sample for concomitant AEDs[h]	X		X	X	X	X		X	
Urinalysis			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Dispense LCM	X		X	X	X^k	X^k	X^l		
LCM return/compliance	X		X	X	X	X	X^l	X	

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	Year 2								Safety Follow-Up
Visit[a]	V10	TC[b]	V11	V12	V13	ETV[c]	Unsch Visit[d]	Final Visit[e]	TC[f]
Weeks in study	60		72	84	96				
Dispense diary	X		X	X	X	X			
Diary assessment	X		X	X	X	X	X	X	
AE reporting	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit.

[e] A Final Visit should be performed 2 weeks after a subject has tapered off LCM

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] An ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 ECGs will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential (ie, females who have begun menstruating), serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[l] As applicable.

Clinical Trial Protocol, Section 17.1. (Declarations and signatures of persons responsible for the study) *Page 53. Original text:*

Senior Medical Director

(Medical Therapeutics)

[redacted], MD, PhD

Was revised as follows:

Medical Director

(Medical Therapeutics)

[redacted], MD

17.2 PROTOCOL AMENDMENT 2

RATIONALE FOR THE AMENDMENT

The primary purposes of this protocol amendment are to define an absolute maximum dose of LCM 600mg/day to be received by subjects in the study, to revise withdrawal criteria and follow-up recommendations for abnormal LFTs, and to specify that subjects who participate in future studies (in addition to SP847) may participate in SP848. The rationales for these changes are described below.

Based on the analysis of SP847 Cohort 1 (subjects aged 5 to 11 years) safety and PK data, the maximum permitted LCM dose in SP848 is 12mg/kg/day (for subjects weighing up to 50kg), or 600mg/day (for subjects weighing >50kg).

The decision to re-insert additional withdrawal criteria and follow-up recommendations for abnormal LFTs is based on the following:

1) Newly adopted FDA Guidance on Drug-Induced Liver Injury (July 2009) and a recommendation from the FDA to re-insert previously included wording regarding additional withdrawal criteria and follow-up recommendations for abnormal LFTs in LCM protocols.

2) Although no new liver-related safety issues with LCM have been identified, LFT abnormal has been added as a postmarketing adverse drug reaction in the LCM Company Core Data Sheet, and the EU Summary of Product Characteristics. Therefore, LCM protocols are being amended to reflect this addition.

With these revisions, liver-related safety signals will continue to be detected via protocol directed monitoring and additional follow-up in ongoing and future LCM clinical studies.

In order to allow subjects who participate in other future LCM pediatric clinical studies in epilepsy (ie, in addition to SP847) to continue receiving LCM treatment, these subjects will be provided the opportunity to participate in SP848.

The remainder of the changes in this amendment were administrative in nature and are described in detail below.

MODIFICATIONS/CHANGES

- The contact information of the Clinical Project Manager, Clinical Pharmacokineticist, and Associate Medical Director (Global Clinical Safety and Pharmacovigilance) were updated.
- Information was added to Section 1 (Summary) and throughout the protocol to specify that subjects who participate in future studies (in addition to SP847) may participate in SP848.
- Information was added to Section 1 (Summary) and throughout the protocol to indicate that the maximum permitted LCM dose in SP848 is 12mg/kg/day (for subjects weighing up to 50kg), or 600mg/day (for subjects weighing >50kg).
- The withdrawal criteria (Section 4.3.3) and follow-up recommendations for abnormal LFTs throughout the protocol were revised.
- Information was added to Section 4.4.1 (Treatments to be administered) to clarify dosing for subjects who switch to the LCM tablet formulation.
- The tabular schedules of trial procedures were updated to reflect the changes to the protocol.

REFERENCE

Clinical Study Protocol, Contact information for the Clinical Project Manager, Clinical Trial Biostatistician, Clinical Pharmacokineticist, and Associate Medical Director (Global Clinical Safety and Pharmacovigilance), pages 2 and 3. Original text:

Clinical Project Manager:

Name: [redacted], BS

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Trial Biostatistician:

Name: [redacted], MPH

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Pharmacokineticist:

Name: [redacted]

Address: UCB S.A.
Chemin du Foriest
B-1420 Braine-l'Alleud

Phone/Fax: [redacted]

E-mail: [redacted]

Associate Medical Director (Drug Safety):

Name: [redacted], MD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Was revised as follows:

Clinical Project Manager:

Name: [redacted]

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Trial Biostatistician:

Name: [redacted] MPH

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Pharmacokineticist:

Name: [redacted]

Address: UCB Celltech
UCB Pharma Ltd
208 Bath Road
Slough, Berkshire SL1 3WE, UK

Phone/Fax: [redacted]

E-mail: [redacted]

Associate Medical Director (Global Clinical Safety and Pharmacovigilance):

Name: [redacted] MD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Study Protocol, List of Abbreviations, page 9. The following abbreviation was deleted:

IRAE	immediately reportable adverse event

Clinical Study Protocol, Section 1 (Summary), paragraphs 1 and 2. Original text:

SP848 is an open-label extension study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with partial-onset seizures treated with lacosamide (LCM) oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

Subjects who complete the SP847 study and choose to enter this open-label extension study will begin on the LCM dose they achieved in SP847. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 8, 10, or 12mg/kg/day (oral solution [syrup]) or 400, 500, or 600mg/day (tablet), depending on the maximum recommended dose in SP847. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

SP848 is an open-label extension study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with partial-onset seizures treated with lacosamide (LCM) oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM. SP848 will also be open to subjects who participate in other future LCM pediatric clinical studies in epilepsy.

Subjects who complete SP847 and choose to enter this open-label extension study will begin on the LCM dose they achieved in SP847. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847. Subjects will be able to receive LCM oral solution (syrup) or LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 2 (Background information). Original text:

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). 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 classification of epilepsies in children was described in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (1989; Aicardi, 1994). Seizures are categorized based on whether the onset is focal or generalized and whether the disorder is idiopathic, symptomatic, or cryptogenic. Specific syndromes are further classified according to a number of criteria including seizure type, cause, anatomy, precipitating factors, age of onset, and sometimes prognosis.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and 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 (CPMP/EWP/566/98, 2000). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander, 1998).

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; Glauser et al, 2000; Glauser et al, 2006). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently-available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). Therefore, a need remains for AEDs with improved effectiveness and tolerability.

Lacosamide (LCM, Vimpat®, SPM 927, [R]-2-acetamido-N-benzyl-3-methoxypropionamide) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) and in patients 17 years of age and older in the United States (oral tablets and solution for iv infusion). The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to 400mg bid (800mg/day) were evaluated in approximately 700 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2200 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in 1308 adult subjects, aged 16 to 70 years, established the efficacy of oral LCM as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with difficult to control partial-onset seizures. In these studies, LCM was initiated at a dose of 100mg/day (in 2 divided doses) and escalated to the randomized dose (200mg/day, 400mg/day, or 600mg/day) in 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, headache, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

SP847, the primary study, is an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. Approximately 30 children (aged 2 to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs will be enrolled. The study consists of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject may be up to approximately 13 weeks.

SP848 is an open-label extension study to obtain long-term safety, tolerability, and PK data in children with partial-onset seizures treated with LCM oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study (or discontinued SP847 due to a dose reduction or status epilepticus), and who, in the investigator's opinion, would benefit from long-term administration of LCM.

Was revised as follows:

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). 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 classification of epilepsies in children was described in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (1989; Aicardi,

1994). Seizures are categorized based on whether the onset is focal or generalized and whether the disorder is idiopathic, symptomatic, or cryptogenic. Specific syndromes are further classified according to a number of criteria including seizure type, cause, anatomy, precipitating factors, age of onset, and sometimes prognosis.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and 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 (CHMP/EWP/566/98, 2010). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander, 1998).

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; Glauser et al, 2000; Glauser et al, 2006). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide (LCM, Vimpat®, SPM 927, [R]-2-acetamido-N-benzyl-3-methoxypropionamide) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) and in patients 17 years of age and older in the United States (oral tablets, oral solution, and solution for iv infusion). The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to 400mg bid (800mg/day) were evaluated in approximately 700 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2200 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in 1308 adult subjects, aged 16 to 70 years, established the efficacy of oral LCM as adjunctive

therapy (1 to 3 concomitant AEDs) in subjects with difficult to control partial-onset seizures. In these studies, LCM was initiated at a dose of 100mg/day (in 2 divided doses) and escalated to the randomized dose (200mg/day, 400mg/day, or 600mg/day) in 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, headache, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

SP847, the current primary study, is an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. Approximately 42 children (aged 1 month to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs will be enrolled. The study consists of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject may be up to approximately 13 weeks. Approximately 300 additional subjects who may participate in other future LCM primary pediatric clinical studies in epilepsy will also be eligible to participate in SP848.

SP848 is an open-label extension study to obtain long-term safety, tolerability, and PK data in children with partial-onset seizures treated with LCM oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study (or discontinued SP847 due to a dose reduction or status epilepticus), and who, in the investigator's opinion, would benefit from long-term administration of LCM. SP848 will also be open to subjects who participate in other future LCM pediatric clinical studies in epilepsy.

Clinical Study Protocol, Section 3 (Objectives), third and objectives. Original text:

- To allow subjects who have completed the SP847 study (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM

Was revised as follows, and a fourth objective was added:

- To allow subjects who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow subjects who have participated in other future LCM pediatric clinical studies in epilepsy to continue receiving LCM

Clinical Study Protocol, Section 4 (Study description). Original text:

Subjects who complete the SP847 study (or discontinue SP847 due to a dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose

they achieved in SP847. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 8, 10, or 12mg/kg/day (oral solution [syrup]) or 400, 500, or 600mg/day (tablet), depending on the maximum recommended dose in SP847. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Subjects who complete SP847 (or discontinue SP847 due to a dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose they achieved in SP847. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 4.3.1 (Inclusion criteria), criterion 2. Original text:

1. Subject has completed SP847 (or the subject discontinued SP847 due to a dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures.

Was revised as follows:

1. Subject has completed SP847 (or the subject discontinued SP847 due to a dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures, or subject has participated in other LCM pediatric clinical studies in epilepsy.

Clinical Study Protocol, Section 4.3.2 (Exclusion criteria), criterion 2. Original text:

1. Subject meets the withdrawal criteria for the primary study (SP847) (with the exception of subjects who discontinued due to a dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).

Was revised as follows:

1. Subject meets the withdrawal criteria for the primary study (with the exception of subjects who discontinued due to a dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).

Clinical Study Protocol, Section 4.3.3 (Criteria for withdrawal). Original text:

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency
3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.

8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
9. Subject experiences status epilepticus
10. In the case of liver function test (LFT) results of transaminases (AST and/or ALT) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST and/or ALT) ≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.

Was revised as follows:

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency
3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
9. Subject experiences status epilepticus
10. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST, ALT, or both)

≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

Clinical Study Protocol, Section 4.4.1 (Treatments to be administered). Original text:

Subjects who complete the SP847 study (or discontinue SP847 due to a dose reduction or status epilepticus) and choose to enter the open-label extension study will begin on the LCM dose they achieved in SP847. The investigator, together with the subject/caregiver (including parent/legal guardian), will be able to choose either the oral solution (syrup) formulation or the tablet formulation of LCM in this study. The study medication will be orally administered bid (at 12-hour intervals, once in the morning and once in the evening) in equally divided doses. The oral solution (syrup) formulation will be measured and orally administered via a dosing syringe. The selection of doses, titration scheme, and rate of taper in SP847 were based on adult studies and were adjusted to a mg/kg basis plus 40% (ie, 600mg/day adult dose of LCM corresponds to [600mg/70kg] x 1.4 = approximately 12mg/kg/day for a child). The selection of doses in this trial is based on the maximum recommended dose in SP847.

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 8, 10, or 12mg/kg/day (oral solution [syrup]) or 400, 500, or 600mg/day (tablet), depending on the maximum recommended dose in SP847. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Subjects achieving a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet) who withdraw during the study should taper off study medication. It is recommended that the dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (see tables below). A slower taper of 2mg/kg/day (oral solution [syrup]) or

100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Subjects who have participated in SP847 (or other future LCM pediatric clinical studies in epilepsy), who are eligible to participate in the open-label extension study SP848, and who choose to enter SP848, will begin SP848 on the LCM dose they achieved in the primary study. The investigator, together with the subject/caregiver (including parent/legal guardian), will be able to choose either the oral solution (syrup) formulation or the tablet formulation of LCM in this study. The study medication will be orally administered bid (at 12-hour intervals, once in the morning and once in the evening) in equally divided doses. The oral solution (syrup) formulation will be measured and orally administered via a dosing syringe. The selection of doses, titration scheme, and rate of taper in SP847 were based on adult studies and were adjusted to a mg/kg basis plus 40% (ie, 600mg/day adult dose of LCM corresponds to [600mg/70kg] x 1.4 = approximately 12mg/kg/day for a child). The selection of doses in this trial is based on the maximum recommended dose in SP847.

The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg.

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup] or the corresponding dose level for the tablet formulation). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Subjects enrolled in SP848 have the option of remaining on the oral solution formulation of LCM or switching to the commercial tablet formulation, if feasible. Consideration of the current LCM milligram dose in the oral solution (syrup) should occur if/when transitioning to the tablet formulation. In cases where the LCM dose received with the oral solution (syrup) is not supported by the tablet strengths available in SP848 (50mg and 100mg), a clinical decision must be made by the investigator or other study physician to either increase or decrease the LCM dose to the next multiple of 100mg with a maximum permitted dose of 600mg/day.

Subjects achieving a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet) who withdraw during the study should taper off study medication. It is recommended that the dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (see tables below). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 4.4.3 (Randomization). Original text:

This is an open-label extension study; subjects will not be randomized. Subjects will keep the unique number assigned in the SP847 study.

Was revised as follows:

This is an open-label extension study; subjects will not be randomized. Subjects will keep the unique number assigned in the primary study.

Clinical Study Protocol, Section 5.1 (Visit 1 [Week 0]). Original text:

For subjects who complete the SP847 study, Visit 1 is Day 2 of the second overnight stay at a hospital or medical facility in SP847 (Day 28 for Cohorts 1 to 3 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 4 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 4 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue the SP847 study due to a dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847.

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by local IRB/IEC, the subject will be requested to give assent to participate in the study.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments, and a complete medical history update will be obtained. The data for the following assessments will be taken from the last assessment during the SP847 study:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential

- Tanner Stage assessment (if applicable)
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Was revised as follows:

For subjects who complete SP847, Visit 1 is Day 2 of the second PK collection time period (which may include an overnight stay at a hospital or medical facility) in SP847 (Day 28 for Cohorts 1, 2, 3, and 5 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 5 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 5 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue SP847 due to a dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847. For subjects in SP847 who are titrated up to the maximum permitted dose of 600mg/day sooner than the study schedule would ordinarily indicate (based on body weight) and who enroll in SP848, the Early Termination Visit of SP847 will also serve as Visit 1 for SP848.

For subjects who enroll in SP848 after participation in future LCM pediatric clinical studies in epilepsy, SP848 Visit 1 will be specified in the respective primary study protocol.

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by local IRB/IEC, the subject will be requested to give assent to participate in the study.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments, and a complete medical history update will be obtained. The data for the following assessments will be taken from the last assessment during SP847 (or other primary study as applicable):

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology

- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Clinical Study Protocol, Section 5.3 (Visit 2 [Week 4]), bullet 5. Original text:

- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)

Was revised as follows:

- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)

Clinical Study Protocol, Section 5.4 (Visit 3 [Week 8), final paragraph. Original text:

- A 12-lead ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 ECGs will be performed approximately 20 to 30 minutes apart prior to vital sign assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

Was revised as follows:

- A 12-lead ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable ECGs will be performed approximately 20 to 30 minutes apart prior to vital sign assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

Clinical Study Protocol, Section 5.6 (Visit 5 [Week 20]), final paragraph. Original text:

A 12-lead ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED

has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 ECGs will be performed approximately 20 to 30 minutes apart prior to vital sign assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

Was revised as follows:

A 12-lead ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable ECGs will be performed approximately 20 to 30 minutes apart prior to vital sign assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

Clinical Study Protocol, Section 5.7 (Visit 6 [Week 28]). Original text:

Assessments for Visit 6 (Week 28) are the same as those described for Visit 3 (Week 8) in Section 5.6, with the following exception: a 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted at Visit 6.

Was revised as follows:

Assessments for Visit 6 (Week 28) are the same as those described for Visit 3 (Week 8) in Section 5.6, with the following exception: a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted at Visit 6.

Clinical Study Protocol, Section 5.10 (Visit 9 [Week 52]). Original text:

Assessments for Visit 9 (Week 52) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exception: a 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted at Visit 9.

Was revised as follows:

Assessments for Visit 9 (Week 52) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exception: a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted at Visit 9.

Clinical Study Protocol, Section 5.12 (Visit 11 [Week 72]). Original text:

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory

blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), and a 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted.

Was revised as follows:

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted.

Clinical Study Protocol, Section 5.14 (Visit 13 [Week 96]). Original text:

Assessments for Visit 13 (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, and a Tanner Stage assessment is conducted (if applicable).

Was revised as follows:

Assessments for Visit 13 (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, and a Tanner Stage assessment is conducted (if applicable).

Clinical Study Protocol, Section 5.15 (Early Termination Visit), bullet 5. Original text:

- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)

Was revised as follows:

- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)

Clinical Study Protocol, Section 5.16 (Unscheduled Visit[s]). Original text:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. The following assessments are required:

- Concomitant medications assessment

- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- LCM return/compliance (as applicable)
- Subject diary assessment
- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

Was revised as follows:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if an LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. If an AE prompts a dose reduction, the reduction can be implemented immediately at the investigator's discretion. However, the subject should return to the clinic as soon as possible for an Unscheduled Visit.

The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- LCM return/compliance (as applicable)
- Subject diary assessment
- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

Clinical Study Protocol, Section 5.17 (Final Visit [2 weeks after the last LCM dose]), bullet 5. Original text:

- 12-lead ECG (2 recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)

Was revised as follows:

- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)

Clinical Study Protocol, Section 6.1 (Seizure counts). Original text:

At Screening of the primary study, SP847, subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous 4 weeks; this will serve as a historical Baseline. After the subject is enrolled in the SP848 study, seizure data will be collected in diaries provided to subjects/caregivers (including parents/legal guardians). Each subject/caregiver (including parent/legal guardian) will keep a diary to note daily seizure activity throughout the current study. The subject/caregiver (including parent/legal guardian) should be reminded to bring the diary with them at each clinic visit. The following information will be recorded:

- Seizure type
- Seizure frequency

Was revised as follows:

At Screening of SP847 (or other primary study as applicable) subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous 4 weeks; this will serve as a historical Baseline. After the subject is enrolled in the SP848 study, seizure data will be collected in diaries provided to subjects/caregivers (including parents/legal guardians). Each subject/caregiver (including parent/legal guardian) will keep a diary to note daily seizure activity throughout the current study. The subject/caregiver (including parent/legal guardian) should be reminded to bring the diary with them at each clinic visit. The following information will be recorded:

- Seizure type
- Seizure frequency

Clinical Study Protocol, Section 6.2.1 (Clinical Global Impression of Change), paragraph 2. Original text:

For the assessment of the Clinical Global Impression of Change, the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (primary study) will serve as Baseline.

Was revised as follows:

For the assessment of the Clinical Global Impression of Change, the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline.

Clinical Study Protocol, Section 6.2.2 (Caregiver Global Impression of Change), paragraph 2. Original text:

For the assessment of the Clinical Global Impression of Change, the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (primary study) will serve as Baseline.

Was revised as follows:

For the assessment of the Clinical Global Impression of Change, the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline.

Clinical Study Protocol, Section 7 (Assessment of pharmacokinetics), paragraph 2. Original text:

Each blood sample drawn will be split into 2 duplicate samples. The samples will be centrifuged and stored at -20ºC until shipped to a central laboratory. The central laboratory will store the plasma samples at -70ºC until analysis. Details of plasma sample collection and processing, sample labeling, and shipment will be provided in the laboratory manual.

Was revised as follows:

Each blood sample drawn will be split into 2 duplicate samples. The samples will be centrifuged and stored at ≤-20ºC until shipped to a central laboratory. The central laboratory will store the plasma samples at -20ºC until analysis. Details of plasma sample collection and processing, sample labeling, and shipment will be provided in the laboratory manual.

Clinical Study Protocol, Section 8.2.2 (AEs of special interest), bullet 1. Original text:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (2nd degree Type I and II and 3rd degree), and marked bradycardia (<45beats/min)

Was revised as follows:

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

Clinical Study Protocol, Section 8.3 (Laboratory measurements). The laboratory parameter:

Acetone

Was replaced with:

Ketone

Clinical Study Protocol, Section 8.3.1 (Liver function tests). Original text:

Transaminases (AST, ALT, or both) ≥3x ULN but <5x ULN, in the presence of total bilirubin ≥2x ULN, or transaminases (AST, ALT, or both) ≥5x ULN will result in immediate discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later (see Section 4.3.3).

Was revised as follows:

Transaminases (AST, ALT, or both) ≥3x ULN but <5x ULN, in the presence of total bilirubin ≥2x ULN, or transaminases (AST, ALT, or both) ≥5x ULN will result in immediate discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later (see Section 4.3.3).

Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

In all cases of transaminases (AST, ALT, or both) ≥3xULN, testing for hepatitis A, B, and C will be done.

Referral to a specialist (ie, hepatologist or gastroenterologist) is at the discretion of the investigator. This is recommended especially if the transaminase abnormalities >3xULN persist after discontinuation of the study medication.

Clinical Study Protocol, Section 9.1 (Manufacturing, packaging, and labeling). The following bullets were added:

- Date bottle opened
- Do not use after (date)

Clinical Study Protocol, Section 10.2 (Monitoring), paragraph 1. Original text:

SCHWARZ BIOSCIENCES or designee will monitor the study to meet the Sponsor's monitoring standard operating procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements and to ensure that study initiation, conduct, and closure are adequate.

Was revised as follows:

SCHWARZ BIOSCIENCES or designee will monitor the study to meet the Sponsor's monitoring standard operating procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by SCHWARZ BIOSCIENCES to a CRO or a contract monitor.

Clinical Study Protocol, Section 12.1 (Description of statistical methods), paragraph 2. Original text:

Visit 1 of SP847 (primary study) will serve as Baseline values for safety and efficacy variables unless otherwise noted.

Was revised as follows:

Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline values for safety and efficacy variables unless otherwise noted.

Clinical Study Protocol, Section 12.1.2.2 (Other safety variables), paragraph 1. Original text:

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, and urinalysis), ECG measurements, vital sign measurements (blood pressure and pulse rate), body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 Visit 1) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different postBaseline status when compared with their Baseline status.

Was revised as follows:

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, and urinalysis), ECG measurements, vital sign measurements (blood pressure and pulse rate), body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 [or other primary study as applicable] Visit 1) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

Clinical Study Protocol, Section 12.1.4.1 (Seizure frequency). Original text:

Seizure frequency will be assessed using seizure diaries in order to evaluate the preliminary efficacy of LCM in this population. Seizure frequency per 7 days will be calculated as ([number of seizures over the specified time interval]) divided by [number of days in the interval])

multiplied by 7 and summarized descriptively and presented graphically at each visit and grouped by dose.

Was revised as follows:

Seizure frequency will be assessed using seizure diaries in order to evaluate the preliminary efficacy of LCM in this population. Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval]) divided by [number of days in the interval]) multiplied by 28 and summarized descriptively and presented graphically at each visit and grouped by dose.

Clinical Study Protocol, Section 12.1.5 (Handling of protocol violators, drop-outs, and missing values), paragraph 1. Original text:

All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter. Protocol deviations will be assessed during data review by a panel consisting of the study manager, the trial biostatistician, a representative of the monitoring team, and other appropriate study team members.

Was revised as follows:

All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter. Protocol deviations will be assessed during data review by a panel consisting of the study manager, the study biostatistician, a representative of the monitoring team, and other appropriate study team members.

Clinical Study Protocol, Section 12.2 (Determination of sample size). Original text:

Up to 30 subjects from the SP847 study will enroll in this open-label extension study.

Was revised as follows:

Approximately 42 subjects from the SP847 study will be eligible to enroll in this open-label extension study. Other subjects will be eligible to enroll as future LCM pediatric clinical studies in epilepsy are undertaken.

Clinical Study Protocol, Section 15 (References). The following reference was updated:

CHMP/EWP/566/98 Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (EMA) Rev 2, 20 Jan 2010.

Clinical Study Protocol, Section 16.1 (Tabular schedule of study procedures) was updated to the following:

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X		X	
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X		X	
Urinalysis	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X		X			
Clinical GIC						X				X	X			
Caregiver GIC						X				X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]	X[n]		
LCM return/ compliance			X	X	X	X	X	X	X	X	X	X[n]	X	
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
AE reporting[o]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] A Final Visit should be performed 2 weeks after a subject has tapered off LCM.

[g] This TC occurs 28 to 35 days after the last dose of LCM.

[h] Assessments should have been done as part of the last visit of the primary study.

[i] An ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 interpretable ECGs will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

[j] Blood samples may be drawn at any time post-dosing with LCM.

[k] For female subjects of childbearing potential (ie, females who have begun menstruating), serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[n] As applicable

[o] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X		X	
Blood sample for concomitant AEDs[h]	X		X	X	X	X		X	
Urinalysis			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Dispense LCM	X		X	X	X^k	X^k	X^l		
LCM return/compliance	X		X	X	X	X	X^l	X	
Dispense diary	X		X	X	X	X			
Diary assessment	X		X	X	X	X	X	X	
AE reporting	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] A Final Visit should be performed 2 weeks after a subject has tapered off LCM.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] An ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 interpretable ECGs will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential (ie, females who have begun menstruating), serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[l] As applicable.

Clinical Study Protocol, Section 16.3 (Declarations and signatures of persons responsible for the study). Original text:

Clinical Project Manager

[redacted], BS

Date / Signature

Clinical Trial Biostatistician

[redacted] MPH

Date / Signature

Medical Director (Medical Therapeutics)

[redacted], MD

Date / Signature

Associate Clinical Program Director

[redacted], BS

Date / Signature

Was revised as follows:

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

Clinical Project Manager

[redacted]

Date / Signature

Clinical Trial Biostatistician

[redacted], MPH

Date / Signature

Medical Director (Medical Therapeutics)

[redacted], MD

Date / Signature

Associate Clinical Program Director

[redacted]

Date / Signature

17.3 PROTOCOL AMENDMENT 3

RATIONALE FOR THE AMENDMENT

The sponsor's name has been changed to UCB BIOSCIENCES, INC. Specific sponsor contact information has been updated.

As recommended by the FDA, text has been added or modified to make it clear that the maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower.

As recommended by the FDA, the C-SSRS has been added to evaluate and identify subjects at risk for suicide while participating in a clinical study of a drug with CNS activity (FDA, Guidance for Industry, 2010).

Beginning with protocol Amendment 3, the oral solution (syrup) formulation of LCM to be used in this study contains 10mg/mL of drug substance (formerly containing 15mg/mL of drug substance).

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

A list of anticipated SAEs has been included in this amendment in compliance with the recent US FDA guidance on safety reporting requirements for studies conducted under an open IND (effective 28 Mar 2011; FDA, Guidance for Industry and Investigators, 2010).

Other changes made in this amendment are administrative in nature and are included in the specific changes below.

MODIFICATIONS/CHANGES

- The name of the sponsor was changed from SCHWARZ BIOSCIENCES to UCB BIOSCIENCES throughout the text; each occurrence of this change is not included in Section REFERENCE.

- The EudraCT number has been added to the cover page.
- The name and contact information for the Safety Physician (Global Clinical Safety and Pharmacovigilance) were updated.
- Information was added to Section 1 (Summary) and throughout the protocol to indicate that the maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower.
- In Section 4.3.2 (Exclusion criteria), Section 4.3.3 (Criteria for withdrawal), and Section 8.4.6 (Assessment of suicidality), language was added to address the recommendations from the FDA to evaluate and identify subjects at risk for suicide while participating in a clinical study of a drug with CNS activity.
- In Section 8.2.6 (Anticipated serious adverse events), a list of anticipated SAEs was added to follow the recent FDA guidance on safety reporting requirements for studies conducted under an open IND (effective 28 Mar 2011; FDA, Guidance for Industry and Investigators, 2010).
- The tabular schedules of study procedures were updated to reflect the changes to the protocol.

REFERENCE

Clinical Study Protocol, cover page. The EudraCT number was added as follows:

EudraCT Number: 2011-001559-35

Clinical Study Protocol, Contact information for the Safety Physician (Global Clinical Safety and Pharmacovigilance). Original text:

Associate Medical Director (Global Clinical Safety and Pharmacovigilance):

Name: [redacted], MD

Address: SCHWARZ BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Was revised as follows:

Safety Physician (Global Clinical Safety and Pharmacovigilance):

Name: [redacted], MB BCh BAO, MRCGP

Address: UCB Pharma S.A. Belgium
Chemin du Foriest
B-1420 Braine-L'Alleud, Belgium

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Study Protocol, List of Abbreviations. The following abbreviations were added:

C-SSRS	Columbia-Suicide Severity Rating Scale
FDA	Food and Drug Administration
PT	preferred term
SOC	system organ class

Clinical Study Protocol, Section 1 (Summary), paragraph 2. Original text:

Subjects who complete SP847 and choose to enter this open-label extension study will begin on the LCM dose they achieved in SP847. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847. Subjects will be able to receive LCM oral solution (syrup) or LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day

(tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Subjects who complete SP847 and choose to enter this open-label extension study will begin on the LCM dose they achieved in SP847. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847. Subjects will be able to receive LCM oral solution (syrup) or LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 2 (Background information), paragraph 9. Original text:

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, headache, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

Was revised as follows:

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported

common TEAEs, including dizziness, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

Clinical Study Protocol, Section 4.1 (Study description). Original text:

Subjects who complete SP847 (or discontinue SP847 due to a dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose they achieved in SP847. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Subjects who complete SP847 (or discontinue SP847 due to a dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose they achieved in SP847. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately

responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 4.3.2 (Exclusion criteria). Exclusion criterion 3 was newly added as follows:

1. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Clinical Study Protocol, Section 4.3.3 (Criteria for withdrawal). Original text:

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency
3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
9. Subject experiences status epilepticus

10. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST, ALT, or both) ≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

Was revised as follows:

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency
3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.

9. Subject experiences status epilepticus
10. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST, ALT, or both) ≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.
11. For subject who did not complete a C-SSRS at Screening, subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the screening version of the C-SSRS. The investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
12. For all subjects, regardless of whether or not a C-SSRS was completed at Screening, subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "since last visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.
5. For subject who did not complete a C-SSRS at Screening, subject had active suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the screening version of the C-SSRS. The investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the patient from the study.

Clinical Study Protocol, Section 4.4.1 (Treatments to be administered), paragraph 2 and paragraph 3. Original text:

The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup] or the corresponding dose level for the tablet formulation). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Was revised as follows:

The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower.

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup] or the corresponding dose level for the tablet formulation). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Clinical Study Protocol, Section 4.4.2 (Description of investigational product), paragraph 1. Original text:

The oral solution (syrup) formulation contains 15mg/mL of drug substance and is colorless to pale yellow in appearance. The oral solution (syrup) will be packaged in amber polyethylene terephthalate (PET) bottles with a white, child-proof, polypropylene screw cap.

Was revised as follows:

Beginning with protocol Amendment 3, the oral solution formulation contains 10mg/mL of drug substance (formerly containing 15mg/mL of drug substance) and is colorless to pale yellow in appearance. The oral solution (syrup) will be packaged in amber polyethylene terephthalate (PET) bottles with a white, child-proof, polypropylene screw cap.

Clinical Study Protocol, Section 5.1 (Visit 1 [Week 0]), list of assessments. Original text:

- Concomitant medications assessment

- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Was revised as follows:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment but 30 minutes to 1 hour after the administration of LCM)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)

- C-SSRS
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Clinical Study Protocol, Section 5.3 (Visit 2 [Week 4]). Original text:

During Visit 2 (Week 4), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry and hematology
- Blood samples for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine pregnancy test for female subjects of childbearing potential
- LCM return/compliance. Subject's caregivers will be instructed to return unused LCM at each study visit. Returned medication will be reconciled by the investigator (or designee) in order to monitor the subject's compliance with the medication schedule. If a subject is found to be noncompliant, a decision will be made by the investigator, in conjunction with SCHWARZ BIOSCIENCES, as to whether the subject should be withdrawn from the study.
- Subject diary assessment
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Was revised as follows:

During Visit 2 (Week 4), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry and hematology
- Blood samples for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine pregnancy test for female subjects of childbearing potential
- LCM return/compliance. Subject's caregivers will be instructed to return unused LCM at each study visit. Returned medication will be reconciled by the investigator (or designee) in order to monitor the subject's compliance with the medication schedule. If a subject is found to be noncompliant, a decision will be made by the investigator, in conjunction with UCB BIOSCIENCES, as to whether the subject should be withdrawn from the study.
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).
- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

- All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.4 (Visit 3 [Week 8]). Original text:

During Visit 3 (Week 8), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Urine pregnancy test for female subjects of childbearing potential
- LCM return/compliance
- Subject diary assessment
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parents/legal guardians) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening.
- A 12-lead ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable ECGs will be performed approximately 20 to 30 minutes apart prior to vital sign assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

Was revised as follows:

During Visit 3 (Week 8), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment

- Brief physical examination
- Brief neurological examination
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Urine pregnancy test for female subjects of childbearing potential
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parents/legal guardians) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).
- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).
- All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.6 (Visit 5 [Week 20]). Original text:

During Visit 5 (Week 20), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination

- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine sample for urinalysis
- Urine pregnancy test for female subjects of childbearing potential
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- LCM return/compliance
- Subject diary assessment
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parents/legal guardians) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

A 12-lead ECG is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable ECGs will be performed approximately 20 to 30 minutes apart prior to vital sign assessment, collection of blood samples (if applicable), and prior to administration of LCM (if applicable).

Was revised as follows:

During Visit 5 (Week 20), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology

- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine sample for urinalysis
- Urine pregnancy test for female subjects of childbearing potential
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs until the next clinic visit)
- Dispense LCM. Subjects and caregivers (including parents/legal guardians) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.14 (Visit 13 [Week 96]). Original text:

Assessments for Visit 13 (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, and a Tanner Stage assessment is conducted (if applicable).

Was revised as follows:

Assessments for Visit 13 (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, and a Tanner Stage assessment is conducted (if applicable).

Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 5.15 (Early Termination Visit). The following assessment was added:

- C-SSRS

Clinical Study Protocol, Section 5.16 (Unscheduled Visit[s]). Original text:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if an LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. If an AE prompts a dose reduction, the reduction can be implemented immediately at the investigator's discretion. However, the subject should return to the clinic as soon as possible for an Unscheduled Visit.

The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- LCM return/compliance (as applicable)
- Subject diary assessment

- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

Was revised as follows:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if an LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. If an AE prompts a dose reduction, the reduction can be implemented immediately at the investigator's discretion. However, the subject should return to the clinic as soon as possible for an Unscheduled Visit.

The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- LCM return/compliance (as applicable)
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.17 (Final Visit [2 weeks after the last LCM dose]). The following assessment was added:

- C-SSRS

Clinical Study Protocol, Section 8.2.6 (Anticipated serious adverse events), was newly added as follows:

The following list of anticipated SAEs has been identified as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol. This list does not change the investigator's obligation to report all SAEs (including anticipated SAEs) as detailed in Section 8.2.4.

Anticipated SAEs for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administrative site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion
	Incontinence
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder
Reproductive system and breast disorders	Menstrual disorder

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

Clinical Study Protocol, Section 8.3.2 (Pregnancy testing). Original text:

Females of childbearing potential (ie, female subjects who have begun menstruating) will have serum and urine pregnancy tests performed during the study according to the tabular schedule of study procedures, Section 16.1.

Was revised as follows:

Females of childbearing potential will have serum and urine pregnancy tests performed during the study according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 8.4.4 (12-lead ECG). Original text:

Standard 12-lead ECGs will be performed according to the tabular schedule of study procedures, Section 16.1, and as described in Section 5.

Care should be taken to assure proper lead placement and quality of ECG recording. Subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording.

Was revised as follows:

Standard 12-lead ECGs will be performed according to the tabular schedule of study procedures, Section 16.1, and as described in Section 5.

Beginning with Protocol Amendment 3, all subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Care should be taken to assure proper lead placement and quality of ECG recording. Subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording.

Clinical Study Protocol, Section 8.4.6 (Assessment of suicidality) was newly added as follows:

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 15 (References). The following references were added:

Columbia University Medical Center. Columbia-Suicide Severity Rating Scale (2008). http://www.cssrs.columbia.edu/. Accessed 19 Jun 2011.

Food and Drug Administration. Guidance for Industry. Suicidality: Prospective assessment of occurrence in clinical trials. US Dept of Health and Human Services, Center for Drug Evaluation and Research, 09/2010. Available upon request.

Food and Drug Administration. Guidance for Industry and Investigators. Safety reporting requirements for INDs and BE/BA studies. US Dept of Health and Human Services, Center for Drug Evaluation and Research, 09/2010. Available upon request.

Clinical Study Protocol, Section 16.1 (Tabular schedule of study procedures) was updated to the following:

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X		X	
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X		X	
Urinalysis	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X		X			
Clinical GIC						X				X	X			
Caregiver GIC						X				X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]	X[n]		
LCM return/compliance			X	X	X	X	X	X	X	X	X	X[n]	X	
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[o]	X		X	X	X	X	X	X	X	X	X	X	X	

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	V1[b]	TC[c]	V2	V3	V4	V5	V6	V7	V8	V9	ETV[d]	Unsch Visit[e]	Final Visit[f]	TC[g]
Weeks in study	0		4	8	12	20	28	36	44	52				
AE reporting[p]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] A Final Visit should be performed 2 weeks after a subject has tapered off LCM

[g] This TC occurs 28 to 35 days after the last dose of LCM.

[h] Assessments should have been done as part of the last visit of the primary study.

[i] An ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

Beginning with Protocol Amendment 3, all subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[j] Blood samples may be drawn at any time post-dosing with LCM.

[k] For female subjects of childbearing potential, serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[n] As applicable

[o] For all subjects ≥6 years of age already enrolled, the screening version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[p] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X		X	
Blood sample for concomitant AEDs[h]	X		X	X	X	X		X	
Urinalysis			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Dispense LCM	X		X	X	X^k	X^k	X^l		
LCM return/compliance	X		X	X	X	X	X^l	X	
Dispense diary	X		X	X	X	X			
Diary assessment	X		X	X	X	X	X	X	
C-SSRS[m]	X		X	X	X	X	X	X	

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
AE reporting	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] A Final Visit should be performed 2 weeks after a subject has tapered off LCM.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] An ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady state. This ECG can be done at the next scheduled visit. When the ECG assessment is performed, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital signs assessment, collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

Beginning with Protocol Amendment 3, all subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable

recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[l] As applicable.

[m] For all subjects ≥6 years of age already enrolled, the screening version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

17.4 PROTOCOL AMENDMENT 4

RATIONALE FOR THE AMENDMENT

The primary purpose of this protocol amendment is to permit (at selected sites) up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy.

In addition, based on regulatory agency recommendations, the Achenbach CBCL, Bayley-III scales, and a LCM palatability and ease of use questionnaire have been added as assessments in SP848.

Other changes made in this amendment are administrative in nature and are included in the specific changes below.

MODIFICATIONS/CHANGES

- With this protocol amendment, approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Therefore, the study title has been updated to reflect that SP848 is no longer exclusively an "extension study."
- Study contact information has been updated (eg, Clinical Program Director, Safety Physician, and SAE reporting).
- Information was added to Section 1 (Summary) and throughout the protocol to indicate that approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. A Screening and Titration Visits have been added for subjects enrolling directly into SP848.
- Information was added to Section 1 (Summary) and throughout the protocol to reflect the addition of the Achenbach CBCL, Bayley-III scales, and a LCM palatability and ease of use questionnaire as assessments in SP848.
- Modifications were made to Section 4.3.1 (Inclusion criteria) and Section 4.3.2 (Exclusion criteria) in order to address subjects who have participated in SP847 or other LCM pediatric clinical studies in epilepsy or who have enrolled directly into SP848 without previous participation in a LCM clinical study.
- Information was added to Section 8.4.4 (12-lead ECG) and throughout the protocol to clarify that all subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM Cmax 1 week after an initial LCM dose increase to a LCM dose that is ≥8mg/kg/day or when a new concomitant AED is introduced.

REFERENCE

Clinical Study Protocol, cover page, study title. Original text:

AN OPEN-LABEL EXTENSION STUDY TO DETERMINE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM ORAL LACOSAMIDE (LCM) AS ADJUNCTIVE THERAPY IN CHILDREN WITH PARTIAL-ONSET SEIZURES

Was revised as follows:

AN OPEN-LABEL STUDY TO DETERMINE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM ORAL LACOSAMIDE (LCM) AS ADJUNCTIVE THERAPY IN CHILDREN WITH EPILEPSY

Clinical Study Protocol, cover page, sponsor information. The following text was deleted:

A member of the UCB Group

Clinical Study Protocol, Contact information for the Clinical Program Director and Safety Physician. Original text:

Associate Clinical Program Director:

Name: [redacted], BS

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Safety Physician (Global Clinical Safety and Pharmacovigilance):

Name: [redacted], MB BCh BAO, MRCGP

Address: UCB Pharma S.A. Belgium
Chemin du Foriest
B-1420 Braine-L'Alleud, Belgium

Phone/Fax: [redacted]

E-mail: [redacted]

Was revised as follows:

Clinical Program Director:

Name: [redacted], BS

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Safety Physician (Drug Safety):

Name: [redacted] MD

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Study Protocol, Serious Adverse Event reporting contact information was added as follows:

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h), safety related issues, and emergency unblinding	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842 **Japan:** +81 3 5283 1869
Email	**Europe and Rest of the World (except Japan):** GCSP@ucb.com **Japan:** JDSO@ucb.com

Clinical Study Protocol, List of Abbreviations. The following abbreviations were added:

C_{max}	maximum plasma concentration
DS	Drug Safety (formerly known as Global Clinical Safety and Pharmacovigilance)
EEG	electroencephalogram
GCSP	Global Clinical Safety and Pharmacovigilance
MAO	monoamine oxidase
TV	Titration Visit

Clinical Study Protocol, Section 1 (Summary). Original text:

SP848 is an open-label extension study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with partial-onset seizures treated with lacosamide (LCM) oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration

of LCM. SP848 will also be open to subjects who participate in other future LCM pediatric clinical studies in epilepsy.

Subjects who complete SP847 and choose to enter this open-label extension study will begin on the LCM dose they achieved in SP847. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label extension study, will also begin on the LCM dose they achieved in SP847. Subjects will be able to receive LCM oral solution (syrup) or LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

The primary variables for assessment of safety and tolerability are:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs

The secondary variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, and the Caregiver Global Impression of Change.

Was revised as follows:

SP848 is an open-label study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with epilepsy (partial-onset seizures and other pediatric epilepsy syndromes) treated with lacosamide (LCM) oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies in other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy. At selected sites, subjects may also be able to participate in a substudy without withdrawing from SP848.

Subjects who complete SP847 or another applicable LCM pediatric epilepsy study and choose to enter this open-label study will begin on the LCM dose they achieved in SP847 or their previous pediatric LCM study. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label study, will also begin on the LCM dose they achieved in SP847. Subjects who meet eligibility requirements and enroll directly into SP848 without previous participation in a LCM clinical study will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (up to a maximum level as described below).

Subjects will be able to receive LCM oral solution (syrup) or LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. An increase in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that LCM be

tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

The primary variables for assessment of safety and tolerability are:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs
- Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)

The secondary variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, and a LCM palatability and ease of use questionnaire.

Clinical Study Protocol, Section 2 (Background information). Original text:

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). 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 classification of epilepsies in children was described in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (1989; Aicardi, 1994). Seizures are categorized based on whether the onset is focal or generalized and whether the disorder is idiopathic, symptomatic, or cryptogenic. Specific syndromes are further classified according to a number of criteria including seizure type, cause, anatomy, precipitating factors, age of onset, and sometimes prognosis.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and 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 (CHMP/EWP/566/98, 2010). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander, 1998).

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; Glauser et al, 2000; Glauser et al, 2006). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide (LCM, Vimpat®, SPM 927, [R]-2-acetamido-N-benzyl-3-methoxypropionamide) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) and in patients 17 years of age and older in the United States (oral tablets, oral solution, and solution for iv infusion). The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to 400mg bid (800mg/day) were evaluated in approximately 700 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2200 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in 1308 adult subjects, aged 16 to 70 years, established the efficacy of oral LCM as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with difficult to control partial-onset seizures. In these studies, LCM was initiated at a dose of 100mg/day (in 2 divided doses) and escalated to the randomized dose (200mg/day, 400mg/day, or 600mg/day) in 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the

most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

SP847, the current primary study, is an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. Approximately 42 children (aged 1 month to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs will be enrolled. The study consists of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject may be up to approximately 13 weeks. Approximately 300 additional subjects who may participate in other future LCM primary pediatric clinical studies in epilepsy will also be eligible to participate in SP848.

SP848 is an open-label extension study to obtain long-term safety, tolerability, and PK data in children with partial-onset seizures treated with LCM oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study (or discontinued SP847 due to a dose reduction or status epilepticus), and who, in the investigator's opinion, would benefit from long-term administration of LCM. SP848 will also be open to subjects who participate in other future LCM pediatric clinical studies in epilepsy.

Was revised as follows:

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people have epilepsy–about 1% of the world's population (Dichek, 1999). 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 classification of epilepsies in children was described in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (1989; Aicardi, 1994). Seizures are categorized based on whether the onset is focal or generalized and whether the disorder is idiopathic, symptomatic, or cryptogenic. Specific syndromes are further classified according to a number of criteria including seizure type, cause, anatomy, precipitating factors, age of onset, and sometimes prognosis.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and 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 (CHMP/EWP/566/98, 2010). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander, 1998).

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; Glauser et al, 2000; Glauser et al, 2006). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide (LCM, Vimpat®, SPM 927, [R]-2-acetamido-N-benzyl-3-methoxypropionamide) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) and in patients 17 years of age and older in the United States (oral tablets, oral solution, and solution for iv infusion). The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to 400mg bid (800mg/day) were evaluated in approximately 700 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2200 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in 1308 adult subjects, aged 16 to 70 years, established the efficacy of oral LCM as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with difficult to control partial-onset seizures. In these studies, LCM was initiated at a dose of 100mg/day (in 2 divided doses) and escalated to the randomized dose (200mg/day, 400mg/day, or 600mg/day) in 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

SP847 is an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. Approximately 42 children (aged 1 month to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs will be enrolled. The study consists of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject may be up to approximately 13 weeks. Approximately 200 additional subjects who may participate in other LCM pediatric clinical studies in epilepsy will also be eligible to participate in SP848.

SP848 is an open-label study to obtain long-term safety, tolerability, and pharmacokinetic (PK) data in children with epilepsy (partial-onset seizures and other pediatric epilepsy syndromes) treated with lacosamide (LCM) oral solution (syrup) or LCM tablets as adjunctive therapy. In addition, the study is designed to obtain preliminary efficacy data on seizure frequency during long-term exposure. The study will also provide continued availability of LCM to subjects who have completed the SP847 epilepsy study and to subjects who have discontinued from SP847 due to a dose reduction or status epilepticus, and who, in the investigator's opinion, would benefit from long-term administration of LCM.

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies in other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures.

Clinical Study Protocol, Section 3 (Study objectives). Original text:

The objectives of this study are:

- To obtain information about the safety, tolerability, and PK of LCM during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long-term exposure
- To allow subjects who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow subjects who have participated in other future LCM pediatric clinical studies in epilepsy to continue receiving LCM

Was revised as follows:

The objectives of this study are:

- To obtain information about the safety, tolerability, and PK of LCM during long-term exposure
- To obtain preliminary efficacy data on seizure frequency during long-term exposure
- To allow subjects who have participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM
- To allow subjects who have participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM
- Beginning with Protocol Amendment 4, at selected sites, to allow up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously received LCM to begin receiving LCM

Clinical Study Protocol, Section 4.1 (Study description). Original text:

Subjects who complete SP847 (or discontinue SP847 due to a dose reduction or status epilepticus) and who choose to enter the open-label extension study, will begin on the LCM dose they achieved in SP847. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows (including additions of subsection headings 4.1.1 [Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy] and 4.1.2 [Subjects enrolling directly in SP848]):

Subjects who complete SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or subjects from another applicable LCM pediatric clinical study in epilepsy and who choose to enter the open-label study, will begin on the LCM dose they achieved in the primary study. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (see Section 4.4.1). Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator.

The same study conditions described in Section 4.1.1 (eg, minimum and maximum LCM dose, required office visits for dose increases, concomitant AEDs, and study medication taper) also apply.

Clinical Study Protocol, Section 4.2.1 (Primary variables). The following variables were added:

- Achenbach CBCL at Baseline for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior

- Bayley-III scales at Baseline for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)

Clinical Study Protocol, Section 4.2.2 (Secondary variables). Original text:

Secondary efficacy variables include:

- Seizure counts, which will be assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population
- Clinical Global Impression of Change
- Caregiver Global Impression of Change

Was revised as follows:

Secondary variables include:

- Seizure counts, which will be assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- LCM palatability and ease of use questionnaire

Clinical Study Protocol, Section 4.3.1 (Inclusion criteria). Original text:

Subjects must fulfill the following inclusion criteria:

1. A signed informed consent form has been obtained from the parent/legal guardian and assent has been obtained from the subject (when possible or as required according to local Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).
2. Subject has completed SP847 (or the subject discontinued SP847 due to a dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures, or subject has participated in other LCM pediatric clinical studies in epilepsy.
3. Subject is expected to benefit from participation, in the opinion of the investigator.
4. Subject and caregiver (which may be a parent, legal guardian, or other delegated caregiver) are willing and able to comply with all study requirements, including maintaining a daily seizure diary.

Was revised as follows:

All subjects in SP848 must fulfill the following inclusion criteria:

1. A signed informed consent form has been obtained from the parent/legal guardian and assent has been obtained from the subject (when possible or as required according to local Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).
4. Subject and caregiver (which may be a parent, legal guardian, or other delegated caregiver) are willing and able to comply with all study requirements, including maintaining a daily seizure diary.

Subjects who have participated in SP847 or other LCM pediatric clinical studies in epilepsy must fulfill the following inclusion criteria:

2. Subject has completed SP847 (or the subject discontinued SP847 due to a dose reduction or status epilepticus) for the treatment of uncontrolled partial-onset seizures, or subject has participated in other LCM pediatric clinical studies in epilepsy.
3. Subject is expected to benefit from participation, in the opinion of the investigator.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study must fulfill the following inclusion criteria:

5. Subject is male or female and ≥4 years to ≤17 years of age.
6. Subject has a diagnosis of epilepsy with partial-onset seizures.
    a. The results of at least 1 prior electroencephalogram (EEG) AND 1 prior magnetic resonance imaging/computerized tomography scan should be consistent with the above diagnosis.
7. Subject has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with at least 1 AED (concurrently or sequentially).
8. Subject has been observed to have at least 2 countable seizures in the 4-week period prior to Screening.
    a. In the case of simple partial seizures, only those with motor signs will be counted towards meeting the inclusion criteria (only partial seizures with a recognizable and countable manifestation).
9. Subject is on a stable dosage regimen of 1 to 3 AEDs. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of at least 1 week prior to Screening. Vagal nerve stimulation is not counted as medical therapy; however, VNS settings must be kept constant for a period of at least 1 week prior to Screening.
10. Subject is an acceptable candidate for venipuncture.

Clinical Study Protocol, Section 4.3.2 (Exclusion criteria). Original text:

Subjects are not permitted to enroll in the study if any of the following criteria are met:

1. Subject is receiving any investigational drugs or using any experimental devices in addition to LCM.
2. Subject meets the withdrawal criteria for the primary study (with the exception of subjects who discontinued due to a dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).
3. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Was revised as follows:

Subjects are not permitted to enroll in the study if any of the following criteria are met:

1. Subject is receiving any investigational drugs or using any experimental devices in addition to LCM.
3. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Subjects who have participated in SP847 or other LCM pediatric clinical studies in epilepsy are not permitted to enroll in the study if any of the following criteria are met:

2. Subject meets the withdrawal criteria for the primary study (with the exception of subjects who discontinued due to a dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study are not permitted to enroll in the study if any of the following criteria are met:

4. Subject has ever received LCM.
5. Subject has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate in this study.
6. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
7. Subject has a known hypersensitivity to any component of the investigational medicinal product.
8. Subject is a female of childbearing potential and does not practice an acceptable method of contraception for the duration of the study.

- Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone, oxcarbazepine]) which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.
- The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit.

9. Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level greater than or equal to 2 times the upper limit of normal (ULN), or creatinine clearance less than 50mL/min.
10. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a QT prolongation greater than 450ms).
11. Subject has hemodynamically significant heart disease (eg, heart failure).
12. Subject has an arrhythmic heart condition requiring medical therapy.
13. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
14. Subject has nonepileptic events, including psychogenic seizures, that could be confused with seizures. If both epileptic and nonepileptic events are present, epileptic events must be distinguished from nonepileptic phenomena.
15. Subject has a history of primary generalized epilepsy.
16. Subject has been treated with vigabatrin or felbamate for at least 12 months prior to entering the study and has experienced any toxicity issues with these treatments. Note: Any subject who is currently treated with vigabatrin or felbamate, and has received vigabatrin for a period of less than 12 months, is excluded from the study. Subjects who have received vigabatrin in the past must have documentation of an assessment for visual field defects after completion of vigabatrin therapy.
17. Subject is taking monoamine oxidase (MAO) inhibitors or narcotic analgesics.
18. Subject has epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen syndrome.
19. Subject has a known sodium channelopathy, such as Brugada syndrome.

Clinical Study Protocol, Section 4.3.3 (Criteria for withdrawal), criterion 9. Original text:

9. Subject experiences status epilepticus

Was revised as follows:

9. Subject experiences convulsive status epilepticus (if none had occurred prior to study entry) and is compliant with study treatment

Clinical Study Protocol, Section 4.4.1 (Treatments to be administered). Original text:

Subjects who have participated in SP847 (or other future LCM pediatric clinical studies in epilepsy), who are eligible to participate in the open-label extension study SP848, and who choose to enter SP848, will begin SP848 on the LCM dose they achieved in the primary study. The investigator, together with the subject/caregiver (including parent/legal guardian), will be able to choose either the oral solution (syrup) formulation or the tablet formulation of LCM in this study. The study medication will be orally administered bid (at 12-hour intervals, once in the morning and once in the evening) in equally divided doses. The oral solution (syrup) formulation will be measured and orally administered via a dosing syringe. The selection of doses, titration scheme, and rate of taper in SP847 were based on adult studies and were adjusted to a mg/kg basis plus 40% (ie, 600mg/day adult dose of LCM corresponds to [600mg/70kg] x 1.4 = approximately 12mg/kg/day for a child). The selection of doses in this trial is based on the maximum recommended dose in SP847.

The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower.

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup] or the corresponding dose level for the tablet formulation). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Subjects enrolled in SP848 have the option of remaining on the oral solution formulation of LCM or switching to the commercial tablet formulation, if feasible. Consideration of the current LCM milligram dose in the oral solution (syrup) should occur if/when transitioning to the tablet formulation. In cases where the LCM dose received with the oral solution (syrup) is not supported by the tablet strengths available in SP848 (50mg and 100mg), a clinical decision must be made by the investigator or other study physician to either increase or decrease the LCM dose to the next multiple of 100mg with a maximum permitted dose of 600mg/day.

Subjects achieving a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet) who withdraw during the study should taper off study medication. It is recommended that the

dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (see tables below). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Recommended LCM dose reduction (taper) for oral solution (syrup) formulation

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
12mg/kg/day (6mg/kg bid)	8mg/kg/day (4mg/kg bid)	4mg/kg/day (2mg/kg bid)	0
10mg/kg/day (5mg/kg bid)	6mg/kg/day (3mg/kg bid)	2mg/kg/day (1mg/kg bid)	0
8mg/kg/day (4mg/kg bid)	4mg/kg/day (2mg/kg bid)	0	–
6mg/kg/day (3mg/kg bid)	2mg/kg/day (1mg/kg bid)	0	–
4mg/kg/day (2mg/kg bid)	0	–	–

bid=twice daily; LCM=lacosamide

[a] Maximum LCM dose achieved is based upon the maximum recommended dose in SP847.

Recommended LCM dose reduction (taper) for tablet formulation

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
600mg/day (300mg bid)	400mg/day (200mg bid)	200mg/day (100mg bid)	0
500mg/day (250mg bid)	300mg/day (150mg bid)	100mg/day (50mg bid)	0
400mg/day (200mg bid)	200mg/day (100mg bid)	0	–
300mg/day (150mg bid)	100mg/day (50mg bid)	0	–
200mg/day (100mg bid)	0	–	–

bid=twice daily; LCM=lacosamide

[a] Maximum LCM dose achieved is based upon the maximum recommended dose in SP847.

Was revised as follows (including additions of subsection headings 4.4.1.1 [Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy], 4.4.1.2 [Subjects enrolling directly in SP848], 4.4.1.3 [All subjects], and 4.4.1.4 [Study completion]):

Subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), who are eligible to participate in the open-label study SP848, and who choose to enter SP848, will begin SP848 on the LCM dose they achieved in the primary study.

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. After Screening, eligible subjects will initiate treatment with LCM (oral solution or tablet, as chosen by the investigator and subject/caregiver), and the LCM dose will be titrated to a level to optimize tolerability and seizure control.

At the first Titration Visit (TV) (see Section 5.2), subjects who have enrolled directly into SP848 will receive a single dose of LCM (1mg/kg [oral solution] or 50mg [tablet]) during the clinic visit. Over the following days, subjects will be administered LCM 1mg/kg bid (oral solution) or LCM 50mg bid (tablet), and will begin titrating in weekly increments of 2mg/kg/day (oral solution) or 100mg/day (tablet) up to a level to optimize tolerability and seizure control (not to exceed 12mg/kg/day [or 600mg/day based on body weight, whichever is lower]). Subjects must be on each LCM dose for at least 5 days before titrating up to the next dose.

A total of up to 6 Titration Visits may be required (eg, for a subject whose dose is titrated to the maximum permitted dose of LCM 12mg/kg/day). However, based on tolerability and seizure control, a subject's LCM dose may be titrated to a lower dose level; in such a case, fewer than 6 Titration Visits would be required.

The following table summarizes the recommended titration steps for the oral solution and tablet formulations:

Recommended LCM dose titration for subjects enrolling directly into SP848

Formulation	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Oral solution (syrup)	2mg/kg/day (1mg/kg bid)	4mg/kg/day (2mg/kg bid)	6mg/kg/day (3mg/kg bid)	8mg/kg/day (4mg/kg bid)	10mg/kg/day (5mg/kg bid)	12mg/kg/day (6mg/kg bid)
Tablet	100mg/day (50mg bid)	200mg/day (100mg bid)	300mg/day (150mg bid)	400mg/day (200mg bid)	500mg/day (250mg bid)	600mg/day (300mg bid)

bid=twice daily; LCM=lacosamide

The investigator, together with the subject/caregiver (including parent/legal guardian), will be able to choose either the oral solution (syrup) formulation or the tablet formulation of LCM in this study. The study medication will be orally administered bid (at 12-hour intervals, once in the morning and once in the evening) in equally divided doses. The oral solution (syrup) formulation will be measured and orally administered via a dosing syringe. The selection of doses, titration

scheme, and rate of taper in SP847 were based on adult studies and were adjusted to a mg/kg basis plus 40% (ie, 600mg/day adult dose of LCM corresponds to [600mg/70kg] x 1.4 = approximately 12mg/kg/day for a child). The selection of doses in this trial is based on the maximum recommended dose in SP847.

The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower.

The investigator may increase the dose of LCM no faster than 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) per week to a maximum of 12mg/kg/day (oral solution [syrup] or the corresponding dose levels for the tablet formulation) not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. The investigator may decrease the dose of LCM to a minimum of 2mg/kg/day (oral solution [syrup] or the corresponding dose level for the tablet formulation). Increases in the LCM dose must occur only during office visits. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these subjects would remain at their assigned dose.

Subjects enrolling from SP847 will have the option of remaining on the oral solution formulation of LCM or switching to the commercial tablet formulation, if feasible. Consideration of the current LCM milligram dose in the oral solution (syrup) should occur if/when transitioning to the tablet formulation. In cases where the LCM dose received with the oral solution (syrup) is not supported by the tablet strengths available in SP848 (50mg and 100mg), a clinical decision must be made by the investigator or other study physician to either increase or decrease the LCM dose to the next multiple of 100mg with a maximum permitted dose of 600mg/day.

Subjects achieving a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet) who withdraw during the study should taper off study medication. It is recommended that the dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (see tables below). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Recommended LCM dose reduction (taper) for oral solution (syrup) formulation

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
12mg/kg/day (6mg/kg bid)	8mg/kg/day (4mg/kg bid)	4mg/kg/day (2mg/kg bid)	0
10mg/kg/day (5mg/kg bid)	6mg/kg/day (3mg/kg bid)	2mg/kg/day (1mg/kg bid)	0
8mg/kg/day (4mg/kg bid)	4mg/kg/day (2mg/kg bid)	0	–

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
6mg/kg/day (3mg/kg bid)	2mg/kg/day (1mg/kg bid)	0	–
4mg/kg/day (2mg/kg bid)	0	–	–

bid=twice daily; LCM=lacosamide

[a] Maximum LCM dose achieved is based upon the maximum recommended dose in SP847.

Recommended LCM dose reduction (taper) for tablet formulation

Maximum LCM dose achieved[a]	Taper schedule		
	Week 1	Week 2	Week 3
600mg/day (300mg bid)	400mg/day (200mg bid)	200mg/day (100mg bid)	0
500mg/day (250mg bid)	300mg/day (150mg bid)	100mg/day (50mg bid)	0
400mg/day (200mg bid)	200mg/day (100mg bid)	0	–
300mg/day (150mg bid)	100mg/day (50mg bid)	0	–
200mg/day (100mg bid)	0	–	–

bid=twice daily; LCM=lacosamide

[a] Maximum LCM dose achieved is based upon the maximum recommended dose in SP847.

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or parent/legal guardian) should taper LCM gradually as described in Section 4.4.1.3. These subjects should complete Visit 13/Termination Visit, followed by the Final Visit which occurs 2 weeks after the final dose of study medication, and then the Safety Follow-Up telephone contact which occurs 28 to 35 days after the last dose of LCM.

Clinical Study Protocol, Section 4.4.3. Original text:

This is an open-label extension study; subjects will not be randomized. Subjects will keep the unique number assigned in the primary study.

Was revised as follows:

This is an open-label study; subjects will not be randomized. Subjects who participated in SP847 or other LCM pediatric clinical studies in epilepsy will keep the unique number assigned in the primary study.

Subjects enrolling directly into SP848 without participation in a previous LCM clinical study will be assigned unique numbers for the purpose of study and subject identification, as well as for subject confidentiality. At the Screening Visit, each subject will be assigned the unique identifying number for this study.

Clinical Study Protocol, Section 4.5 (Expected duration of the study), first sentence. Original text:

The maximum duration of LCM administration will be approximately 2 years.

Was revised as follows:

The maximum duration of LCM administration for an individual subject will be approximately 2 years.

Clinical Study Protocol, Section 5.1 (Screening Visit) was newly added as follows and subsequent section numbers were adjusted accordingly:

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848.

At the Screening Visit, subjects entering directly into SP848 (ie, subjects who have not participated in SP847 or another applicable LCM pediatric clinical study in epilepsy) will be evaluated for their suitability for enrollment in SP848. The Screening Visit is not applicable for subjects who have participated in SP847 or another applicable LCM pediatric clinical study in epilepsy; the first visit in SP848 for these subjects is Visit 1 (see Section 5.3).

The Screening assessments will be conducted up to 14 days prior to the first administration of LCM. It is acceptable for the Screening assessments to be conducted on more than 1 day, although it should not be done over longer than 1 week. Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by the local IRB/IEC, the subject will be requested to give

assent to participate in the study. Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria and the results of the following pretreatment assessments (for further details of the assessments and the required procedures and methods, please refer to Section 6, Section 7, and Section 8 of this protocol).

- Concomitant medications assessment
- Concomitant AEDs assessment
- Medical history assessment
- Seizure history over the past 4 weeks (historical Baseline)
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample)
- Vital signs assessment (blood pressure and pulse)
- Body weight assessment
- Height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- C-SSRS
- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries
- Adverse event reporting
- Dispense subject diary

The subject will be scheduled to return for a clinic visit (TV) less than 14 days from the last Screening Visit assessment(s).

Clinical Study Protocol, Section 5.2 (Titration Visit[s] [TV1, TV2, TV3, TV4, TV5, TV6]) was newly added as follows and subsequent section numbers were adjusted accordingly:

Eligible subjects who enter directly into SP848 (without prior participation in SP847 or another applicable LCM primary study) will initiate treatment with LCM at TV1, and the LCM dose will be titrated over the following week(s). Titration Visits are not applicable for subjects who have participated in SP847 or another LCM primary study; the first visit in SP848 for these subjects is Visit 1 (see Section 5.3).

At TV1, subjects who have enrolled directly into SP848 will receive a single dose of LCM (1mg/kg [oral solution] or 50mg [tablet]) during the clinic visit. Over the following days, subjects will be administered LCM 1mg/kg bid (oral solution) or LCM 50mg bid (tablet), and will begin titrating in weekly increments of 2mg/kg/day (oral solution) or 100mg/day (tablet) up to a level to optimize tolerability and seizure control (not to exceed 12mg/kg/day [or 600mg/day based on body weight, whichever is lower]). Subjects must be on each LCM dose for at least 5 days before titrating up to the next dose. It should be noted, in cases of incomplete doses (eg, subject spits out all or a portion of the syrup), missed doses, or administration of an erroneous volume of syrup, study medication should not be readministered and these cases would not be considered dose reductions. The LCM dose titration steps are summarized in Section 4.4.1.2.

A total of up to 6 Titration Visits may be required (eg, for a subject whose dose is titrated to the maximum permitted dose of LCM 12mg/kg/day). However, based on tolerability and seizure control, a subject's LCM dose may be titrated to a lower dose level; in such a case, fewer than 6 Titration Visits would be required.

The following assessments are required for each TV:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- Blood sample for clinical chemistry, hematology, and endocrinology (TV2 and TV4 only)
- Urine sample for urinalysis (TV2 and TV4 only)
- LCM return/compliance (as applicable)
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense subject diary

- Dispense LCM (as applicable)

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM maximum plasma concentration (C_{max}) 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/day or a new concomitant AED is introduced. Subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.3 (Visit 1 [Week 0]). Original text:

For subjects who complete SP847, Visit 1 is Day 2 of the second PK collection time period (which may include an overnight stay at a hospital or medical facility) in SP847 (Day 28 for Cohorts 1, 2, 3, and 5 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 5 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 5 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue SP847 due to a dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847. For subjects in SP847 who are titrated up to the maximum permitted dose of 600mg/day sooner than the study schedule would ordinarily indicate (based on body weight) and who enroll in SP848, the Early Termination Visit of SP847 will also serve as Visit 1 for SP848.

For subjects who enroll in SP848 after participation in future LCM pediatric clinical studies in epilepsy, SP848 Visit 1 will be specified in the respective primary study protocol.

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by local IRB/IEC, the subject will be requested to give assent to participate in the study.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments, and a complete medical history update will be obtained. The data for the following assessments will be taken from the last assessment during SP847 (or other primary study as applicable):

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment but 30 minutes to 1 hour after the administration of LCM)
- Vital signs assessment (blood pressure and pulse)

- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- C-SSRS
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Was revised as follows:

For subjects who complete SP847, Visit 1 for SP848 is the same as Day 2 of the second PK collection time period (which may include an overnight stay at a hospital or medical facility) in SP847 (Day 28 for Cohorts 1, 2, 3, and 5 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 5 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 5 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue SP847 due to a dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847. For subjects in SP847 who are titrated up to the maximum permitted dose of 600mg/day sooner than the study schedule would ordinarily indicate (based on body weight) and who enroll in SP848, the Early Termination Visit of SP847 will also serve as Visit 1 for SP848.

For subjects who enroll in SP848 after participation in other LCM pediatric clinical studies in epilepsy, SP848 Visit 1 will be specified in the respective primary study protocol.

For subjects who enter directly into SP848 (without prior participation in SP847 or other LCM pediatric clinic studies in epilepsy), the LCM dose will be titrated at weekly intervals as described in Section 4.4.1.2 and Section 5.2. These subjects will reach Visit 1 either (1) when the LCM dose is titrated to a level that, in the opinion of the investigator, optimizes tolerability and seizure control, or (2) when the maximum permitted LCM dose is reached (12mg/kg/day [or 600mg/day based on body weight, whichever is lower]). In the case of a subject who requires a dose reduction during the Titration Visits, the subject's LCM dose will be returned to the previous dose level and the next clinic visit will be Visit 1 at the reduced level. Visit 1 should occur at least 5 days after the final TV. At Visit 1, the progress in SP848 for subjects who entered directly into SP848 and for subjects who have enrolled from SP847 or other LCM pediatric clinical studies in epilepsy will be aligned; subsequent regularly scheduled clinic visits for all subjects will be at 4-week intervals as outlined in the following sections.

The informed consent process for SP848 will be conducted at Visit 1 for subjects who have not previously been through the informed consent process at the Screening Visit (ie, subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy for whom Visit 1 is the first study visit in SP848). Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent Form. When possible, or as required by local IRB/IEC, the subject will be requested to give assent to participate in the study.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments (applicable only for subjects for whom Visit 1 is the first clinic visit for SP848), and a complete medical history update will be obtained. The data for the following assessments will be taken from the last assessment during SP847 (or other primary study as applicable):

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment but 30 minutes to 1 hour after the administration of LCM)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- Tanner Stage assessment (if applicable)
- C-SSRS
- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older) (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- Adverse event reporting

- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs for the following 4 weeks)
- Dispense LCM. Subjects and caregivers (including parent/legal guardian) will be instructed to administer LCM at approximately 12-hour intervals (once in the morning and once in the evening).

Clinical Study Protocol, Section 5.5 (Visit 2 [Week 4]), final 2 paragraphs. Original text:

- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Was revised as follows:

- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.6 (Visit 3 [Week 8]), final 2 paragraphs. Original text:

- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Was revised as follows:

- A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.8 (Visit 5 [Week 20]), final 2 paragraphs. Original text:

A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Was revised as follows:

A 12-lead ECG (2 interpretable recordings) is also required when the dose of LCM is increased to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. The ECG should be performed after the increased dose of LCM or the new AED has reached steady-state. This ECG can be done at the next scheduled visit. When the ECG assessment is done, 2 interpretable recordings will be performed approximately 20 to 30 minutes apart prior to vital sign assessment and collection of blood samples (if applicable), but 30 minutes to 1 hour after the administration of LCM (if applicable).

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.9 (Visit 6 [Week 28]). Original text:

Assessments for Visit 6 (Week 28) are the same as those described for Visit 3 (Week 8) in Section 5.6, with the following exception: a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted at Visit 6.

Was revised as follows:

Assessments for Visit 6 (Week 28) are the same as those described for Visit 3 (Week 8) in Section 5.6, with the following exception: completion of the palatability and ease of use questionnaire and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) are conducted at Visit 6.

Clinical Study Protocol, Section 5.2 (Visit 9 [Week 52]). Original text:

Assessments for Visit 9 (Week 52) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exception: a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted at Visit 9.

Was revised as follows:

Assessments for Visit 9 (Week 52) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exception: completion of the palatability and ease of use questionnaire and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) are conducted at Visit 9.

Clinical Study Protocol, Section 5.14 (Visit 11 [Week 72]). Original text:

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted.

Was revised as follows:

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), the palatability and ease of use questionnaire is completed, and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted.

Clinical Study Protocol, Section 5.16 (Visit 13/Termination Visit [Week 96]). Original text:

Assessments for Visit 13 (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, and a Tanner Stage assessment is conducted (if applicable).

Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or

100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or parent/legal guardian) should taper LCM gradually as described in Section 4.4.1.3. These subjects should complete Visit 13/Termination Visit, followed by the Final Visit which occurs 2 weeks after the final dose of study medication, and then the Safety Follow-Up telephone contact which occurs 28 to 35 days after the last dose of LCM.

Assessments for Visit 13/Termination Visit (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, a Tanner Stage assessment is conducted (if applicable), an Achenbach CBCL is conducted, Bayley-III scales are conducted, and the palatability and ease of use questionnaire is completed.

Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian.

Clinical Study Protocol, Section 5.17 (Early Termination Visit). Original text:

Subjects who withdraw from the study prematurely must complete an Early Termination Visit.

The following will be performed:

- Concomitant medication assessment
- Concomitant AEDs assessment
- Complete physical examination

- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine sample for urinalysis
- Serum pregnancy test for females of childbearing potential
- Tanner Stage assessment (if applicable)
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs)
- Dispense LCM. Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Subjects who withdraw from the study prematurely must complete an Early Termination Visit.

At the time of withdrawal from the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete the Early Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after the Early Termination

Visit. The Final Visit is not required for subjects who withdraw from the study prematurely and who do not undergo taper of LCM.

Subjects who withdraw from the study prematurely and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or parent/legal guardian) should taper LCM gradually as described in Section 4.4.1.3. These subjects should complete the Early Termination Visit, followed by the Final Visit which occurs 2 weeks after the final dose of study medication, and then the Safety Follow-Up telephone contact.

The following will be performed at the Early Termination Visit:

- Concomitant medication assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine sample for urinalysis
- Serum pregnancy test for females of childbearing potential
- Tanner Stage assessment (if applicable)
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries
- Palatability and ease of use questionnaire
- Adverse event reporting

- Dispense subject diary (to assess seizure frequency, document the intake of concomitant AEDs, and record AEs)
- Dispense LCM. Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet) (Section 4.4.1). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian.

Clinical Study Protocol, Section 5.18 (Unscheduled Visit[s]). Original text:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if an LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. If an AE prompts a dose reduction, the reduction can be implemented immediately at the investigator's discretion. However, the subject should return to the clinic as soon as possible for an Unscheduled Visit.

The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- LCM return/compliance (as applicable)
- Subject diary assessment
- C-SSRS
- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit,

if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Was revised as follows:

An Unscheduled Visit may be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, if an LCM dose increase is required at any time, or if a new concomitant AED is introduced, the subject must return for an Unscheduled Visit. If an AE prompts a dose reduction, the reduction can be implemented immediately at the investigator's discretion. However, the subject should return to the clinic as soon as possible for an Unscheduled Visit.

The following assessments are required:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Brief physical examination
- Brief neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of any blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight
- LCM return/compliance (as applicable)
- Subject diary assessment
- C-SSRS (only if Unscheduled Visit is conducted due to an AE)
- Adverse event reporting
- Dispense LCM (as applicable)

Additional assessments can be performed at the investigator's discretion.

All subjects will be required to have an ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or after a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 5.19 (Final Visit). Original text:

During the Final Visit (2 weeks after the last LCM dose), the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)
- Vital signs assessment (blood pressure and pulse)
- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting

Was revised as follows:

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

During the Final Visit, the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Complete physical examination
- Complete neurological examination
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples)
- Vital signs assessment (blood pressure and pulse)

- Body weight and height assessment
- Blood sample for clinical chemistry, hematology, and endocrinology
- Urine sample for urinalysis
- Serum pregnancy test for female subjects of childbearing potential
- LCM return/compliance
- Subject diary assessment
- C-SSRS
- Adverse event reporting

Clinical Study Protocol, Section 5.20 (Safety Follow-up telephone contact). Original text:

The Safety Follow-Up telephone contact is required for all subjects (those who have withdrawn prematurely from the study or completed the study as planned). This telephone contact will occur 28 to 35 days after the last dose of LCM. The following should be performed via telephone:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Adverse event reporting. If an AE is reported at this telephone contact, the investigator will follow the AE until a definite outcome is achieved (Section 8.1.2).

Was revised as follows:

The Safety Follow-Up telephone contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). For subjects who complete the study, this telephone contact will occur 28 to 35 days after Visit 13/Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]). For subjects who withdraw prematurely from the study, this telephone contact will occur 28 to 35 days after the Early Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]).

The following should be performed via telephone:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Adverse event reporting. If an AE is reported at this telephone contact, the investigator will follow the AE until a definite outcome is achieved (Section 8.1.2).

Clinical Study Protocol, Section 6.1 (Seizure counts), first sentence. Original text:

At Screening of SP847 (or other primary study as applicable) subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous 4 weeks; this will serve as a historical Baseline.

Was revised as follows:

At Screening of SP847 (or other primary study as applicable) or at the Screening Visit of SP848 (for subjects who entered directly into SP848) subjects/caregivers (including parents/legal guardians) will be asked how many seizures the subject has had in the previous 4 weeks; this will serve as a historical Baseline.

Clinical Study Protocol, Section 6.2.1 (Clinical Global Impression of Change), second paragraph. Original text:

For the assessment of the Clinical Global Impression of Change, the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline.

Was revised as follows:

For the assessment of the Clinical Global Impression of Change, the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline; the Screening Visit of SP848 will serve as Baseline for those subjects entering directly into SP848.

Clinical Study Protocol, Section 6.2.2 (Caregiver Global Impression of Change), second paragraph. Original text:

For the assessment of the Clinical Global Impression of Change, the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline.

Was revised as follows:

For the assessment of the Clinical Global Impression of Change, the caregiver (including parent/legal guardian) should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence

of AEs, and subject's functional status. Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline; the Screening Visit of SP848 will serve as Baseline for those subjects entering directly into SP848.

Clinical Study Protocol, Section 8.1.8 (Safety signal detection in ongoing clinical studies and Data Monitoring Committees), second and third paragraphs. Original text:

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

As appropriate for the stage of development and accumulated experience with the investigational medicinal product, medically qualified personnel at UCB may identify additional safety measures (examples: AEs, vital signs, laboratory or electrocardiogram results) for which data will be periodically reviewed during the course of the study.

Was revised as follows:

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

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

Clinical Study Protocol, Section 8.2.4 (Procedures for reporting serious adverse events), first sentence. Original text:

If an SAE is reported, UCB BIOSCIENCES must be informed within 24 hours of receipt of this information by the site (see contact numbers for SAE reporting listed in the Study Contact Information section).

Was revised as follows:

If an SAE is reported, UCB BIOSCIENCES must be informed within 24 hours of receipt of this information by the site (see contact details for SAE reporting listed in the Study Contact Information section).

Clinical Study Protocol, Section 8.2.5 (Follow-up of serious adverse events), final sentence. Original text:

Information on SAEs obtained after clinical database lock will be captured through the Global Clinical Safety & Pharmacovigilance database without limitation of time.

Was revised as follows:

Information on SAEs obtained after clinical database lock will be captured through the Drug Safety database without limitation of time.

Clinical Study Protocol, Section 8.4.4 (12-lead ECG), second paragraph. Original text:

Beginning with Protocol Amendment 3, all subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM C_{max} 1 week after an initial LCM dose increase. This ECG can be conducted at an Unscheduled Visit, if necessary. These subjects will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Was revised as follows:

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM C_{max} 1 week after an initial LCM dose increase or when a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

Clinical Study Protocol, Section 8.4.7 (Achenbach CBCL) was newly added as follows and subsequent section numbers were adjusted accordingly:

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. Behavioral problems will be scored by the parent(s)/legal representative(s). Depending on the subject's age, 2 versions of the CBCL will be used. The CBCL/1½-5 checklist is intended for use in children 18 months to 5 years and 11 months of age. For subjects ≥6 years to ≤17 years of age, the CBCL/6-18 version will be used.

The same scale will be completed at the Screening Visit (subjects enrolling directly into SP848), Visit 1 (subjects enrolling from SP847 or other pediatric clinical studies in epilepsy), and Visit 13/Termination Visit (or Early Termination Visit) (all subjects) by the parent(s)/legal representative(s). The completion of the Achenbach CBCL will require approximately 45 minutes.

In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

- 0=not true (as far as known)
- 1=somewhat or sometimes true
- 2=very true or often true

Eight syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each score on the question, syndrome, and total level, categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

In addition, the Achenbach CBCL/6-18 includes ratings related to performance in school, activities in leisure time, and special interests.

Clinical Study Protocol, Section 8.4.8 (Bayley Scales of Infant and Toddler Development, Third Edition) was newly added as follows and subsequent section numbers were adjusted accordingly:

The Bayley-III scales are recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) are a standardized individually administered adaptive assessment that measures the developmental functioning of infants and young children from 1 month to 42 months of age (Bayley, 2006). The Bayley-III scales measure cognitive, language, motor, social-emotional, and adaptive development and are a revision of the predecessor, the Bayley Scales of Infant Development, Second Edition (BSID-II) (Bayley, 1993). The Bayley-III scales are a technically sound instrument, with strong internal consistency, as well as test-retest stability. The Bayley-III scales are validated only in English.

This scale is validated as a tool for assessment of neurological development in young children and is therefore considered appropriate for SP848.

The Bayley-III scales are an individually administered adaptive assessment that presents children with situations and tasks designed to produce an observable set of behavioral responses. They consist of a cognitive scale, a language composite scale with receptive and expressive language subscales, and a motor composite scale with fine and gross motor subscales to be completed by the Investigator or designee, and of a social-emotional scale, comprising social emotional competence, and sensory processing, and an adaptive behavior scale, which assesses the attainment of skills necessary for the development of independence, to be completed by the child's parent or caregiver.

The completion of the Bayley-III scales will require approximately 50 minutes for children who are 12 months old or younger and 90 minutes for children aged 13 months and older.

The same scale will be completed at the Screening Visit (subjects enrolling directly into SP848), Visit 1 (subjects enrolling from SP847 or other pediatric clinical studies in epilepsy), and Visit 13/Termination Visit (or Early Termination Visit) (all subjects) for children from 1 month to <18 months of age enrolled in English-speaking countries.

Clinical Study Protocol, Section 8.4.9 (Palatability and ease of use questionnaire) was newly added as follows:

UCB BIOSCIENCES has created a palatability and ease of use questionnaire to collect data from the subject or caregiver regarding different aspects of LCM and its administration. The questionnaire will assess the subject or caregiver's response regarding the formulation of LCM the subject is receiving for palatability items (eg taste, smell, ability to swallow, aftertaste), mode of administration, and administration device as applicable.

Clinical Study Protocol, Section 10.1 (Site qualification), first sentence. Original text:

A site visit will be performed by UCB BIOSCIENCES or designee prior to the start of the primary study (SP847) to discuss the protocol, to ensure the availability of appropriate study personnel, adequate resources, and to assess their ability to properly conduct the study according to International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and local requirements.

Was revised as follows:

A site visit will be performed by UCB BIOSCIENCES or designee to discuss the protocol, to ensure the availability of appropriate study personnel, adequate resources, and to assess their ability to properly conduct the study according to International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and local requirements.

Clinical Study Protocol, Section 10.2.1 (Definition of source data), final sentence. Original text:

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

Was revised as follows:

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

Clinical Study Protocol, Section 12.1 (Description of statistical methods), second paragraph. Original text:

Visit 1 of SP847 (or other primary study as applicable) will serve as Baseline values for safety and efficacy variables unless otherwise noted.

Was revised as follows:

Visit 1 of SP847 (or other primary study as applicable) or the Screening Visit of SP848 (for subjects who enter directly into SP848) will serve as Baseline values for safety and efficacy variables unless otherwise noted.

Clinical Study Protocol, Section 12.1.1 (Definition of analysis sets), second sentence. Original text:

All subjects from the SS with valid concentration data and the absence of major protocol deviations that may have an influence on the concentration data will be included in the PK Set (PKS).

Was revised as follows:

All subjects from the SS with valid concentration data and the absence of major protocol deviations that may have an influence on the concentration data will be included in the Pharmacokinetic Per-Protocol Set (PK-PPS).

Clinical Study Protocol, Section 12.1.2.2 (Other safety variables). Original text:

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, and urinalysis), ECG measurements, vital sign measurements (blood pressure and pulse rate), body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 [or other primary study as applicable] Visit 1) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

The shift from Baseline to the subject's last visit at which a physical and/or neurological examination was performed post-Baseline will be summarized by category.

Laboratory, ECG, and vital signs data outside of the respective reference ranges will be listed and highlighted.

Was revised as follows:

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, and urinalysis), ECG measurements, vital sign measurements (blood pressure and pulse rate), body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 [or other primary study as applicable] Visit 1) or the Screening Visit (for subjects who entered directly into SP848) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

The shift from Baseline to the subject's last visit at which a physical and/or neurological examination was performed post-Baseline will be summarized by category.

Laboratory, ECG, and vital signs data outside of the respective reference ranges will be listed and highlighted.

Changes in behavior and development from Baseline as measured using the Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) and Bayley-III scales for children <18 months of age will be summarized descriptively and presented by visit. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

Clinical Study Protocol, Section 12.1.4.3 (Palatability and ease of use questionnaire) was newly added as follows:

Data from the palatability and ease of use questionnaire will be summarized descriptively at each visit where it is assessed.

Clinical Study Protocol, Section 12.2 (Determination of sample size). Original text:

Approximately 42 subjects from the SP847 study will be eligible to enroll in this open-label extension study. Other subjects will be eligible to enroll as future LCM pediatric clinical studies in epilepsy are undertaken.

Was revised as follows:

Approximately 42 subjects from the SP847 study will be eligible to enroll in this open-label study. Other subjects will be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

Clinical Study Protocol, Section 15 (References). The following references were added:

Sattler JM, Hoge RD. Assessment of children: behavioral, social, and clinical foundations. 5th ed. La Mesa: Jerome M Sattler; 2006.

Bayley N. Bayley Scales of Infant Development. 2nd ed. San Antonio: The Psychological Corporation; 1993.

Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio: Pearson Education Inc; 2006.

Clinical Study Protocol, Section 16.1 (Tabular schedule of study procedures) was updated to the following (including the addition of Table 3).

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X			
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X			
Urinalysis (subjects aged 5 to 17 years)	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X		X			
Clinical GIC						X				X	X			
Caregiver GIC						X				X	X			
Palatability and ease of use questionnaire							X			X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]	X[n]		
LCM return/compliance			X	X	X	X	X	X	X	X	X	X[n]	X	
Dispense diary	X		X	X	X	X	X	X	X	X	X			

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	V1[b]	TC[c]	V2	V3	V4	V5	V6	V7	V8	V9	ETV[d]	Unsch Visit[e]	Final Visit[f]	TC[g]
Weeks in study	0		4	8	12	20	28	36	44	52				
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[o]	X[h]		X	X	X	X	X	X	X	X	X	X[p]	X	
Achenbach CBCL	X										X			
Bayley-III scales	X										X			
AE reporting[q]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] For subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[g] This TC occurs 28 to 35 days after the last dose of LCM.

[h] Assessments should have been done as part of the last visit of the primary study.

[i] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[j] Blood samples may be drawn at any time post-dosing with LCM.

[k] For female subjects of childbearing potential, serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[n] As applicable

[o] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[p] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[q] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X			
Blood sample for concomitant AEDs[h]	X		X	X	X	X			
Urinalysis (subjects aged 5 to 17 years)			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Palatability and ease of use questionnaire			X		X	X			
Dispense LCM	X		X	X	X^k	X^k	X^l		
LCM return/compliance	X		X	X	X	X	X^l	X	
Dispense diary	X		X	X	X	X			

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Diary assessment	X		X	X	X	X	X	X	
C-SSRS[m]	X		X	X	X	X	X[n]	X	
Achenbach CBCL					X	X			
Bayley-III scales					X	X			
AE reporting	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; TermV=Termination Visit; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at

the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[l] As applicable.

[m] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[n] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Table 3. Schedule of study procedures for SP848 (Screening Visit and Titration Visits, subjects enrolling directly into SP848)

Study SP848	**Screening**	**Titration Visits**					
Visit	**Screening Visit**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**
Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Seizure history	X						
Concomitant medications	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X
Physical exam (complete)	X						
Physical exam (brief)		X	X	X	X	X	X
Neurological exam (complete)	X						
Neurological exam (brief)		X	X	X	X	X	X
12-lead ECG[a]	X	X	X	X	X	X	X
Blood pressure and pulse	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X
Height	X						
Clinical chemistry and hematology blood sample	X		X		X		
Endocrinology blood sample	X		X		X		
Urinalysis (subjects aged 5 to 17 years)	X		X		X		
Pregnancy test[b]	X						
Tanner Stage	X						
Clinical GIC	X						
Caregiver GIC	X						
Dispense LCM		X	X	X	X	X	X
LCM return/compliance		X	X	X	X	X	X
Dispense diary	X	X	X	X	X	X	X
Diary assessment		X	X	X	X	X	X
C-SSRS[c]	X	X	X	X	X	X	X
Achenbach CBCL	X						

Table 3. Schedule of study procedures for SP848 (Screening Visit and Titration Visits, subjects enrolling directly into SP848)

Study SP848	**Screening**	**Titration Visits**					
Visit	**Screening Visit**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**
Bayley-III scales	X						
AE reporting	X	X	X	X	X	X	X

AE=adverse event; AEDs=antiepileptic drugs; C_{max}=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; GIC=Global Impression of Change; LCM=lacosamide

[a] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[b] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Screening Visit.

[c] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

17.5 PROTOCOL AMENDMENT 5

RATIONALE FOR THE AMENDMENT

In the FDA Division of Neurology Products' 06 Aug 2012 Request for Information regarding SP847 protocol Amendment 5, the Agency recommended that UCB revise an inclusion criterion to require the use of more than 1 AED as monotherapy before initiating adjunctive LCM therapy in SP847. UCB has made this recommended change in the SP847 protocol (Amendment 6). In alignment with SP847, the primary purpose of this protocol amendment for SP848 is to modify inclusion criterion 7 to require that each subject in SP848 has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with at least 2 AEDs (concurrently or sequentially). Inclusion criterion 7 applies only to subjects who enroll directly into SP848 without previous participation in a LCM clinical study.

In addition, the BRIEF/BRIEF-P, PedsQL, and health care resource use have been added as assessments in SP848.

Other changes made in this amendment are included in the specific changes below.

MODIFICATIONS/CHANGES

- Study contact information has been updated (eg, Clinical Project Manager, Safety Physician, and SAE reporting).
- The List of Abbreviations was updated.
- Information was added to Section 1 (Summary) and throughout the protocol as appropriate to reflect the addition of the BRIEF/BRIEF-P, the PedsQL, and assessment of health care resource use.
- Inclusion criterion 7 (Section 4.3.1) was modified to require that each subject in SP848 has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with at least 2 AEDs (concurrently or sequentially). Inclusion criterion 7 applies only to subjects who enroll directly into SP848 without previous participation in a LCM clinical study.
- Information was added to Section 8.4.6 (Assessment of suicidality) to provide for monitoring for any changes in mood, ideas, or behavior for warning signs of depression in subjects <6 years of age for whom the C-SSRS is not used.

REFERENCE

Clinical Study Protocol, Contact information for the Clinical Project Manager and Safety Physician. Original text:

Clinical Project Manager:

Name: [redacted]

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Safety Physician (Drug Safety):

Name: [redacted], MD

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Was revised as follows:

Clinical Project Manager:

Name: [redacted], RN, MSN

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Safety Physician (Drug Safety):

Name: [redacted], MD

Address: UCB Pharma S.A. Belgium
Chemin du Foriest
B-1420 Braine-L'Alleud, Belgium

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Study Protocol, Serious Adverse Event reporting contact information. Original text:

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h), safety related issues, and emergency unblinding	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842 **Japan:** +81 3 5283 1869
Email	**Europe and Rest of the World (except Japan):** GCSP@ucb.com **Japan:** JDSO@ucb.com

Was revised as follows:

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842 **Japan:** +81 3 5283 1869
Email	**Global (except Japan): DS_ICT**@ucb.com **Japan:** JDSO@ucb.com

List of Abbreviations. The following abbreviations were added:

BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
CBCL	Child Behavior Checklist
HRQoL	health-related quality of life
PedsQL™	Pediatric Quality of Life Inventory

Clinical Study Protocol, Section 1 (Summary). Original text:

The primary variables for assessment of safety and tolerability are:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs

- Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior

Bayley-III scales for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)The secondary variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, and a LCM palatability and ease of use questionnaire.

Was revised as follows:

The primary variables for assessment of safety and tolerability are:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner stage (if applicable)
- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs
- Achenbach Child Behavior Checklist (CBCL) for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)
- Cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]/BRIEF®-Preschool Version [BRIEF®-P]) (if applicable)

The secondary variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]), health care resource use, and a LCM palatability and ease of use questionnaire.

Clinical Study Protocol, Section 4.2.1 (Primary variables). The following variable was added:

- Cognitive function assessments (BRIEF-P/BRIEF) (if applicable)

Clinical Study Protocol, Section 4.2.2 (Secondary variables). The following variables were added:

- Quality of life assessments (PedsQL) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)

Clinical Study Protocol, Section 4.3.1 (Inclusion criteria). The following criterion:

7. Subject has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with at least 1 AED (concurrently or sequentially).

Was revised as follows:

7. Subject has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with at least 2 AEDs (concurrently or sequentially).

Clinical Study Protocol, Section 4.3.2 (Exclusion criteria). The following criterion:

3. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Was revised as follows:

3. Subject ≥6 years of age has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

Clinical Study Protocol, Section 4.3.3 (Criteria for withdrawal). The following criteria:

11. For subject who did not complete a C-SSRS at Screening, subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) of the screening version of the C-SSRS. The investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
12. For all subjects, regardless of whether or not a C-SSRS was completed at Screening, subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4

or Question 5 of the "since last visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

5. For subject who did not complete a C-SSRS at Screening, subject had active suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the screening version of the C-SSRS. The investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the patient from the study.

Were revised as follows:

11. For subject who did not complete a C-SSRS at Screening, subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) of the screening version of the C-SSRS. The investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
12. For all subjects ≥6 years of age, regardless of whether or not a C-SSRS was completed at Screening, subject has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "since last visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
5. For subject who did not complete a C-SSRS at Screening, subject had actual suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the screening version of the C-SSRS. The investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the patient from the study.

Clinical Study Protocol, Section 5.1 (Screening Visit). The following assessments were added:

- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Health care resource use

Clinical Study Protocol, Section 5.2 (Titration Visit[s] [TV1, TV2, TV3, TV4, TV5, TV6]). The following assessments:

- Blood sample for clinical chemistry, hematology, and endocrinology (TV2 and TV4 only)
- Urine sample for urinalysis (TV2 and TV4 only)

Were revised as follows:

- Blood sample for clinical chemistry, hematology, and endocrinology (TV4 only)

- Urine sample for urinalysis (TV4 only)

Clinical Study Protocol, Section 5.2 (Titration Visit[s] [TV1, TV2, TV3, TV4, TV5, TV6]). The following assessment was added:

- Health care resource use

Clinical Study Protocol, Section 5.3 (Visit 1 [Week 0]). The following assessments were added:

- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Health care resource use

Clinical Study Protocol, Section 5.5 (Visit 2 [Week 4]). The following assessment was added:

- Health care resource use

Clinical Study Protocol, Section 5.6 (Visit 3 [Week 8]). The following assessment was added:

- Health care resource use

Clinical Study Protocol, Section 5.8 (Visit 5 [Week 20]). The following assessments were added:

- Achenbach CBCL to be completed by the parent(s)/legal representative(s) (CBCL/1½-5 for children from 18 months to 5 years 11 months and CBCL/6-18 for children 6 years and older) (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- Bayley-III scales for children <18 months of age enrolled in English-speaking countries (subjects enrolling from SP847 or another applicable LCM pediatric clinical study in epilepsy)
- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Health care resource use

Clinical Study Protocol, Section 5.16 (Visit 13/Termination Visit [Week 96]), third paragraph. Original text:

Assessments for Visit 13/Termination Visit (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, a Tanner Stage assessment is conducted (if applicable), an Achenbach CBCL is conducted, Bayley-III scales are conducted, and the palatability and ease of use questionnaire is completed.

Was revised as follows:

Assessments for Visit 13/Termination Visit (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, a Tanner Stage assessment is conducted (if applicable), an Achenbach CBCL is conducted, Bayley-III scales are conducted, BRIEF-P/BRIEF and PedsQL scores are obtained, and the palatability and ease of use questionnaire is completed.

Clinical Study Protocol, Section 5.17 (Early Termination Visit). The following assessments were added:

- BRIEF-P/BRIEF score (if applicable)
- PedsQL score (if applicable)
- Health care resource use

Clinical Study Protocol, Section 5.18 (Unscheduled Visit[s]). The following assessment was added:

- Health care resource use

Clinical Study Protocol, Section 5.19 (Final Visit). The following assessment was added:

- Health care resource use

Clinical Study Protocol, Section 6.3 (Pediatric Quality of Life Inventory) was newly added as follows:

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001;

Varni et al, 2011). The PedsQL will be administered according to the tabular schedule of study procedures, Section 16.1.

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects ≥1 month to ≤12 months; ≥13 months to ≤24 months; >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≥1 month to ≤18 years of age.

The multidimensional PedsQL scale encompasses the essential core domains for pediatric HRQoL measurement: 1) Physical Functioning/Symptoms, 2) Emotional Functioning, 3) Social Functioning, and 4) Cognitive/School Functioning. The PedsQL assessment is retrospective to the prior month, and individual items are scored using a 5-point Likert scale (never, almost never, sometimes, often, or always). A total health summary score is calculated from the sum of the raw scores of the individual items, with higher scores indicating higher HRQoL.

Clinical Study Protocol, Section 6.4 (Health care resource use) was newly added as follows:

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations not related to study, and hospitalizations not related to study. Health care resource use parameters will be collected according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 8.4 section heading. Original text:

Other safety measurements

Was revised as follows:

Other measurements

Clinical Study Protocol, Section 8.4.2 (Neurological examination), final sentence. Original text:

The investigator or subinvestigator is responsible for confirming the diagnosis of partial-onset seizures.

Was revised as follows:

The investigator or subinvestigator is responsible for confirming the diagnosis of partial-onset seizures or other epilepsy syndrome.

Clinical Study Protocol, Section 8.4.6 (Assessment of suicidality), the following paragraph was added:

The C-SSRS is not validated and will not be used for subjects <6 years of age. Subjects 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. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Parents and caregivers should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

Clinical Study Protocol, Section 8.4.10 (Behavior Rating Inventory of Executive Function) was newly added as follows:

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P/BRIEF will be administered according to the tabular schedule of study procedures, Section 16.1.

The BRIEF-P and BRIEF include rating forms used by parents to assess subjects' executive functioning. Executive functions broadly encompass a set of cognitive skills that are responsible for the planning, initiation, sequencing, and monitoring of complex goal-directed behavior.

The BRIEF-P rating form consists of items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The clinical scales form 3 broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition) and 1 composite score (Global Executive Composite).

The BRIEF rating form contains items in nonoverlapping clinical scales. These theoretically and statistically derived scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

Both the BRIEF-P and the BRIEF include validity scales to measure negativity and inconsistency of responses.

Clinical Study Protocol, Section 12.1.2.2 (Other safety variables), final paragraph. Original text:

Changes in behavior and development from Baseline as measured using the Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) and Bayley-III scales for children <18 months of age will be summarized descriptively and presented by visit. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

Was revised as follows:

Changes in behavior and development from Baseline as measured using the Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) and Bayley-III scales for

children <18 months of age will be summarized descriptively and presented by visit. Changes in cognitive function as measured using the BRIEF-P/BRIEF will be summarized by descriptive statistics at each visit. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

Clinical Study Protocol, Section 12.1.4.4 (PedsQL) was newly added as follows:

The PedsQL score and change from Baseline scores will be analyzed in a descriptive manner. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

Clinical Study Protocol, Section 12.1.4.5 (Health care resource use) was newly added as follows:

Descriptive statistics will be presented for the number of medical resources used (medications, consultations, procedures, hospitalizations, and length of hospital stays).

Clinical Study Protocol, Section 15 (References). The following references were added:

Varni JW, Limbers CA, Neighbors K, Schulz K, Lieu JE, Heffer RW, et al. The PedsQL™ Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Qual Life Res. 2011;20:45-55.

Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39:800-12.

Clinical Study Protocol, Section 16.1 (Tabular schedule of study procedures) was updated to the following:

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X			
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X			
Urinalysis (subjects aged 5 to 17 years)	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X		X			
Clinical GIC	X[h]					X				X	X			
Caregiver GIC	X[h]					X				X	X			
Palatability and ease of use questionnaire							X			X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]	X[n]		
LCM return/compliance			X	X	X	X	X	X	X	X	X	X[n]	X	

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	V1[b]	TC[c]	V2	V3	V4	V5	V6	V7	V8	V9	ETV[d]	Unsch Visit[e]	Final Visit[f]	TC[g]
Weeks in study	0		4	8	12	20	28	36	44	52				
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[o]	X[h]		X	X	X	X	X	X	X	X	X	X[p]	X	
Achenbach CBCL	X					X				X	X			
Bayley-III scales	X					X				X	X			
BRIEF-P/BRIEF	X					X				X	X			
PedsQL	X					X				X	X			
AE reporting[q]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] For subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[g] This TC occurs 28 to 35 days after the last dose of LCM.

[h] For subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy, assessments should have been done as part of the last visit of the primary study. For subjects enrolling directly into SP848, these asssessments should be completed at Visit 1.

[i] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[j] Blood samples may be drawn at any time post-dosing with LCM.

[k] For female subjects of childbearing potential, serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[n] As applicable

[o] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[p] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[q] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X			
Blood sample for concomitant AEDs[h]	X		X	X	X	X			
Urinalysis (subjects aged 5 to 17 years)			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Palatability and ease of use questionnaire			X		X	X			
Dispense LCM	X		X	X	X^k	X^k	X^l		
LCM return/compliance	X		X	X	X	X	X^l	X	
Dispense diary	X		X	X	X	X			

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Diary assessment	X		X	X	X	X	X	X	
C-SSRS[m]	X		X	X	X	X	X[n]	X	
Achenbach CBCL			X		X	X			
Bayley-III scales			X		X	X			
BRIEF-P/BRIEF			X		X	X			
PedsQL			X		X	X			
AE reporting	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; TermV=Termination Visit; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[l] As applicable.

[m] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[n] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Table 3. Schedule of study procedures for SP848 (Screening Visit and Titration Visits, subjects enrolling directly into SP848)

Study SP848	**Screening**	**Titration Visits**					
Visit	**Screening Visit**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**
Informed Consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Seizure history	X						
Concomitant medications	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X
Physical exam (complete)	X						
Physical exam (brief)		X	X	X	X	X	X
Neurological exam (complete)	X						
Neurological exam (brief)		X	X	X	X	X	X
12-lead ECG[a]	X	X	X	X	X	X	X
Blood pressure and pulse	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X
Height	X						
Clinical chemistry and hematology blood sample	X				X		
Endocrinology blood sample	X				X		
Urinalysis (subjects aged 5 to 17 years)	X				X		
Pregnancy test[b]	X						
Tanner Stage	X						
Clinical GIC							
Caregiver GIC							
Dispense LCM		X	X	X	X	X	X
LCM return/compliance		X	X	X	X	X	X
Dispense diary	X	X	X	X	X	X	X
Diary assessment		X	X	X	X	X	X
C-SSRS[c]	X	X	X	X	X	X	X
Achenbach CBCL	X						

Table 3. Schedule of study procedures for SP848 (Screening Visit and Titration Visits, subjects enrolling directly into SP848)

Study SP848	**Screening**	**Titration Visits**					
Visit	**Screening Visit**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**
Bayley-III scales	X						
BRIEF-P/BRIEF	X						
PedsQL	X						
AE reporting	X	X	X	X	X	X	X
Health care resource use	X	X	X	X	X	X	X

AE=adverse event; AEDs=antiepileptic drugs; C_{max}=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; GIC=Global Impression of Change; LCM=lacosamide

[a] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[b] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Screening Visit.

[c] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

Clinical Study Protocol, Section 16.3 (Declaration and signatures of person responsible for the study). The signature block for the Clinical Project Manager was updated as follows:

Clinical Project Manager

[redacted], RN, MSN

_____

Date / Signature

17.6 PROTOCOL AMENDMENT 6

RATIONALE FOR THE AMENDMENT

The primary purpose of this protocol amendment is to permit enrollment of up to approximately 75 eligible pediatric subjects ≥4 years to <17 years of age with partial-onset seizures (deemed appropriate for treatment with LCM) who previously participated in the iv LCM clinical study, EP0060. The purpose of enrolling these subjects is to obtain additional long-term safety exposures in the age range of ≥4 years to <17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy.

In addition, Sponsor language for monitoring of PDILI events was added to increase clarity for the sites and to align across programs. Addition of this language is to align with FDA guidance regarding monitoring of PDILI events and does not reflect a change in the liver safety signal for LCM.

Furthermore, administrative changes, including the update of the study team and minor corrections (ie, CRF to eCRF and Drug Safety to Patient Safety), incorporation of updated protocol template language, and update of the Sponsor Declaration for electronic signature, have been made.

MODIFICATIONS/CHANGES

- The name and contact information for the Clinical Project Manager, Medical Director (Medical Therapeutics), and Safety Representative (Patient Safety) were updated. Update to Sponsor site fax number to other contacts is not detailed below.
- Serious AE reporting number was updated for Canada and was removed for Japan (falls under global number)
- Clarifications were added that SP847 is a completed study and that new subjects enrolling into SP848 either enroll directly or from other pediatric studies of LCM.
- Text added to clarify that up to 75 subjects may enroll in SP848 from EP0060.
- Background information was updated for current status of LCM clinical development program
- Exclusion Criterion 2 was revised to potentially allow subjects from EP0060 who either withdrew consent for the sole reason of route of LCM administration or who required more than 10 infusions to participate in SP848 pending discussion with and agreement from the Medical Monitor.
- Exclusion Criterion 9 was modified to update creatinine clearance exclusion to <30mL/min to align with the rest of the LCM program. The liver function requirements from Exclusion Criterion 9 were moved to a new exclusion criterion (19).
- Exclusion Criterion 16, which excluded use of vigabatrin or felbamate, was removed.
- Exclusion Criterion 17 and the list of prohibited medications were updated to exclude use of MAOI-A inhibitors and cannabidiols.

- Exclusion Criterion 20 was added such that subjects who initiated treatment in EP0060 could not enter SP848 if they had previously participated in a long-term open-label study.
- Clarification was added to withdrawal criteria for subjects transitioning to SP848 from EP0060.
- Sponsor language for monitoring of PDILI events was added to increase clarity for the sites and to align across programs .
- Clarification was added for prohibited concomitant medications.
- Routine blood samples for LCM PK analysis during Year 2 will be collected for subjects enrolled at sites in Japan. Across all sites, a blood sample for LCM PK analysis may be collected if the subject has an Unscheduled Visit due to a SAE.
- Blood samples for concomitant AED PK analysis were removed from Year 2 visits; however, a sample may be collected if the subject has an Unscheduled Visit due to a SAE.
- Updates to the CRF language were incorporated to accommodate use of an eCRF. Minor edits to change CRF to eCRF in Section 8 are not itemized below.
- Updated protocol template language was incorporated regarding suspected transmission of infectious agent, AEs of special interest, drug supply, drug accountability, auditing, and data handling and record keeping.
- Schedules of Assessments were updated to reflect changes above and to indicate which Visit 1 assessments would need to be performed for subjects enrolling from EP0060.
- The Sponsor Declaration has been updated for electronic signature.

REFERENCE

Clinical Study Protocol, Contact information for the Clinical Project Manager, Medical Director (Medical Therapeutics), and Safety Representative (Patient Safety) were updated. Original text:

Clinical Project Manager:

Name: [redacted], RN, MSN

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Medical Director (Medical Therapeutics):

Name: [redacted] MD

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Safety Physician (Drug Safety):

Name: [redacted], MD

Address: UCB Pharma S.A. Belgium
Chemin du Foriest
B-1420 Braine-L'Alleud, Belgium

Phone/Fax: [redacted]

E-mail: [redacted]

Were revised as follows:

Clinical Project Manager:

Name: [redacted]

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Medical Director (Medical Therapeutics):

Name: [redacted], MD

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Safety Representative (Patient Safety):

Name: [redacted]

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Study Protocol, Serious Adverse Event Reporting details were updated. Original text:

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842 **Japan:** +81 3 5283 1869
Email	**Global (except Japan): DS_ICT**@ucb.com **Japan:** JDSO@ucb.com

Was revised as follows:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global: DS_ICT**@ucb.com

List of Abbreviations:

The abbreviations of ALP, CDMS, PDILI, and RDC were added. The abbreviation eCRF and PS replaced the terms CRF and DS, respectively. The term MAO was clarified to MAOI, and the definition of ICH was updated to reflect the recent name change.

Clinical Study Protocol, Section 1 (Summary, Original text, second and third paragraphs:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies in other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy. At selected sites, subjects may also be able to participate in a substudy without withdrawing from SP848.

Subjects who complete SP847 or another applicable LCM pediatric epilepsy study and choose to enter this open-label study will begin on the LCM dose they achieved in SP847 or their previous pediatric LCM study. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label study, will also begin on the LCM dose they achieved in SP847. Subjects who meet eligibility requirements and enroll directly into SP848 without previous participation in a LCM clinical study will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (up to a maximum level as described below).

Was revised as follows:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy.

Protocol Amendment 6 allows up to approximately 75 additional eligible pediatric subjects with epilepsy who participated in EP0060 to enroll into SP848. In addition, subjects already enrolled in SP848 may participate in EP0060, if eligible, and then resume participation in SP848. These subjects may either voluntarily choose to have an iv LCM infusion even though they are capable of taking oral LCM or require iv LCM infusion due to a medical reason or procedure (ie, unable to take oral LCM).

Subjects who complete SP847 or another applicable LCM pediatric epilepsy study and choose to enter this open-label study will begin on the LCM dose they achieved in SP847 or their previous pediatric LCM study. Subjects who discontinued from SP847 due to a dose reduction or status epilepticus, but for whom it is determined medically appropriate to enter this open-label study, will also begin on the LCM dose they achieved in SP847. Subjects who enroll from EP0060 will begin SP848 with an equivalent LCM dose as they last received in EP0060; however, the LCM dose may be further titrated/adjusted to a level to optimize tolerability and seizure control (up to a maximum level as described below). Subjects who meet eligibility requirements and enroll directly into SP848 without previous participation in a LCM clinical study will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (up to a maximum level as described below).

Clinical Study Protocol, Section 2 (Background information). Original text, first paragraph:

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people have epilepsy–about 1% of the world's population (Dichek, 1999). 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.

Was revised as follows:

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.

Clinical Study Protocol, Section 2 (Background information). Original text, fourth paragraph:

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; Glauser et al, 2000; Glauser et al, 2006). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Was revised as follows:

Among the newer AEDs, only 6 (gabapentin, lamotrigine, oxcarbazepine, topiramate, levetiracetam, and perampanel) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Rheims and Ryvlin, 2013; Glauser et al, 2006; Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently

available AEDs, or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Clinical Study Protocol, Section 2 (Background information). Original text, sixth and seventh paragraphs:

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) and in patients 17 years of age and older in the United States (oral tablets, oral solution, and solution for iv infusion). The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to 400mg bid (800mg/day) were evaluated in approximately 700 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2200 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

Were revised as follows:

Lacosamide (200mg/day to 400mg/day) is approved and indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16 to 18 years of age) patients with epilepsy and was first approved in Aug 2008 by the European Commission. Lacosamide is available in tablet (50mg, 100mg, 150mg, and 200mg) and syrup (10mg/mL) oral formulations as well as solution for infusion (10mg/mL) formulation for use as temporary iv replacement when oral administration is not feasible. Lacosamide (200mg/day to 400mg/day) was approved in the US in Oct 2008 as adjunctive therapy and in Aug 2014 as monotherapy in the treatment of partial-onset seizures in patients 17 years of age and older. Initiation of adjunctive LCM treatment with a single loading dose of LCM 200mg (oral tablets, syrup, or iv infusion) followed 12 hours later by a LCM 100mg twice daily (200mg/day) maintenance dose regimen was also approved by the European Commission in Nov 2012. Use of a LCM 200mg loading dose for initiation of initial LCM monotherapy, conversion to LCM monotherapy, or adjunctive therapy was approved in the US in Aug 2014.

The oral solution (syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

Clinical Study Protocol, Section 2 (Background information). Original text, tenth paragraph:

SP847 is an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. Approximately 42 children (aged 1 month to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs will be enrolled. The study consists of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject may be up to approximately 13 weeks. Approximately 200 additional subjects who may participate in other LCM pediatric clinical studies in epilepsy will also be eligible to participate in SP848.

Was revised as follows:

SP847 was an open-label, dose-titration, safety, tolerability, and PK study to evaluate LCM as adjunctive therapy in children with uncontrolled partial-onset seizures. The study completed on 26 Aug 2014. Forty-seven subjects (aged 1 month to 17 years) with uncontrolled partial-onset seizures on a stable dose regimen of at least 1 but no more than 3 AEDs were enrolled and treated during the study. The study consisted of a Screening Phase, a Treatment Phase, and an End-of-Study Phase. The duration of treatment for an individual subject was up to approximately 13 weeks.

Clinical Study Protocol, Section 2 (Background information). Original text, last paragraph:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies in other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures.

Was revised as follows:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures.

Clinical Study Protocol, Section 4.1.1 (Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy). Original text:

Subjects who complete SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or subjects from another applicable LCM pediatric clinical study in epilepsy and who choose to enter the open-label study, will begin on the LCM dose they achieved in the primary study. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Was revised as follows:

Subjects who complete SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or subjects from another applicable LCM pediatric clinical study in epilepsy and who choose to enter the open-label study, will begin with an equivalent LCM dose as they last received in the primary study. Subjects will be able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators will be allowed to increase or decrease the dose of LCM and/or concomitant AEDs to optimize tolerability and seizure reduction for each subject. The investigator may titrate/adjust the LCM dose to a minimum of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) and a maximum of 12mg/kg/day (oral solution [syrup]) or the corresponding dose levels for the tablet formulation), not to exceed 600mg/day based on body weight, even if the subject's body weight exceeds 50kg. The maximum permitted LCM dose in SP848 is 12mg/kg/day or 600mg/day, whichever is lower. Increases in the LCM dose must occur only during office visits. If needed to optimize tolerability and seizure reduction in selected subjects, 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 subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdraw from the study, it is

recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who have achieved a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

Clinical Study Protocol, Section 4.3.2 (Exclusion criteria). Original text:

2. Subject meets the withdrawal criteria for the primary study (with the exception of subjects who discontinued due to a dose reduction or status epilepticus), or is experiencing an ongoing serious AE (SAE).
9. Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level greater than or equal to 2 times the upper limit of normal (ULN), or creatinine clearance less than 50mL/min.
16. Subject has been treated with vigabatrin or felbamate for at least 12 months prior to entering the study and has experienced any toxicity issues with these treatments. Note: Any subject who is currently treated with vigabatrin or felbamate, and has received vigabatrin for a period of less than 12 months, is excluded from the study. Subjects who have received vigabatrin in the past must have documentation of an assessment for visual field defects after completion of vigabatrin therapy.
17. Subject is taking monoamine oxidase (MAO) inhibitors or narcotic analgesics.

Were revised as follows:

2. Subject meets either of the following:

b. Withdrawal criteria for the primary study (with the exception of subjects who discontinued due to a dose reduction or status epilepticus). For subjects entering from EP0060, if the subject (or legal guardian) withdraws consent solely due to route of LCM administration (iv) or if the subject requires more than 10 iv LCM infusions, the subject may be allowed to participant in SP848 after discussion with and agreement from the Medical Monitor.

c. Ongoing serious AE (SAE).

9. Subject has a creatinine clearance less than 30mL/min.
16. Subject is taking monoamine oxidase inhibitors-A (MAOI-A) or narcotic analgesics.
19. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.

Subjects who were directly enrolled in EP0060 for iv LCM replacement therapy or to initiate LCM treatment are not permitted to enroll in the study if any of the following criteria are met:

20. Subjects have previously participated in a long-term, open-label LCM study.

Clinical Study Protocol, Section 4.3.3 (Criteria for withdrawal). Original text:

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency
3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
9. Subject experiences convulsive status epilepticus (if none had occurred prior to study entry) and is compliant with study treatment
10. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST, ALT, or both) ≥5x ULN, the study medication must be immediately discontinued and the subject

withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

11. For subject who did not complete a C-SSRS at Screening, subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) of the screening version of the C-SSRS. The investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
12. For all subjects ≥6 years of age, regardless of whether or not a C-SSRS was completed at Screening, subject has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "since last visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.
5. For subject who did not complete a C-SSRS at Screening, subject had actual suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the screening version of the C-SSRS. The investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the patient from the study.

Was revised as follows:

All subjects discontinuing treatment with study medication for any reason should taper off medication as described in Section 4.4.1. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable. The following criteria for subject withdrawal from SP848 are outlined below. Additional discontinuation criteria for potential drug-induced liver injury are presented in Section 4.3.3.1.

Participation in this study **must** be discontinued for any of the following reasons:

1. Intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study
2. The request of the Sponsor or a Regulatory Agency

3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has a corrected QT interval (QTc) of greater than or equal to 500ms as confirmed by a cardiologist overread on any ECG.
6. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block at any time.
7. Subject is unwilling or unable to continue, or the caregiver/parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
9. Subject experiences convulsive status epilepticus (if none had occurred prior to study entry) and is compliant with study treatment
11. For subject who did not complete a C-SSRS at Screening, subject has a lifetime history (prior to study entry or since study start) of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) of the screening version of the C-SSRS. The investigator must withdraw the subject from the study and immediately refer the subject to a Mental Healthcare Professional.
12. For all subjects ≥6 years of age, regardless of whether or not a C-SSRS was completed at Screening, subject has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "since last visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Participation in this study **may** be discontinued for any of the following reasons:

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol.
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
5. For subject who did not complete a C-SSRS at Screening, subject had actual suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the screening version of the C-SSRS. The investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the patient from the study.

If a subject from SP848 enrolls in EP0060 and either withdraws consent solely due to route of LCM administration (iv) or if the subject requires more than 10 iv LCM infusions, the subject may be allowed to return to SP848 after discussion with and agreement from the Medical Monitor. If a subject from SP848 is advised to withdraw from the SP848 after participation in EP0060, the subject will be required to return to the SP848 to complete the required ETV and Safety Follow-up assessments.

Investigators should attempt to obtain information on subjects in the case of withdrawal. For subjects considered as lost to follow up, the investigator should make efforts (at least 1 phone call and 1 written message to the subject), and document his/her efforts (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 subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

4.3.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be 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 IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects 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 subjects to continue on IMP at the discretion of the investigator.

- Subjects 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).

Evaluation of PDILI must be initiated as described in Section 8.3.2. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI 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 IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Clinical Study Protocol, Section 4.4.1.1 (Subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy).

The following text was added as a last paragraph:

Subjects who enroll from EP0060 will begin SP848 with an equivalent dose to the last dose they received in EP0060; however, the LCM dose may be further titrated/adjusted to a level to optimize tolerability and seizure control (up to a maximum level as described in Section 4.4.1.3). For those subjects who initiated adjunctive LCM treatment in EP0060, the recommended LCM dose titration approach is outlined in Section 4.4.1.2.

Clinical Study Protocol, Section 4.6 (Concomitant medication[s]/treatment[s]). Original text, through second paragraph:

The following medications/therapies are prohibited during the course of this study:

- Monoamine oxidase inhibitors
- Narcotic analgesics

All concomitant medications and treatments must be recorded in the appropriate study documents (case report form [CRF] and source document).

Was revised as follows:

The following medications/therapies are prohibited during the course of this study:

- Monoamine oxidase inhibitor-A compounds
- Narcotic analgesics
- Cannabidiols not approved or indicated for epilepsy by a local health authority

All concomitant medications and treatments must be recorded in the appropriate study documents (eCRF and source document).

Clinical Study Protocol, Section 5.3 (Visit 1[Week 0]). Original text, first, second, and fifth paragraphs:

For subjects who complete SP847, Visit 1 for SP848 is the same as Day 2 of the second PK collection time period (which may include an overnight stay at a hospital or medical facility) in SP847 (Day 28 for Cohorts 1, 2, 3, and 5 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 5 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 5 with maximum recommended dose of 12mg/kg/day). For subjects who discontinue SP847 due to a dose reduction or status epilepticus, Visit 1 is the Early Termination Visit in SP847. For subjects in SP847 who are titrated up to the maximum permitted dose of 600mg/day sooner than the study schedule would ordinarily indicate (based on body weight) and who enroll in SP848, the Early Termination Visit of SP847 will also serve as Visit 1 for SP848.

For subjects who enroll in SP848 after participation in other LCM pediatric clinical studies in epilepsy, SP848 Visit 1 will be specified in the respective primary study protocol.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments (applicable only for subjects for whom Visit 1 is the first clinic visit for SP848), and a complete medical history update will be obtained. The data for the following assessments will be taken from the last assessment during SP847 (or other primary study as applicable):

Were revised as follows:

For subjects who completed SP847, Visit 1 for SP848 was the same as Day 2 of the second PK collection time period (which may include an overnight stay at a hospital or medical facility) in SP847 (Day 28 for Cohorts 1, 2, 3, and 5 with maximum recommended dose of 8mg/kg/day; Day 35 for Cohorts 2 to 5 with maximum recommended dose of 10mg/kg/day; and Day 42 for Cohorts 2 to 5 with maximum recommended dose of 12mg/kg/day). For subjects who discontinued SP847 due to a dose reduction or status epilepticus, Visit 1 was the Early Termination Visit in SP847. For subjects in SP847 who were titrated up to the maximum permitted dose of 600mg/day sooner than the study schedule would ordinarily indicate (based on body weight) and who enroll in SP848, the Early Termination Visit of SP847 also served as Visit 1 for SP848.

For subjects who enroll in SP848 after participation in other LCM pediatric clinical studies besides SP847 (ie, SP0966 and EP0060) in epilepsy, SP848 Visit 1 will be specified in the respective primary study protocol.

Each subject's eligibility will be determined on the basis of the inclusion/exclusion criteria and the results of the following assessments (applicable only for subjects for whom Visit 1 is the first clinic visit for SP848), and a complete medical history update will be obtained. If available, the data for the following assessments will be taken from the last assessment during SP847 (or other primary study, as applicable):

Clinical Study Protocol, Section 5.13 (Visit 10 [Week 60]). Original text:

Assessments for Visit 10 (Week 60) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exception: a 12-lead ECG is not conducted at Visit 10.

Was revised as follows:

Assessments for Visit 10 (Week 60) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exceptions: a 12-lead ECG is not conducted at Visit 10 (all sites) and a PK sample is routinely drawn at sites in Japan (removed for all other sites).

Clinical Study Protocol, Section 5.14 (Visit 11 [Week 72]). Original text:

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), the palatability and ease of use questionnaire is completed, and a 12-lead ECG (2 interpretable

recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted.

Was revised as follows:

Assessments for Visit 11 (Week 72) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions for all sites: brief physical and neurological exams are conducted (instead of complete physical and neurological exams as indicated for Visit 5), the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), the palatability and ease of use questionnaire is completed, and a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted. In addition to the noted differences, a PK sample is routinely drawn at sites in Japan (removed for all other sites).

Clinical Study Protocol, Section 5.15 (Visit 12 [Week 84]). Original text:

Assessments for Visit 12 (Week 84) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exceptions: the laboratory blood sample is collected for endocrinology as well as clinical chemistry and hematology and a 12-lead ECG is not conducted.

Was revised as follows:

Assessments for Visit 12 (Week 84) are the same as those described for Visit 2 (Week 4), in Section 5.5, with the following exceptions for all sites: the laboratory blood sample is collected for endocrinology as well as clinical chemistry and hematology and a 12-lead ECG is not conducted. In addition to the noted differences, a PK sample is routinely drawn at sites in Japan (removed for all other sites).

Clinical Study Protocol, Section 5.16 (Visit 13/Termination Visit [Week 96]). Original text, third paragraph:

Assessments for Visit 13/Termination Visit (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, a Tanner Stage assessment is conducted (if applicable), an Achenbach CBCL is conducted, Bayley-III scales are conducted, BRIEF-P/BRIEF and PedsQL scores are obtained, and the palatability and ease of use questionnaire is completed.

Was revised as follows:

Assessments for Visit 13/Termination Visit (Week 96) are the same as those described for Visit 5 (Week 20), in Section 5.8, with the following exceptions for all sites: the laboratory blood sample is collected only for clinical chemistry and hematology (ie, no endocrinology), a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood sample) is conducted, a Tanner Stage assessment is conducted (if applicable), an Achenbach CBCL is conducted, Bayley-III scales are conducted,

BRIEF-P/BRIEF and PedsQL scores are obtained, and the palatability and ease of use questionnaire is completed. In addition to the noted differences, a PK sample is routinely drawn at sites in Japan (removed for all other sites).

Clinical Study Protocol, Section 5.17 (Early Termination Visit). Original text, ninth bullet:

- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)

Was revised as follows:

- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM)
  - Under any circumstance for an ETV during Year 1
  - If possible, if the early termination during Year 2 is due to a SAE and the event is ongoing

Clinical Study Protocol, Section 5.18 (Unscheduled Visit[s]). The final bullet point was added:

- If possible, a blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM) if the unscheduled visit is due to a SAE

Clinical Study Protocol, Section 8.1.7 (Suspected transmission of an infectious agent via a medicinal product). Was added to align with new protocol template and subsequent sections were renumbered as a result:

8.1.7 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clinical Study Protocol, Section 8.2.1 (Definition of serious adverse event). Original text, fifth bullet point:

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious

  Important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Was revised as follows:

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious

  (Important medical events include, but are not limited to, potential Hy's Law [see Section 8.2.2], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

Clinical Study Protocol, Section 8.2.2 (AEs of special interest). Original text:

The following are AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree Type I and II and third degree), and marked bradycardia (<45beats/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 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 one 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 ≥2x ULN
  - AST ≥2x ULN

Was revised as follows:

An AE of special interest is any AE that a regulatory authority has mandated to be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

The following are the LCM AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree Type I and II and third degree), and marked bradycardia (<45beats/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 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 one 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 ≥2x ULN
  - AST ≥2x ULN
- 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, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

Clinical Study Protocol, Section 8.2.5 (Follow up of serious adverse events). Original text:

A SAE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

Information on SAEs obtained after clinical database lock will be captured through the Drug Safety database without limitation of time.

Was revised as follows:

A SAE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This

follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events are provided in Section 8.3.2.4.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety database without limitation of time.

Clinical Study Protocol, Section 8.2.6 (Anticipated serious adverse events). Original text, first paragraph:

The following list of anticipated SAEs has been identified as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol. This list does not change the investigator's obligation to report all SAEs (including anticipated SAEs) as detailed in Section 8.2.4.

Was revised as follows:

The following list of anticipated SAEs is 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 8.2.4.

Clinical Study Protocol, Section 8.3.1 (Liver function tests). Original text:

8.3.1 Liver function tests

Transaminases (AST, ALT, or both) ≥3x ULN but <5x ULN, in the presence of total bilirubin ≥2x ULN, or transaminases (AST, ALT, or both) ≥5x ULN will result in immediate discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later (see Section 4.3.3).

Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

In all cases of transaminases (AST, ALT, or both) ≥3xULN, testing for hepatitis A, B, and C will be done.

Referral to a specialist (ie, hepatologist or gastroenterologist) is at the discretion of the investigator. This is recommended especially if the transaminase abnormalities >3xULN persist after discontinuation of the study medication.

Was revised as follows:

8.3.2 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 4.3.3.1 with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning

of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 8.2.2), and, if applicable, also reported as an SAE (see Section 8.2.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 8–1 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 8.3.2.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 8.3.2.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 4.3.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 8-1: Required investigations and follow up of PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 8.3.2.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥5xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 8.3.2.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Table 8-1: Required investigations and follow up of PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 8.3.2.3)	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

a Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

b If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

c Details provided in Section 8.3.2.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

d Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

8.3.2.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 8.3.2.3) and SAE report (if applicable).

8.3.2.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 4.3.3.1 and Table 8–1 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

8.3.2.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 8–2 (laboratory measurements) and Table 8–3 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 8-2: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

a Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 8-3: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

8.3.2.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 8–1. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

Clinical Study Protocol, Section 8.3.2 (Pregnancy testing). Number revised to Section 8.3.1.

Clinical Study Protocol, Section 9.1 (Manufacturing, packaging, and labeling). Original text, first paragraph:

Lacosamide oral solution (syrup) and tablets are manufactured and supplied by UCB BIOSCIENCES GmbH, Monheim am Rhein, Germany. Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws and

regulations. It is suitably packaged, in such a way as to protect the product from deterioration during transport and storage.

Was revised as follows:

Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws and regulations. It is suitably packaged, in such a way as to protect the product from deterioration during transport and storage.

Clinical Study Protocol, Section 9.2 (Supply, handling, and storage). Original text:

Lacosamide (oral solution [syrup] and tablet) is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be frozen.

The investigator (or designee) is responsible for safe and proper storage of LCM at the site. Lacosamide stored by the investigator is to be kept in a secured area with limited access.

Was revised as follows:

Lacosamide (oral solution [syrup] and tablet) is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be frozen.

The investigator (or designee) is responsible for safe and proper storage of LCM at the site. Lacosamide stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature and by completion of a temperature log in accordance with local requirements on a regular basis, showing minimum and maximum temperatures reached over the time interval.

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

The investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

Clinical Study Protocol, Section 9.3 (Drug accountability procedures). Original text:

Responsibility for drug accountability at the study site rests with the investigator.

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 LCM is used only in accordance with the protocol.

The investigator (or designee) is expected to collect and retain all used, unused, and partially used containers of LCM until collection.

The investigator should maintain records that document the drug's delivery to the study site, the inventory at the site, the use by each subject, and return to UCB BIOSCIENCES or alternative. These records include dates, quantities, batch numbers, expiry dates, and the unique code

numbers assigned to the LCM and study subjects. The investigator (or designee) should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all LCM received from UCB BIOSCIENCES.

Completed accountability records and all used/unused dosing containers will be returned to UCB BIOSCIENCES or Contract Research Organization (CRO) at completion of the study.

Was revised as follows:

A Drug Accountability form will be used to record LCM dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any LCM 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 LCM until returned or destroyed by a UCB representative.

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 LCM is used only in accordance with the 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 LCM must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs 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.

Clinical Study Protocol, Section 10.3 (Auditing). Original text:

As a quality assurance measure, UCB BIOSCIENCES or regulatory authorities may undertake audits before, during, and after the study.

Regulatory authorities and representatives of the relevant IRB/IEC must be allowed to conduct inspections at the site.

The investigator should notify UCB BIOSCIENCES if regulatory authorities contact them to schedule an inspection.

Was revised as follows:

The investigator will permit study-related audits mandated by UCB, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the

protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

Clinical Study Protocol, Section 11.1 (Data handling) and Section 11.2 (Record keeping)
Original text:

11.1 Data handling

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

Any change or correction to the CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted.

Corrections made after the investigator's review and signature of the completed CRF will be re-signed and dated by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the CRF.

The investigator will keep a list containing all subjects enrolled into the study. This list remains with the investigator and is used for unambiguous identification of each subject. The list contains the subject identification number, full name, date of birth, date of enrollment in the study, and the hospital number or National Health Security number, if applicable.

The parent/legal guardian's consent, subject's assent, and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.2 Record keeping

To comply with international regulations, the investigator will arrange for the retention of essential study documents as described in the ICH-GCP guideline. The guideline requires that the documents be retained at least 2 years after the last approval of a marketing application in an ICH region when there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of LCM. However, UCB BIOSCIENCES requires the documents be retained at least 15 years after completion of the study. The documents should be retained for a longer period if required by the applicable regulatory authorities. UCB BIOSCIENCES will inform the investigator/institution when records no longer need to be retained.

The investigator should take measures to prevent accidental or premature destruction of records. If archiving can no longer be maintained at the site, the investigator will notify the Sponsor.

Were revised as follows:

The parent/legal guardian's consent, subject's assent, and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.1 Case Report form completion

This study is performed using remote data capture (RDC); 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.

11.2 Database entry and reconciliation

Electronic Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. This study is performed using RDC; the data are entered into the eCRFs once and are subsequently verified. An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

11.4 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). 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.

Clinical Study Protocol, Section 11.3 (Data Management) is now numbered Section 11.5.

Clinical Study Protocol, Section 12.1.1 (Definition of analysis sets). Original text:

The primary analysis set will be the Safety Set (SS), which is defined as all subjects who meet the inclusion/exclusion criteria, sign an informed consent form, and take at least 1 dose of LCM.

All subjects from the SS with valid concentration data and the absence of major protocol deviations that may have an influence on the concentration data will be included in the Pharmacokinetic Per-Protocol Set (PK-PPS). The validity of concentration data will be determined by the responsible UCB BIOSCIENCES study team including the responsible clinical pharmacokineticist and bioanalytic personnel.

Was revised as follows:

The Safety Set (SS), which is defined as all enrolled subjects who take at least 1 dose of LCM in this study. All safety analyses will be performed on the SS.

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects from the SS having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) on at least 1 visit with documented LCM intake times.

The full-analysis set will be used for the analysis of seizure data and will consist of all subjects in the SS, who have at least 1 completed post-Baseline seizure diary.

Clinical Study Protocol, Section 12.1.5 (Handling of protocol violators, drop-outs, and missing values). Original text, first paragraph:

All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter. Protocol deviations will be assessed during data review by a panel consisting of the study manager, the study biostatistician, a representative of the monitoring team, and other appropriate study team members.

Was revised as follows:

All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

Clinical Study Protocol, Section 12.2 (Determination of sample size). The following final paragraph was added:

Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848.

Clinical Study Protocol, Section 15 (References). The following references were added:

Clinical Global Impression of Change, the Caregiver Global Impression of Change, quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]). http://www.pedsql.org/PedsQL-CostStructure.pdf and http://plaza.umin.ac.jp/qol-research/. Accessed on 10 July 2014.

Cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]/BRIEF® Preschool Version [BRIEF® P]. http://www4.parinc.com/Products/PermsLicensing.aspx?id=6 and http://www4.parinc.com/products/PermsLicensing.aspx?id=8. Accessed 10 July 2014.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

Kyoto International; Social Welfare Exchange Centre (KISWEC). Achenbach Child Behavior Checklist (CBCL) for children 18 months and older. http://www.kiswec.com/aseba%20-%20order.html. Accessed 10 July 2014.

Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: A systematic review and meta-analysis. Neurology. 2011; 77(10): 1005–12.

Rheims S, Ryvlin P. Profile of perampanel and its potential in the treatment of partial onset seizures. Neuropsychiatr Dis Treat. 2013;9:629-37.

And the following reference was deleted:

Dichek B. Epilepsy: an ancient ailment that still eludes a cure. Scrip Magazine. 1999;Feb:9-11.

Clinical Study Protocol, Section 16.1(Table 1 Schedule of study procedures for SP848 [Year 1]). Original table:

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h]					X				X	X		X	
Blood sample for LCM PK[j]	X[h]		X			X		X		X	X			
Blood sample for concomitant AEDs[j]	X[h]		X			X		X		X	X			
Urinalysis (subjects aged 5 to 17 years)	X[h]					X				X	X		X	
Pregnancy test[k]	X[h,S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[l]	X[h]								X		X			
Clinical GIC	X[h]					X				X	X			
Caregiver GIC	X[h]					X				X	X			
Palatability and ease of use questionnaire							X			X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[m]	X[n]		
LCM return/compliance			X	X	X	X	X	X	X	X	X	X[n]	X	

Table 1. Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[o]	X[h]		X	X	X	X	X	X	X	X	X	X[p]	X	
Achenbach CBCL	X					X				X	X			
Bayley-III scales	X					X				X	X			
BRIEF-P/BRIEF	X					X				X	X			
PedsQL	X					X				X	X			
AE reporting[q]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] For subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[g] This TC occurs 28 to 35 days after the last dose of LCM.

[h] For subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy, assessments should have been done as part of the last visit of the primary study. For subjects enrolling directly into SP848, these asssessments should be completed at Visit 1.

[i] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[j] Blood samples may be drawn at any time post-dosing with LCM.
[k] For female subjects of childbearing potential, serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.
[l] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.
[m] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.
[n] As applicable
[o] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.
[p] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.
[q] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Was revised to:

Table 16-1: Schedule of study procedures for SP848 (Year 1)

Study SP848	**Year 1**													**Safety Follow-Up**
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Informed Consent	X													
Inclusion/exclusion criteria	X													
Medical history update	X													
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)	X[h]					X				X	X		X	
Physical exam (brief)			X	X	X		X	X	X			X		
Neurological exam (complete)	X[h]					X				X	X		X	
Neurological exam (brief)			X	X	X		X	X	X			X		
12-lead ECG[i]	X[h]		X				X			X	X	X	X	
Blood pressure and pulse	X[h]		X	X	X	X	X	X	X	X	X	X	X	
Body weight and height	X[h, j]		X	X	X	X	X	X	X	X	X	X	X	

Table 16-1: Schedule of study procedures for SP848 (Year 1)

Study SP848	Year 1													Safety Follow-Up
Visit[a]	**V1[b]**	**TC[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ETV[d]**	**Unsch Visit[e]**	**Final Visit[f]**	**TC[g]**
Weeks in study	**0**		**4**	**8**	**12**	**20**	**28**	**36**	**44**	**52**				
Clinical chemistry and hematology blood sample	X[h]		X			X		X		X	X		X	
Endocrinology blood sample	X[h, j]					X				X	X		X	
Blood sample for LCM PK[k]	X[h, j]		X			X		X		X	X			
Blood sample for concomitant AEDs[k]	X[h, j]		X			X		X		X	X			
Urinalysis (subjects aged 5 to 17 years)	X[h, j]					X				X	X		X	
Pregnancy test[l]	X[h, j, S]		X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[m]	X[h, j]								X		X			
Clinical GIC	X[h, j]					X				X	X			
Caregiver GIC	X[h, j]					X				X	X			
Palatability and ease of use questionnaire							X			X	X			
Dispense LCM	X		X	X	X	X	X	X	X	X	X[n]	X[o]		
LCM return/compliance			X	X	X	X	X	X	X	X	X	X[o]	X	
Dispense diary	X		X	X	X	X	X	X	X	X	X			
Diary assessment			X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[p]	X[h]		X	X	X	X	X	X	X	X	X	X[q]	X	
Achenbach CBCL	X					X				X	X			
Bayley-III scales	X					X				X	X			
BRIEF-P/BRIEF	X					X				X	X			
PedsQL	X					X				X	X			
AE reporting[r]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; TC=telephone contact; S=serum; SAE= serious adverse event; U=urine; Unsch=Unscheduled; V=Visit

Note: All subjects who directly enrolled into SP848 should follow the titration schedule in Table 16–3.

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] For subjects who have participated in SP847 (or other LCM pediatric clinical studies in epilepsy), Visit 1 is also the last visit of the primary study. At Visit 1, the informed consent will be signed (and assent, if applicable) and eligibility assessed, the medical history will be updated, body weight and height and concomitant medications including AEDs will be recorded, AEs will be assessed, and the subject diary and LCM dispensed.

[c] Telephone contacts are scheduled during the following weeks during Year 1: Weeks 2, 6, 10, 16, 24, 32, 40, and 48.

[d] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[e] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[g] This TC occurs 28 to 35 days after the last dose of LCM.

[h] For subjects enrolling from SP847 or other LCM pediatric clinical studies in epilepsy, assessments may have been done as part of the last visit of the primary study. For subjects enrolling directly into SP848, these assessments should be completed at Visit 1.

[i] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[j] For subjects enrolling from EP0060, these assessments should be completed at Visit 1.

[k] Blood samples may be drawn at any time post-dosing with LCM.

[l] For female subjects of childbearing potential, serum pregnancy tests will be performed at Visit 1, the Early Termination Visit, and the Final Visit. Urine pregnancy tests will be performed at Visits 2, 3, 4, 5, 6, 7, 8, and 9.

[m] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[n] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[o] As applicable

[p] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[q] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[r] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

Clinical Study Protocol, Section 16.1 (Table 2 Schedule of study procedures for SP848 [Year 2]). Original table:

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	
Blood sample for LCM PK[h]	X		X	X	X	X			
Blood sample for concomitant AEDs[h]	X		X	X	X	X			
Urinalysis (subjects aged 5 to 17 years)			X		X	X		X	
Pregnancy test[i]	X^U		X^U	X^U	X^U	X^S		X^S	
Tanner Stage[j]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Palatability and ease of use questionnaire			X		X	X			
Dispense LCM	X		X	X	X^k	X^k	X^l		
LCM return/compliance	X		X	X	X	X	X^l	X	
Dispense diary	X		X	X	X	X			

Table 2. Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Diary assessment	X		X	X	X	X	X	X	
C-SSRS[m]	X		X	X	X	X	X[n]	X	
Achenbach CBCL			X		X	X			
Bayley-III scales			X		X	X			
BRIEF-P/BRIEF			X		X	X			
PedsQL			X		X	X			
AE reporting	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; TermV=Termination Visit; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[h] Blood samples may be drawn at any time post-dosing with LCM.

[i] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[j] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[k] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[l] As applicable.

[m] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[n] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Was revised to:

Table 16-2: Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/ TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Concomitant medications	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X
Physical exam (complete)					X	X		X	
Physical exam (brief)	X		X	X			X		
Neurological exam (complete)					X	X		X	
Neurological exam (brief)	X		X	X			X		
12-lead ECG[g]			X		X	X	X	X	
Blood pressure and pulse	X		X	X	X	X	X	X	
Body weight and height	X		X	X	X	X	X	X	
Clinical chemistry and hematology blood sample	X		X	X	X	X		X	
Endocrinology blood sample				X		X		X	

Table 16-2: Schedule of study procedures for SP848 (Year 2)

Study SP848	**Year 2**								**Safety Follow-Up**
Visit[a]	**V10**	**TC[b]**	**V11**	**V12**	**V13/ TermV**	**ETV[c]**	**Unsch Visit[d]**	**Final Visit[e]**	**TC[f]**
Weeks in study	**60**		**72**	**84**	**96**				
Blood sample for LCM PK	X[h]		X[h]	X[h]	X[h]	X[i]	X[i]		
Blood sample for concomitant AEDs						X[i]	X[i]		
Urinalysis (subjects aged 5 to 17 years)			X		X	X		X	
Pregnancy test[j]	X[U]		X[U]	X[U]	X[U]	X[S]		X[S]	
Tanner Stage[k]					X	X			
Clinical GIC			X		X	X			
Caregiver GIC			X		X	X			
Palatability and ease of use questionnaire			X		X	X			
Dispense LCM	X		X	X	X[l]	X[l]	X[m]		
LCM return/compliance	X		X	X	X	X	X[m]	X	
Dispense diary	X		X	X	X	X			
Diary assessment	X		X	X	X	X	X	X	
C-SSRS[n]	X		X	X	X	X	X[o]	X	
Achenbach CBCL			X		X	X			
Bayley-III scales			X		X	X			
BRIEF-P/BRIEF			X		X	X			
PedsQL			X		X	X			
AE reporting	X	X	X	X	X	X	X	X	X
Health care resource use	X		X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; LCM=lacosamide; PK=pharmacokinetics; S=serum; TC=telephone contact; TermV=Termination Visit; U=urine; Unsch=Unscheduled; V=Visit

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact).

[b] Telephone contacts are scheduled during the following weeks during Year 2: Weeks 66 and 78.

[c] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

[d] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the LCM dose is decreased between scheduled clinic visits due to an AE, or if a LCM dose increase is required between scheduled clinic visits, the subject must return for an Unscheduled Visit. Height will not be recorded at an Unscheduled Visit.

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[f] This TC occurs 28-35 days after the last dose of LCM.

[g] All subjects will be required to have a 12-lead ECG (2 interpretable recordings) conducted at LCM C_{max} 1 week after an initial LCM dose increase to a LCM dose level that is ≥8mg/kg/day or a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state C_{max}).

[h] Blood sample for LCM PK will be routinely collected for subjects enrolled at sites in Japan. Blood samples may be drawn at any time post-dosing with LCM.

[i] Blood samples for LCM and concomitant other AEDs may be collected at an Unscheduled Visit or Early Termination Visit if the visit is related to an ongoing SAE.

[j] For female subjects of childbearing potential, serum pregnancy tests will be performed at the Early Termination Visit and at the Final Visit. Urine pregnancy tests will be performed at Visits 10, 11, 12, and 13.

[k] The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.

[l] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥6mg/kg/day (oral solution [syrup]) or ≥300mg/day (tablet). It is recommended that the LCM dose be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablet). A slower taper of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablet) is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

[m] As applicable.

[n] For all subjects ≥6 years of age already enrolled, the "already enrolled" version should be completed at the next clinic visit, and the "since last visit" version should be completed thereafter.

[o] The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Clinical Study Protocol, Section 16.3 (Declarations and signatures of persons responsible for study) and Section 16.4 (Declaration and signature of investigator) were moved to new Section 18 (Declaration and signature of investigator) and new Section 19 (Sponsor declaration), respectively.

17.7 PROTOCOL AMENDMENT 7

RATIONALE FOR THE AMENDMENT

This administrative amendment is to fix the numbering of exclusion criteria. During Protocol Amendment 6, Exclusion Criterion 16 was deleted. The remaining criteria should have been numbered 17 through 21, inclusive, to align with the CRF.

The rationale for removal of Exclusion Criterion 16 during Protocol Amendment 6 was to allow physicians to have these medications as options for treatment during the open-label study.

MODIFICATIONS/CHANGES

- Exclusion Criteria 16 through 20, inclusive, were mistakenly misnumbered.

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REFERENCE

Clinical Study Protocol, Section 4.3.2 (Exclusion criteria). Original text:

16. Subject is taking monoamine oxidase inhibitors-A (MAOI-A) or narcotic analgesics.
17. Subject has epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen syndrome.
18. Subject has a known sodium channelopathy, such as Brugada syndrome.
19. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.

Subjects who were directly enrolled in EP0060 for iv LCM replacement therapy or to initiate LCM treatment are not permitted to enroll in the study if any of the following criteria are met:

20. Subjects have previously participated in a long-term, open-label LCM study.

Were revised as follows:

17. Subject is taking monoamine oxidase inhibitors-A (MAOI-A) or narcotic analgesics.
18. Subject has epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen syndrome.
19. Subject has a known sodium channelopathy, such as Brugada syndrome.
20. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.

Subjects who were directly enrolled in EP0060 for iv LCM replacement therapy or to initiate LCM treatment are not permitted to enroll in the study if any of the following criteria are met:

21. Subjects have previously participated in a long-term, open-label LCM study.

17.8 PROTOCOL AMENDMENT 8

RATIONALE FOR THE AMENDMENT

The primary purpose of this protocol amendment is to align with modifications made to the Paediatric Investigation Plan. The primary changes include:

- A new categorization for main primary and secondary endpoints key binding element was proposed in order to ensure reporting compliance with registries (EudraCT, clinicaltrials.gov). This categorization does not affect the type or processing of data collected and reported in the study report as they will be assessed as initially planned.
- UCB also took the occasion to provide further clarification to the study duration as well as the primary, secondary, and other variables wording and categorization.

In addition, language specifying applicable study conduct modifications due to the COVID-19 pandemic has been added.

Furthermore, minor administrative changes have been done, including the update of the study team and minor editorial corrections to correct typographical errors and to update document abbreviations.

MODIFICATIONS/CHANGES

- The name and contact information for the Clinical Program Director, Clinical Project Manager, Clinical Trial Biostatistician, and Medical Director (Medical Therapeutics) were updated.
- Reorganization and clarification of the study variables and corresponding statistical analyses sections was completed.
- Text added to allow 100 subjects to enroll in SP848 from EP0060.
- Text added to identify the subjects directly enrolling from sites in Japan and China.
- Text added to clarify study conduct due the COVID-19 pandemic.
- Text updated to clarify the study duration.
- Text updated to clarify that the Safety Follow-Up Visit or the Safety Follow-Up telephone contact is not required for subjects who participate in EP0151 or EP0152.

REFERENCE

Contact information for the Clinical Program Director, Clinical Project Manager, Clinical Trial Biostatistician, and Medical Director (Medical Therapeutics) were updated. Original text:

Clinical Program Director:

Name: [redacted], BS

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Project Manager:

Name: [redacted]

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Clinical Trial Biostatistician:

Name: [redacted] MPH

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Medical Director (Medical Therapeutics):

Name:	[redacted], MD
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone/Fax:	[redacted]
E-mail:	[redacted]

Were revised as follows:

Clinical Program Director:

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone/Fax:	[redacted]
E-mail:	[redacted]

Clinical Project Manager:

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
E-mail:	[redacted]

Clinical Trial Biostatistician:

Name: [redacted]

Address: UCB BIOSCIENCES, Inc.
8010 Arco Corporate Drive, Suite 100 (courier)
Raleigh, NC 27617, USA
PO Box 110167 (mail)
Research Triangle Park, NC 27709, USA

Phone/Fax: [redacted]

E-mail: [redacted]

Medical Director (Medical Therapeutics):

Name: [redacted] MD

Address: UCB BIOSCIENCES, GmbH
Alfred-Nobel- Straße 10
40789 Monheim am Rhein
GERMANY

Phone: [redacted]

E-mail: [redacted]

Serious Adverse Event Reporting phone numbers and emails were updated. Original text:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global: DS_ICT**@ucb.com

Were revised as follows:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175 **Japan:** + 81 3 6864 7400

Email	**Europe and Rest of the World:** DS_ICT@ucb.com or DSICT.-@ucb.com **Japan:** JDSO@ucb.com

Clinical Study Protocol, Section 1 (Summary). Original text, second, third, and fourth paragraphs:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy.

Protocol Amendment 6 allows up to approximately 75 additional eligible pediatric subjects with epilepsy who participated in EP0060 to enroll into SP848. In addition, subjects already enrolled in SP848 may participate in EP0060, if eligible, and then resume participation in SP848. These subjects may either voluntarily choose to have an iv LCM infusion even though they are capable of taking oral LCM or require iv LCM infusion due to a medical reason or procedure (ie, unable to take oral LCM).

Were revised as follows:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes. SP848 includes subjects ≥1 month to ≤18 years of age since subjects who complete SP847 or another applicable LCM pediatric epilepsy study in subjects <18 years of age may have aged to 18 years old by the time they complete that study and enroll in SP848.

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites

in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain sufficient long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures in pediatric subjects ≥4 years to ≤17 years of age with epilepsy.

Protocol Amendment 6 allows up to approximately 75 additional eligible pediatric subjects with epilepsy who participated in EP0060 to enroll into SP848. Protocol Amendment 8 allows an enrollment increase from 75 to 100 eligible pediatric subjects ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of subjects down to 1 month of age. In addition, subjects already enrolled in SP848 may participate in EP0060, if eligible, and then resume participation in SP848. These subjects may either voluntarily choose to have an iv LCM infusion even though they are capable of taking oral LCM or require iv LCM infusion due to a medical reason or procedure (ie, unable to take oral LCM).

Approximately 200 subjects who may participate in other LCM pediatric clinical studies in epilepsy will be eligible to participate in SP848. In total, up to approximately 400 subjects may be eligible to participate in SP848.

Clinical Study Protocol, Section 1 (Summary). Original text, seventh and eighth paragraphs:

The primary variables for assessment of safety and tolerability are:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner stage (if applicable)
- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs
- Achenbach Child Behavior Checklist (CBCL) for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)

- Cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]/BRIEF®-Preschool Version [BRIEF®-P]) (if applicable)

The secondary variables include seizure counts (assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population), the Clinical Global Impression of Change, the Caregiver Global Impression of Change, quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]), health care resource use, and a LCM palatability and ease of use questionnaire.

Were revised as follows:

The study variables to be assessed are defined in Section 4.2.

Clinical Study Protocol, Section 2 (Background Information). Original text, final paragraph:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures.

Was revised as follows:

SP848 was originally designed as an open-label extension study for pediatric subjects in SP847 with partial-onset seizures. SP848 is now amended to be open to subjects who participate in other LCM pediatric clinical studies, including partial-onset seizures and other epilepsy syndromes. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range of ≥4 years to ≤17 years of age; the additional long-term safety data will be included in planned regulatory submissions for LCM as adjunctive therapy for partial-onset seizures.

Clinical Study Protocol, Section 4.1.2 (Subjects enrolling directly into SP848). Original text, first and second paragraph, new third paragraph:

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (see Section 4.4.1). Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator.

Was revised as follows:

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848.

Subjects who enroll directly into SP848 without previous participation in a LCM clinical study will undergo screening. Eligible subjects will initiate treatment with LCM, and the LCM dose will be titrated to a level to optimize tolerability and seizure control (see Section 4.4.1). Subjects will be able to receive LCM oral solution or LCM tablets for up to 2 years as determined appropriate by the investigator.

SP848 includes subjects ≥1 month to ≤18 years of age since subjects who complete SP847 or another applicable LCM pediatric epilepsy study in subjects <18 years of age may have aged to 18 years old by the time they complete that study and enroll in SP848.

Clinical Study Protocol, Section 4.2 (Variables to be assessed). Original text, Section 4.2.1 and Section 4.2.2:

4.2 Variables to be assessed

4.2.1 Primary variables

Safety and tolerability will be assessed using the following variables:

- Adverse events reported spontaneously by the subject and/or caregiver, or observed by the investigator

- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead ECGs
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated BMI
- Tanner Stage (if applicable)
- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs
- Achenbach CBCL at Baseline for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales at Baseline for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)
- Cognitive function assessments (BRIEF-P/BRIEF) (if applicable)

4.2.2 Secondary variables

Secondary variables include:

- Seizure counts, which will be assessed using seizure diaries in order to evaluate preliminary evidence of efficacy during long-term exposure in this population
- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Quality of life assessments (PedsQL) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)
- LCM palatability and ease of use questionnaire

Was revised as follows:

4.2 Variables to be assessed

4.2.1 Safety variables

4.2.1.1 Primary safety variables

The primary safety variables are:

- Incidence of TEAEs
- Incidence of serious AEs (SAEs)
- Subject withdrawal from the study due to TEAEs

4.2.1.2 Other safety variables

The other safety variables are:

- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner Stage (if applicable)
- Achenbach Child Behavior Checklist (CBCL) at Baseline for children 18 months and older (CBCL/1½-5 and CBCL/6-18) assessing behavior
- Bayley-III scales at Baseline for children <18 months of age at time of enrollment (applicable only to subjects enrolled in English-speaking countries)
- Cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]/BRIEF®-Preschool Version [BRIEF®-P]) (if applicable)
- LCM palatability and ease of use questionnaire

4.2.2 PK variables

4.2.2.1 Primary PK variables

No primary PK variables are defined for this study.

4.2.2.2 Other PK variables

The other PK variables are:

- Plasma concentrations of LCM (for population PK analysis) and concomitant AEDs

4.2.3 Efficacy variables

4.2.3.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

4.2.3.2 Secondary efficacy variables

The secondary efficacy variables, based on daily seizure diaries, are:

- Percent change from Baseline in 28-day partial-onset seizure frequency
- ≥50% reduction in 28-day partial-onset seizure frequency
- ≥75% reduction in 28-day partial-onset seizure frequency
- Seizure days per 28 days (subjects with generalized seizures only)

- Seizure-free status

4.2.3.3 Other efficacy variables

The other efficacy variables are:

- Clinical Global Impression of Change
- Caregiver Global Impression of Change
- Quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]) (if applicable)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)
- All seizure frequency analyses as described in the secondary efficacy variables (presented for the overall Treatment Period only) may be additionally presented by modal daily dose group, by seizure type, by seizure classification subgroup, by time interval, by visit or time period, or by completer cohort

Clinical Study Protocol, Section 4.3.3.1 (Potential drug-induced liver injury IMP discontinuation criteria). Original text, first, second, third, and fourth paragraphs:

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be 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 IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects 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 subjects to continue on IMP at the discretion of the investigator.

- Subjects 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).

Was revised as follows:

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP 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 IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN
- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below requires discussion with the Medical Monitor to decide whether the subject is allowed to continue on IMP.

- Subjects 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).

Clinical Study Protocol, Section 4.4.1.2 (Subjects enrolling directly into SP848). Original text, first paragraph:

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. After Screening, eligible subjects will initiate treatment with LCM (oral solution or tablet, as chosen by the investigator and subject/caregiver), and the LCM dose will be titrated to a level to optimize tolerability and seizure control.

Was revised as follows:

Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. After Screening, eligible subjects will initiate treatment with LCM (oral solution or tablet, as chosen by the investigator and subject/caregiver), and the LCM dose will be titrated to a level to optimize tolerability and seizure control.

Clinical Study Protocol, Section 4.4.1.4 (Study completion). Original text, first paragraph:

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM.

Was revised as follows:

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up telephone contact are not required for subjects who participate in EP0151 or EP0152.

Clinical Study Protocol, Section 4.5 (Expected duration of the study). Original text, first paragraph:

The maximum duration of LCM administration for an individual subject will be approximately 2 years.

Was revised as follows:

The maximum duration of LCM administration for an individual subject will be approximately 2 years or until approval of the marketing application (for Japan only), whichever comes first.

Clinical Study Protocol, Section 5 (Treatment Procedures By Visit). Original text, first and second paragraphs:

For all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact), a visit window of ±7 days relative to Visit 1 is applicable. The Safety Follow-Up telephone contact will be performed 28-35 days after the last dose of LCM. A detailed tabular schedule of study procedures is provided in Section 16.1. For further details of the assessments and the required procedures and methods, please refer to Section 6, Section 7, and Section 8.

Were revised as follows:

For all scheduled visits and telephone contacts (with the exception of the Safety Follow-Up telephone contact), a visit window of ±7 days relative to Visit 1 is applicable. The Safety

Follow-Up telephone contact will be performed 28-35 days after the last dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up telephone contact are not required for subjects who participate in EP0151 or EP0152.

Assessments will be done during monthly visits for the first 3 months, every 2 months for the remainder of Year 1, and every 3 months for Year 2. A detailed tabular schedule of study procedures is provided in Section 16.1. For further details of the assessments and the required procedures and methods, please refer to Section 6, Section 7, and Section 8.

Clinical Study Protocol, Section 5.16 (Visit 13/Termination Visit [Week 96]). Original text, first paragraph:

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM.

Was revised as follows:

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up telephone contact 28 to 35 days after Visit 13/Termination Visit. The Final Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up telephone contact are not required for subjects who participate in EP0151 or EP0152.

Clinical Study Protocol, Section 5.19 (Final Visit). Original text, first paragraph:

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

Was revised as follows:

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication. The Final Visit is not required for subjects who participate in EP0151 or EP0152.

Clinical Study Protocol, Section 5.20 (Safety Follow-Up telephone contact). Original text, first paragraph:

The Safety Follow-Up telephone contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). For subjects who complete the study, this telephone contact will occur 28 to 35 days after Visit 13/Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]). For subjects who withdraw prematurely from the study, this telephone contact will occur 28 to 35 days after the Early Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]).

Was revised as follows:

The Safety Follow-Up telephone contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study) who do not participate in EP0151 or EP0152. For subjects who complete the study, this telephone contact will occur 28 to 35 days after Visit 13/Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]). For subjects who withdraw prematurely from the study, this telephone contact will occur 28 to 35 days after the Early Termination Visit (subjects who do not undergo taper of LCM) or 28 to 35 days after the last dose of LCM (subjects who discontinue use of LCM [ie, taper]). The Safety Follow-Up telephone contact is not required for subjects who participate in EP0151 or EP0152.

Clinical Study Protocol, Section 5.21(Study conduct due to coronavirus disease 2019 pandemic) was newly added as follows:

The protocol-mandated visit schedule should be followed to the extent possible, considering the individual benefit-risk assessment by the investigator. If necessary, remote visits may be conducted and the subjects or caregivers will be contacted by telephone or videoconference. Remote follow-up, at minimum with a telephone call after 3 months, must be done (preferably more frequently and as needed to follow-up on participant safety assessments).

Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the coronavirus disease 2019 (COVID-19) pandemic (eg, any measures that may limit access to the site or may require additional actions by the study participant prior to entry to the site).

If a subject needs to be discontinued and cannot come into the clinic, then appropriate tapering instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible.

In situations where a subject is unable to return to the study site, investigators will assess and document the subject's safety via telephone contact. Based on information gathered from the telephone contact, investigators will confirm whether the subject could continue the current

study treatment based upon the outcome of the safety assessment. Subjects' agreement to implement this procedure should be obtained and documented prior to implementing any changes. Changes in the study treatment supply in this situation are described in Section 9.5.

If a subject visits another facility for a medical issue (or has to switch sites for a COVID-19-related reason), the investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the clinical study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

Deviations to data collection including inability to perform some assessments, such as ECG, blood collection for safety laboratory assessments and PK, or alternative methods of assessment, such as phone calls, should be recorded in the source documentation and notated as "not done" in the eCRF.

In cases where subjects cannot return to the clinic, and it will not be possible to dispense a new seizure diary, subjects will be instructed to continue recording of seizures in a manner that is mutually agreed with the investigator (eg, hand-written notes, recording on a smart device). Any recording of seizures in a manner outside of the study seizure diary must be carefully documented in the source medical records (copies/print-screen printouts of these recordings will be brought to and retained at the site).

Clinical Study Protocol, Section 6.2.1 (Clinical Global Impression of Change). Original text, first paragraph:

The Clinical Global Impression of Change will be completed according to the tabular schedule of study procedures, Section 16.1.

Was revised as follows:

The Clinical Global Impression of Change will be assessed at least once per year and be completed according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 6.2.2 (Caregiver Global Impression of Change). Original text, first paragraph:

The Caregiver Global Impression of Change will be completed according to the tabular schedule of study procedures, Section 16.1.

Was revised as follows:

The Caregiver Global Impression of Change will be assessed at least once per year and be completed according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 6.3 (Pediatric Quality of Life Inventory). Original text, first paragraph:

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001; Varni et al, 2011). The PedsQL will be administered according to the tabular schedule of study procedures, Section 16.1.

Was revised as follows:

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001; Varni et al, 2011). The PedsQL will be completed up to two times per year and will be administered according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 8.1.10 (Occurrence of COVID-19) was newly added as follows:

Occurrence of COVID-19 in subjects should be reported as either "suspected COVID-19" or "confirmed COVID-19" along with all available relevant data including diagnostic and laboratory data. For subjects where COVID-19 is still suspected despite a negative viral test, please report as "suspected COVID-19" and provide relevant data to support the diagnosis as well as the test results.

Clinical Study Protocol, Section 8.3 (Laboratory measurements). Original text, laboratory test table:

Urinalysis	**Hematology**	**Clinical chemistry**		**Endocrinology**
Specific gravity	RBC	Total serum protein	Cholesterol	FSH
pH	WBC	Albumin	Triglycerides	LH
Albumin	Differential count	Calcium	Total bilirubin	Testosterone
Glucose	Platelet count	Phosphorus	Alkaline phosphatase	TSH
Ketone	Hemoglobin	Glucose	Creatinine	T3 (total and serum-free)
Microscopic exam for blood cells for casts/hpf	Hematocrit	Serum electrolytes (sodium, potassium, chloride, bicarbonate)	AST ALT GGT	T4 (total and serum-free)
		Uric acid	BUN	

Was revised as follows:

Urinalysis	**Hematology**	**Clinical chemistry**		**Endocrinology**
Specific gravity	RBC	Total serum protein	Cholesterol	FSH
pH	WBC	Albumin	Triglycerides	LH
Protein	Differential count	Calcium	Total bilirubin	Testosterone

Urinalysis	Hematology	Clinical chemistry		Endocrinology
Glucose	Platelet count	Phosphorus	Alkaline phosphatase	TSH
Ketone	Hemoglobin	Glucose	Creatinine	T3 (total and serum-free)
Microscopic exam for blood cells for casts/hpf	Hematocrit	Serum electrolytes (sodium, potassium, chloride, bicarbonate)	AST ALT GGT	T4 (total and serum-free)
		Uric acid	BUN	

Clinical Study Protocol, Section 8.3.2 (Liver function tests and evaluation of PDILI). Original text, seventh paragraph:

When IMP is stopped due to PDILI (as described in Section 4.3.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings.

Was revised as follows:

When IMP is stopped due to PDILI (as described in Section 4.3.3.1), IMP must be permanently discontinued.

Clinical Study Protocol, Section 8.3.2.3 (Testing: identification/exclusion of alternative etiology). Original text, Table 8-2:

Table 8–2: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

Was revised as follows:

Table 8–2: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Hematocrit
	Hemoglobin
	Platelet count
	RBC count
	WBC count
	WBC differential count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
	ALT
	AST
	ALP
	GGT
	Albumin
Additional	Prothrombin time/INR[a]

	Serum pregnancy test
	PK sample

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma-glutamyltransferase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RBC=red blood cell; RNA=ribonucleic acid; ULN=upper limit of normal; WBC=white blood cell

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

Clinical Study Protocol, Section 8.4.5 (Tanner Stage). New final paragraph added as follows:

The evaluation of Tanner Stage for applicable subjects will be completed according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 8.4.6 (Assessment of suicidality). New second paragraph added as follows:

Subjects enrolling directly who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version used at subsequent visits.

Clinical Study Protocol, Section 8.4.7 (Achenbach CBCL). Original text, second, third, and fourth paragraphs:

The same scale will be completed at the Screening Visit (subjects enrolling directly into SP848), Visit 1 (subjects enrolling from SP847 or other pediatric clinical studies in epilepsy), and Visit 13/Termination Visit (or Early Termination Visit) (all subjects) by the parent(s)/legal representative(s). The completion of the Achenbach CBCL will require approximately 45 minutes.

In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

- 0=not true (as far as known)
- 1=somewhat or sometimes true
- 2=very true or often true

Eight syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each score on the question, syndrome, and total level,

categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

Was revised as follows:

The Achenbach CBCL will be completed according to the tabular schedule of study procedures, Section 16.1.

In both questionnaires, the occurrence of certain problems and behaviors (in the past 2 months for the CBCL/1½-5 version and in the past 6 months for the CBCL/6-18 version) will be scored on the following scale:

- 0=not true (as far as known)
- 1=somewhat or sometimes true
- 2=very true or often true

Syndrome scores will be calculated from these questions, which will in turn be summarized by 2 composite scores. Additionally, for each syndrome and composite scores, categorizations based on a normative sample will be used to evaluate normal, borderline, or clinically relevant behavior.

Clinical Study Protocol, Section 8.4.8 (Bayley Scales of Infant and Toddler Development, Third Edition). Original text, final paragraph:

The same scale will be completed at the Screening Visit (subjects enrolling directly into SP848), Visit 1 (subjects enrolling from SP847 or other pediatric clinical studies in epilepsy), and Visit 13/Termination Visit (or Early Termination Visit) (all subjects) for children from 1 month to <18 months of age enrolled in English-speaking countries.

Was revised as follows:

The Bayley-III scales will be completed according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 8.4.9 (Palatability and ease of use questionnaire for LCM). New final paragraph added as follows:

The questionnaire will be completed according to the tabular schedule of study procedures, Section 16.1.

Clinical Study Protocol, Section 8.4.10 (Behavior Rating Inventory of Executive Function). Original text, fourth paragraph:

The BRIEF rating form contains items in nonoverlapping clinical scales. These theoretically and statistically derived scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

Was revised as follows:

The BRIEF rating form consists of items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of materials, and Monitor. These clinical scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

Clinical Study Protocol, Section 9.2 (Supply, handling, and storage). Original text, first paragraph:

Lacosamide (oral solution [syrup] and tablet) is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be frozen.

Was revised as follows:

Lacosamide (oral solution [syrup] and tablet) is stable at room temperature and is to be stored at temperatures not exceeding 25.4°C (77.7°F) or below 14.5°C (58.1°F). Lacosamide should not be frozen or refrigerated.

Clinical Study Protocol, Section 9.5 (Alternative study treatment supply due to COVID-19 pandemic) was newly added as follows:

When a subject can no longer return to the study site due to general circumstances but will continue in the study, the following methods may be used to provide study treatment:

- Site to subject: In instances where site staff can ship study treatment dispensed from the site pharmacy supply directly to the subject.
- Depot to subject: In instances where it is not possible for the site staff to access study treatment in the site pharmacy and/or ship study treatment dispensed from the site pharmacy supply directly to the subject.

Clinical Study Protocol, Section 12.1.2 (Statistical analysis of safety variables). Original text, Section 12.1.2.1 and Section 12.1.2.2:

12.1.2 Statistical analysis of primary variables

The primary variables, for assessment of safety and tolerability, are AEs as well as subject withdrawals due to AEs; changes in vital signs, ECGs, clinical laboratory tests, body weight, height, and calculated BMI; and physical and neurological examination findings.

12.1.2.1 AEs

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), and tabulated by system organ class and preferred term.

Treatment-emergent AEs will be defined as those events which started on or after the date of first SP848 LCM administration, or whose severity worsened on or after the date of first SP848 LCM administration. Adverse events occurring within 30 days after last dose of LCM will be considered treatment emergent. The incidence of TEAEs will be presented by system organ class and preferred term. Serious AEs will also be tabulated and listed.

12.1.2.2 Other safety variables

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, and urinalysis), ECG measurements, vital sign measurements (blood pressure and pulse rate), body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 [or other primary study as applicable] Visit 1) or the Screening Visit (for subjects who entered directly into SP848) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

The shift from Baseline to the subject's last visit at which a physical and/or neurological examination was performed post-Baseline will be summarized by category.

Laboratory, ECG, and vital signs data outside of the respective reference ranges will be listed and highlighted.

Changes in behavior and development from Baseline as measured using the Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) and Bayley-III scales for children <18 months of age will be summarized descriptively and presented by visit. Changes in cognitive function as measured using the BRIEF-P/BRIEF will be summarized by descriptive statistics at each visit. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

Was revised as follows:

12.1.2 Statistical analysis of safety variables

12.1.2.1 Primary safety variables

The primary variables, for assessment of safety and tolerability, are the incidence of TEAEs and the incidence of SAEs.

12.1.2.1.1 AEs

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), and tabulated by system organ class and preferred term.

Treatment-emergent AEs will be defined as those events which started on or after the date of first SP848 LCM administration, or whose severity worsened on or after the date of first SP848 LCM administration. Adverse events occurring within 30 days after last dose of LCM will be

considered treatment-emergent. The incidence of TEAEs will be presented by system organ class and preferred term. Serious AEs will also be tabulated and listed.

12.1.2.2 Other safety variables

The other safety variables include changes in laboratory parameters (ie, hematology, clinical chemistry, endocrinology, and urinalysis), 12-lead ECG measurements, vital sign measurements (blood pressure and pulse rate), physical and neurological exam findings, body weight, height, calculated BMI, and Tanner Stage (if applicable). The actual measurement and its change from Baseline (SP847 [or other primary study as applicable] Visit 1) or the Screening Visit (for subjects who entered directly into SP848) will be analyzed descriptively and presented by visit. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

The shift from Baseline to the subject's last visit at which a physical and/or neurological examination was performed post-Baseline will be summarized by category.

Laboratory, ECG, and vital signs data outside of the respective reference ranges will be listed and highlighted.

Changes in behavior and development from Baseline as measured using the Achenbach CBCL for children 18 months and older (CBCL/1½-5 and CBCL/6-18) and Bayley-III scales for children <18 months of age will be summarized descriptively and presented by visit. Changes in cognitive function as measured using the BRIEF-P/BRIEF will be summarized by descriptive statistics at each visit. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

12.1.2.2.1 Palatability and ease of use questionnaire

Data from the palatability and ease of use questionnaire will be summarized descriptively at each visit where it is assessed.

Clinical Study Protocol, Section 12.1.4 (Statistical analysis of secondary variables). Original text, Section 12.1.4.1 and Section 12.1.4.2:

12.1.4 Statistical analysis of secondary variables

12.1.4.1 Seizure frequency

Seizure frequency will be assessed using seizure diaries in order to evaluate the preliminary efficacy of LCM in this population. Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval]) divided by [number of days in the interval]) multiplied by 28 and summarized descriptively and presented graphically at each visit and grouped by dose.

12.1.4.2 Clinical Global Impression of Change and Caregiver Global Impression of Change

The number and percentage of subjects with each Clinical Global Impression of Change and Caregiver Global Impression of Change value will be summarized at each visit in which they are assessed and grouped by dose.

12.1.4.3 Palatability and ease of use questionnaire

Data from the palatability and ease of use questionnaire will be summarized descriptively at each visit where it is assessed.

12.1.4.4 PedsQL

The PedsQL score and change from Baseline scores will be analyzed in a descriptive manner. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

12.1.4.5 Health care resource use

Descriptive statistics will be presented for the number of medical resources used (medications, consultations, procedures, hospitalizations, and length of hospital stays).

Was revised as follows:

12.1.4 Statistical analysis of efficacy variables

12.1.4.1 Secondary efficacy variables

12.1.4.1.1 Percent change from Baseline in 28-day partial-onset seizure frequency

Seizure frequency will be assessed using seizure diaries in order to evaluate the preliminary efficacy of LCM in this population. Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval]) divided by [number of days in the interval]) multiplied by 28 and summarized descriptively for the overall Treatment Period.

12.1.4.1.2 ≥50% reduction in 28-day partial-onset seizure frequency

For subjects with POS, the number and percentage with ≥50% reduction in 28-day partial-onset seizure frequency (≥50% responders) will be summarized for the overall Treatment Period.

12.1.4.1.3 ≥75% reduction in 28-day partial-onset seizure frequency

For subjects with POS, the number and percentage with ≥75% reduction in 28-day partial-onset seizure frequency (≥75% responders) will be summarized for the overall Treatment Period.

12.1.4.1.4 Seizure days per 28 days (subjects with generalized seizures only)

For subjects with generalized seizures, the number of seizure days per 28 days will be summarized descriptively for the overall Treatment Period.

12.1.4.1.5 Seizure-free status

The number and percentage of subjects achieving a seizure-free status for the overall Treatment Period will be presented.

12.1.4.2 Other efficacy variables

12.1.4.2.1 Clinical Global Impression of Change and Caregiver Global Impression of Change

The number and percentage of subjects with each Clinical Global Impression of Change and Caregiver Global Impression of Change value will be summarized at each visit in which they are assessed and grouped by dose.

12.1.4.2.2 PedsQL

The PedsQL score and change from Baseline scores will be analyzed in a descriptive manner. Baseline is defined as Visit 1 for subjects from SP847 or other epilepsy studies. Baseline values for subjects who enroll directly into SP848 will be taken from the Screening Visit.

12.1.4.2.3 Health care resource use

Descriptive statistics will be presented for the number of medical resources used (medications, consultations, procedures, hospitalizations, and length of hospital stays).

12.1.4.2.2 Seizure frequency analyses

All seizure frequency analyses as described in the secondary efficacy variables (Section 12.1.4.1) may be additionally presented by modal daily dose group, by seizure type, by seizure classification subgroup, by time interval, by visit or time period, or by completer cohort. Additional details will be provided in the Statistical Analysis Plan.

Clinical Study Protocol, Section 12.1.5 (Handling of protocol violators, drop-outs, and missing values). New final paragraph added as follows:

Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.

Clinical Study Protocol, Section 12.2 (Determination of sample size). Original text, second and third paragraphs:

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated in a LCM clinical study will be permitted to enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848.

Was revised as follows:

In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects ≥4 years to ≤17 years of age who have not previously participated

in a LCM clinical study will be permitted to enroll directly into SP848. Beginning with local Protocol Amendment 5.2 for sites in Japan, approximately 46 eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who have not previously received LCM will directly enroll at approximately 9 sites in Japan. Beginning with local Protocol Amendment 5.4 for sites in China, approximately 60 additional eligible pediatric subjects with partial-onset seizures aged ≥4 years to ≤17 years, who have not previously participated in a LCM clinical study, will enroll directly into SP848. The purpose of enrolling these subjects directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects ≥4 years of age.

Beginning with Protocol Amendment 6, up to 75 eligible pediatric subjects ≥4 years to <17 years of age who have participated in EP0060 will be permitted to enroll into SP848. Protocol Amendment 8 allows an enrollment increase from 75 to 100 eligible pediatric subjects ≥1 month to ≤17 years of age with epilepsy who participated in EP0060 to enroll in SP848 in order to reflect EP0060's inclusion of subjects down to 1 month of age.

In total, up to approximately 400 subjects may be eligible to participate in SP848.

Clinical Study Protocol, Section 16.1 (Tabular schedule of study procedures). Original text, Table 16-1 (Schedule of study procedures for SP848 [Year 1]), footnotes f and g:

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[g] This TC occurs 28 to 35 days after the last dose of LCM.

Were revised as follows:

[f] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication. The Final Visit is not required for subjects who participate in EP0151 or EP0152.

[g] This TC occurs 28 to 35 days after the last dose of LCM. The Safety Follow-Up TC is not required for subjects who participate in EP0151 or EP0152.

Clinical Study Protocol, Section 16.1 (Tabular schedule of study procedures). Original text, Table 16-2 (Schedule of study procedures for SP848 [Year 2]), footnotes e and f:

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication.

[f] This TC occurs 28 to 35 days after the last dose of LCM.

Were revised as follows:

[e] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM (ie, taper), should complete the Final Visit 2 weeks after the final dose of study medication. The Final Visit is not required for subjects who participate in EP0151 or EP0152.

[f] This TC occurs 28 to 35 days after the last dose of LCM. The Safety Follow-Up TC is not required for subjects who participate in EP0151 or EP0152.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I received and have read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB BIOSCIENCES.

All rights of publication of the results reside with UCB BIOSCIENCES, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

19 SPONSOR DECLARATION

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

Approval Signatures

Name: SP848-protocol-amend-8

Version: 2.0

Document Number: CLIN-000127983

Title: SP848 Protocol Amendment Version 8

Approved Date: 26 Oct 2020

Document Approvals	
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