PROTOCOL SP0967 AMENDMENT 3

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN SUBJECTS WITH EPILEPSY ≥1 MONTH TO <4 YEARS OF AGE WITH PARTIAL-ONSET SEIZURES

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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ADF	average daily frequency
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
bid	twice daily
BMI	body mass index
BP	blood pressure
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
BZD	benzodiazepine
CBCL	Childhood Behavior Checklist
CDMS	clinical data management system
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
DAP	Data Analysis Plan
eCRF	electronic Case Report form
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
IXRS	interactive voice/web response system
LCM	lacosamide
LFT	liver function test
LSM	least square means
MedDRA®	Medical Dictionary for Regulatory Activities®
PBO	placebo
PDILI	potential drug-induced liver injury
PedsQL™	Pediatric Quality of Life Inventory™
PET	polyethylene terephthalate
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PT	preferred term
QTc	corrected QT interval
RDC	remote data capture

SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VNS	vagus nerve stimulation

1 SUMMARY

SP0967 is a Phase 3, multicenter, double-blind, randomized, placebo (PBO)-controlled, parallel-group study to evaluate the efficacy and safety of lacosamide (LCM) (VIMPAT®; SPM 927; previously referred to as harkoseride; [R]-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) 8mg/kg/day to LCM 12mg/kg/day as adjunctive therapy in subjects with epilepsy ≥1 month to <4 years of age with uncontrolled partial-onset seizures. This study is 1 of 2 pivotal studies in a pediatric partial-onset seizure population. In addition to SP0967, SP0969 is a Phase 3, multicenter, double-blind, randomized, PBO-controlled, parallel-group study to evaluate the efficacy and safety of LCM as an adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial-onset seizures.

The primary objective of SP0967 is to evaluate the efficacy of LCM administered concomitantly with 1 to 3 antiepileptic drugs (AEDs) in pediatric subjects (≥1 month to <4 years of age) with epilepsy who currently have uncontrolled partial-onset seizures. The secondary objective is to evaluate the safety and tolerability of LCM in pediatric subjects with partial-onset seizures. An additional objective is to evaluate the pharmacokinetics (PK) of LCM in subjects ≥1 month to <4 years of age.

A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized at approximately 140 sites in North America, Europe, Asia Pacific, and Latin America, with possible extension to other countries and regions. Stratification of subjects will be done by age category (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age). A target of 50% of the randomized subjects should consist of subjects <2 years of age. The maximum duration of study medication administration in SP0967 is 55 days (this includes a 20-day Titration Period, a 7-day Maintenance Period, a 12-day Transition Period, and/or up to a 16-day Taper Period), and the maximum study duration is 93 days (not withstanding visit windows).

The study is comprised of the following: a 7-day Baseline Period; a 20-day blinded Titration Period (with study medication dosing flexibility allowed based on tolerability) to attain the target dose of study medication for the 7-day blinded Maintenance Period (LCM 8mg/kg/day to LCM 12mg/kg/day, or matching PBO, with no adjustments to study medication dose allowed during the Maintenance Period); and a 12-day blinded Transition Period for subjects who complete the study and choose to enter the open-label extension study (EP0034) or a Taper Period (up to 16 days) followed by a 30-day Safety Follow-Up Period for subjects who are not eligible or who choose not to enter EP0034. The Transition Period will be required for eligible subjects who complete the Maintenance Period and choose to enter EP0034. The Taper Period and Safety Follow-Up Period are required for subjects who complete the study but choose not to enroll in EP0034 or for subjects who do not complete the Titration, Maintenance, and Transition Periods.

Based on US Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements, 2 (co-) primary efficacy variables have been defined for this study based on electrographic partial-onset seizures with or without clinical correlate depending upon subject age. The primary efficacy variable will be the change in average daily frequency (ADF) of electrographic partial-onset seizures (US) or proportion of subjects experiencing ≥50% reduction in their ADF of electrographic partial-onset seizures (EU) as measured on the

End-of-Maintenance Period video-electroencephalogram (EEG) compared to the End-of-Baseline Period video-EEG. Partial-onset seizures will be counted locally by the investigator, subinvestigator, or qualified designated reader based on evaluating the characteristic ictal patterns of electrographic seizures. At the request of FDA, a contingent primary efficacy variable has also been defined based on the percentage of subjects who discontinue early from the study prior to completing the End-of-Maintenance Period video-EEG. Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy parameter for the US will become identical to the primary efficacy parameter for the EU. The endpoint not designated as primary will still be summarized as a secondary efficacy parameter.

Secondary and other efficacy variables will aid further exploration of the effect of LCM on partial-onset seizure frequency, global impressions of change, quality of life assessment (Pediatric Quality of Life Inventory™ [PedsQL™]), and healthcare resource use. Plasma concentrations of LCM will be obtained in order to develop a population PK model of LCM, to investigate the effect of LCM on the steady-state plasma concentrations of concomitant AEDs, and to investigate the correlation between LCM plasma concentrations and efficacy or safety.

Safety and tolerability will be assessed primarily based on the occurrence of adverse events (AEs) reported spontaneously by the subject's parent(s) and/or his/her legal representative(s)/caregiver(s) or observed by the investigator, and subject withdrawals due to AEs. Other safety variables will include assessment for change in hematology and clinical chemistry parameters; results of periodic physical and neurological examination, body mass index (BMI), 12-lead electrocardiogram (ECG), and vital sign measurements. Baseline behavioral function assessment (Achenbach Childhood Behavior Checklist [CBCL]) and cognitive function assessment (Behavior Rating Inventory of Executive Function®-Preschool Version [BRIEF®-P]) will be conducted for analysis in EP0034.

2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy (Ngugi et al, 2011). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). The Institute of Medicine of the National Academies recently provided a review of the burdens of epilepsy, global incidence and prevalence of epilepsy, classification systems for seizure types and syndromes, gaps in information about epilepsy, and general recommendations (Institute of Medicine, 2012). Several newer options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

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 at 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; Glauser et al, 2000; 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 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.

In the US, LCM has been approved as monotherapy and adjunctive therapy in the treatment of partial-onset seizures in patients 4 years of age and older for tablets and oral solution, and 17 years of age and older for intravenous [iv] infusion. In the EU, LCM has been approved as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 4 years of age with epilepsy (tablets, oral solution, and solution for iv infusion). The oral solution (also referred to as syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution formulations, comparing 2 tablets of LCM 100mg and the oral solution containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and SPM 12809 (major LCM metabolite in humans) in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution.

In the clinical development program for LCM, safety and tolerability of multiple doses of up to LCM 400mg bid (LCM 800mg/day) were evaluated in approximately 800 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 2400 adult subjects in other indications (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 (220 patients) who were receiving adjunctive LCM tablets.

Three double-blind, PBO-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 (LCM 200mg/day, LCM 400mg/day, or LCM 600mg/day) in LCM 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to LCM 600mg/day in the 3 double-blind, PBO-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 AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

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

Lacosamide is being evaluated in pediatric subjects 1 month to 17 years of age with partial-onset seizures in completed and ongoing studies. The completed pediatric studies include: SP847 (open-label, safety, tolerability, and PK study) and SP1047 (PK study for subjects prescribed LCM). The ongoing pediatric studies include: SP848 and EP0034 (open-label, long-term safety studies). In SP847, SP848, and EP0034, subjects with uncontrolled partial-onset seizures have received LCM oral solution at doses up to 12mg/kg/day based on tolerability. In SP1047, subjects with epilepsy received LCM oral tablets (50mg, 100mg, 150mg, or 200mg), or LCM oral solution (syrup; LCM 10mg/mL) that they had been prescribed for epilepsy and brought with them to the clinic for dosing. Preliminary data have not demonstrated any clinically relevant changes in vital signs, in ECGs, or in clinical laboratory values; or evidence of cardiac related TEAEs or body weight changes.

SP0967 is a Phase 3, multicenter, double-blind, randomized, PBO-controlled, parallel-group study to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day, or matching PBO) as adjunctive therapy in subjects ≥1 month to <4 years of age with epilepsy with uncontrolled partial-onset seizures.

3 STUDY OBJECTIVE(S)

The primary objective of this study is to evaluate the efficacy of LCM administered concomitantly with 1 to 3 AEDs in subjects ≥1 month to <4 years of age with epilepsy who currently have uncontrolled partial-onset seizures.

The secondary objective is to evaluate the safety and tolerability of LCM in subjects ≥1 month to <4 years of age with epilepsy who currently have uncontrolled partial-onset seizures.

An additional objective is to evaluate the PK of LCM in children ≥1 month to <4 years of age.

4 STUDY VARIABLES

4.1 Efficacy variables

Primary and secondary efficacy variables will be based on video-EEGs (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording).

4.1.1 Primary efficacy variable

For the US, the primary efficacy variable will be contingent on the percentage of subjects that discontinue from the study after the first dose of study medication but prior to performance of the End-of-Maintenance Period video-EEG (ie, early discontinuation).

The following variable will be considered primary for the US given that ≤10% of subjects discontinue early from the study:

- The change in ADF of electrographic partial-onset seizures as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

If >10% of subjects discontinue early from the study, the following contingency endpoint will be considered primary for the US (same as the primary efficacy variable for the EU):

- The proportion of responders where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

For the EU:

The primary efficacy variable will be the proportion of responders where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

4.1.2 Secondary efficacy variables

The secondary efficacy variables are described below.

- Percent and absolute change in ADF of electrographic partial-onset seizures from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG
- Proportion of subjects who achieved “seizure-free” status (yes/no) from all seizure types, and from partial-onset seizure types only for subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG
- Proportion of subjects experiencing a ≥25% to <50%, 50% to 75%, or >75% reduction in ADF of electrographic partial-onset seizures from the end-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG
- Proportion of subjects experiencing no change in ADF of electrographic partial-onset seizures (between <25% reduction and <25% increase) from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG
- Proportion of subjects experiencing an increase in ADF of electrographic partial-onset seizures of ≥25% from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG

4.1.3 Other efficacy variables

Other efficacy variables to be examined include:

- Clinical Global Impression of Change at the end of the Maintenance Period
- Caregiver's Global Impression of Change at the end of the Maintenance Period
- Change from Baseline in PedsQL health summary score at the end of the Maintenance Period
- Healthcare resource use: concomitant medications, medical procedures, healthcare provider consultations not related to the study, and hospitalizations not related to the study

4.2 Pharmacokinetic and pharmacodynamic variables

Plasma concentrations of LCM will be obtained in order to:

- Develop a population PK model of LCM
- Investigate the correlation between LCM plasma concentrations and efficacy or safety

4.3 Safety variables

4.3.1 Primary safety variables

Safety and tolerability will be assessed using the following primary safety variables:

- Adverse events reported spontaneously by the subject's parent(s) and/or legal representative(s)/caregiver(s) (in accordance with local regulation) or observed by the investigator
- Subject withdrawals due to AEs

4.3.2 Other safety variables

- Change in hematology and clinical chemistry parameters
- Change in 12-lead ECGs
- Change in vital signs measurements (ie, blood pressure [BP] and pulse rate)
- Physical and neurological examination findings
- Changes in body weight, height, and calculated BMI

5 STUDY DESIGN

5.1 Study description

SP0967 is a Phase 3, multicenter, double-blind, randomized, PBO-controlled, parallel-group study to evaluate the efficacy and safety of LCM 8mg/kg/day to LCM 12mg/kg/day as adjunctive therapy in subjects ≥1 month to <4 years of age with epilepsy with partial-onset seizures.

Primary and secondary efficacy variables will be based on video-EEGs (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording). The video-EEGs will be conducted in an inpatient setting. Assessment of video-EEG seizure count will be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of both assessment of eligibility and study analyses.

Baseline Period

At Visit 1 (Day -7), subjects who meet the selection criteria will begin a 7-day Baseline Period (Day -7 to Day -1). In the event that additional time is needed to access inpatient facilities to perform the video-EEG, a maximum of 7 days may be added to the period between Visit 1 and 2. From Visit 2 (Day -3 to Day -1) to Visit 3 (Day 1), an End-of-Baseline Period video-EEG will be performed.

After completion of the End-of-Baseline video-EEG at Visit 3, subjects who meet the selection criteria will be randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or PBO in a 1:1 ratio.

Titration Period

Subjects will begin a 20-day blinded Titration Period (Day 1 to Day 20) to attain the target dose for the Maintenance Period (LCM 8mg/kg/day to LCM 12mg/kg/day, or matching PBO).

Subjects will be dispensed study medication and will begin treatment with LCM oral solution 4mg/kg/day or matching PBO for 4 days. Subjects will then be titrated at 4-day intervals as recommended in Table 7–1. The current 4-day titration step approach has been selected as it is generally accepted that frequent seizures require a rapid titration of AEDs.

Dosing flexibility during the Titration Period based on tolerability is allowed in SP0967. After completion of Day 4, investigators will assess whether a subject would tolerate a further dose increase or whether a subject should hold the dose for a longer duration. In addition to holds, subjects may have the study medication titrated to a higher dose or back titrated by LCM 1mg/kg/day or 2mg/kg/day (or matching PBO) steps. If study medication is titrated to a higher dose, the subject should remain on the higher dose for ≥4 days unless a back titration step based on tolerability is required.

If study medication is back titrated, the back titrated dose must never be lower than LCM 4mg/kg/day (or matching PBO) and must be maintained for ≥3 days (in order to reach steady state) before a subsequent dose increase. After study medication is back titrated, if a subject returns to a higher dose previously administered, the dose must be maintained for ≥3 days before subsequent titration to a higher dose. There is no limit to the number of titration steps or dose holds allowed and all are at the investigator's discretion; however, subjects must achieve at least the minimum target dose (LCM 8mg/kg/day or matching PBO) for the final 3 days of the Titration Period. If it becomes apparent that the subject will not be able to reach the minimum target dose, then the subjects should be withdrawn from the Titration Period and enter the Taper Period.

No adjustments in dose of study medication will be permitted after Day 20. Subjects who are not able to tolerate the study medication during the Titration Period or who will not be able to achieve the target dose by the end of the Titration Period will be withdrawn from the Titration Period and enter the Taper Period.

Maintenance Period

Subjects who achieve at least the minimum target study medication (LCM 8mg/kg/day or matching PBO) dose for the final 3 days of the Titration Period will enter a 7-day blinded Maintenance Period on the dose achieved on the final day of the Titration Period (LCM 8mg/kg/day to LCM 12mg/kg/day, or matching PBO). No adjustments to study

medication dose will be allowed during the Maintenance Period. Subjects who complete the Maintenance Period may be eligible to participate in the open-label extension study (EP0034).

Transition Period

A 12-day blinded Transition Period will be required for eligible subjects who complete the Maintenance Period and who plan to enter EP0034. For subjects randomized to LCM, the Maintenance Period dose will be maintained during the Transition Period. Subjects randomized to PBO will be transitioned in a double-blind fashion as described in Table 7–2.

Taper Period

A blinded Taper Period (8 to 16 days, depending on dose level achieved) will be required for subjects who discontinue study medication prematurely and for subjects who complete the Maintenance Period but will not be entering EP0034. Study medication will be tapered as described in Table 7-3.

At the discretion of the investigator, AEDs may be added or adjusted and VNS adjustments may be made once the subject enters the Taper Period.

Safety Follow-Up Period

There will be a 30-day Safety Follow-Up Period for subjects not entering the open-label extension study (EP0034). The Safety Follow-Up Period will include a Safety Follow-Up Clinic Visit 14 days (±2 days) after the final dose of study medication, and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of study medication.

Unscheduled visits can be conducted at the discretion of the investigator.

Detailed schedules of study procedures are provided in Section 5.2, and study schematic diagrams are included in Section 5.3.

5.1.1 Study duration per subject

For each subject, the maximum total study duration can be up to 93 days (not withstanding visit windows), including the 30-day Safety Follow-Up Period. Each subject's participation in the study begins with a 7-day Baseline Period (no administration of study medication). Each subject's maximum total duration of study medication administration in SP0967 can be up to 55 days. This includes a 20-day Titration Period, a 7-day Maintenance Period, a 12-day Transition Period (for subjects who plan to enter the open-label extension study [EP0034]) and/or up to a 16-day Taper Period (for subjects who will not be entering EP0034).

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

5.1.2 Planned number of subjects and sites

A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized. Approximately 50% of the 244 randomized subjects should be <2 years of age. Of these (n=122), every attempt will be made to enroll a minimum target of 20% (n=25) of subjects in each of the 3 age categories: ≥1 month to <6 months, ≥6 months to <1 year, and ≥1 year to <2 years.

Every attempt will be made to enroll subjects in the following age categories as detailed below:

- ≥1 month to <6 months of age (≥25 subjects)
- ≥6 months to <1 year of age (≥25 subjects)
- ≥1 year to <2 years of age (≥25 subjects)
- ≥2 years to <4 years of age (≥20 subjects)

Approximately 140 sites are planned in order to recruit the required subjects; additional sites will be added if deemed necessary.

5.1.3 Anticipated regions and countries

The study will be conducted in North America, Europe, Asia Pacific, and Latin America with possible extension to other countries and regions. A target of approximately 30% of the randomized subjects should consist of subjects originating from sites in North America and Europe.

5.2 Schedule of study assessments

A tabular schedule of study procedures for the Baseline and Treatment Periods is presented in Table 5–1. A tabular schedule of study procedures for the Transition Period is presented in Table 5–2. A tabular schedule of study procedures for the Taper and Safety Follow-Up Periods is presented in Table 5–3.

Table 5–1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
Informed consent	X														
Demographics[c]	X														
Inclusion/exclusion criteria	X	X			X										
Medical history	X														
Seizure history/count	X														
Concomitant medications	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VNS assessment[f]	X	X					X				X			X	X
Physical examination (complete)	X													X	
Physical examination (brief)		X					X		X		X				
Vital signs (including BP and pulse rate)[g]	X	X					X		X		X			X	X
Body weight	X	X					X		X					X	X
Height	X													X	
Head circumference	X													X	
Neurological examination (complete)	X													X	
Neurological examination (brief)		X					X		X		X				
ECG (12-lead)[h]	X				X[q]				X					X	

Table 5–1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
Video-EEG[i]		X	X	X	X						X	X	X	X	
Rescue medication[j]		X	X	X	X						X	X	X	X	
Clinical chemistry/hematology	X								X					X	
LCM plasma concentration									X					X	
Clinical GIC														X	
Caregiver's GIC														X	
Contact IXRS	X				X		X		X		X			X	
Randomization					X[k]										
Dispense study medication					X[k]		X		X		X			X	
Return study medication							X		X		X			X	
Dosing instructions[l]						X		X		X					
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare resource use					X									X	
Bayley-III scales[m]					X										
BRIEF-P[n]					X										

Table 5–1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
PedsQL[o]					X									X	
Achenbach CBCL[p]					X										

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Childhood Behavior Checklist; ECG=electrocardiogram; EEG=electroencephalogram; ET=Early Termination; GIC=Global Impression of Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; T=Telephone Contact; UV=Unscheduled Visit; V=Visit; VNS=vagus nerve stimulation.

[a] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion.

[b] The Day -3 and Day 24 assessments should be conducted prior to the start of video-EEG monitoring. A maximum of 7 days may be added to the period between Visit 1 and 2 in the event that additional time is needed to access inpatient facilities to perform the video-EEG.

[c] Demographics: date of birth, age group category, age in months and years, race, ethnicity, and gender. In countries where recording of complete date of birth is not permitted, only permitted data will be collected.

[d] The concomitant medications recording will include any current medication intake as well as any medications taken ≤30 days prior to Visit 1.

[e] The concomitant AED recording will include any current medication intake as well as any previous AED taken prior to Visit 1.

[f] The VNS setting will be assessed as applicable.

[g] Orthostatic assessments of BP and pulse rate will be assessed where it is feasible according to investigator judgment.

[h] A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recording. The second recording will be conducted approximately 20 to 30 minutes after the first recording. Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader and at a central ECG laboratory. The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality; however, 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.

[i] The video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) will be conducted in an inpatient setting. Upon completion of the End-of-Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the video-EEG data, the subject may be randomized at Visit 3. Assessment of video-EEG seizure count will be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of both assessment of eligibility and study analyses. The End-of-Maintenance Period video-EEG will be done at Visit 6. Subjects who discontinue on or before Day 20 will not require a video-EEG.

Table 5–1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	

[j] Additional assessment for changes in VNS or rescue medication taken within 24 hours prior to and until the end of the video-EEG monitoring.
[k] Randomization and initial dispensing of study medication will occur at Visit 3 and after the completion of the video-EEG and confirmation that the subject has met selection criteria.
[l] Dosing instructions will be provided to the caregiver(s) during the telephone contacts. At a minimum, AEs and tolerability should be discussed with the caregiver(s) in order to determine the next dose for the subject. See Section 7.2.1 for additional details on dosing options.
[m] Investigators must make every attempt to administer the Bayley Scales of Infant and Toddler Development, Third Edition, for subjects who are <18 months of age who originate in English-speaking countries. The investigators may utilize trained pediatric psychologists or other appropriately skilled individuals to administer the scale.
[n]The BRIEF-P will be used only for subjects who are ≥2 years of age at Visits 3. BRIEF-P will be used only in countries where a translated version is available.
[o] The version of the PedsQL used at Visit 3 should be consistent with the subject's age at Visit 3 and should be maintained for each subject for the duration of the study. The PedsQL will be used only in countries where a translated version is available.
[p] The Achenbach CBCL/1½-5 will be completed by the parent(s)/legal representative(s)/caregiver(s) of subjects ≥18 months of age at Visit 3. The Achenbach CBCL will be administered only in countries where a translated version is available.
[q] ECG at Visit 3 will be performed at the discretion of the investigator.

Table 5–2: Schedule of study assessments (Transition Period)

Assessments	Transition Period (12 days)		
Visit	**TV1**	**TT1**	**TV2**[a]
Study Day	**32**	**36**	**40**
Concomitant medications	X	X	X[b]
Concomitant AEDs	X	X	X[b]
VNS assessment[c]	X		X[b]
Physical examination (brief)	X		
Physical examination (complete)			X[b]
Vital signs (including BP and pulse rate)[d]	X		X[b]
Body weight	X		X[b]
Neurological examination (brief)	X		
Neurological examination (complete)			X[b]
ECG (12-lead)[e]			X[b]
Clinical chemistry/hematology			X[b]
Contact IXRS	X		X
Dosing instructions[f]		X	
Dispense study medication	X		
Return study medication	X		X
AE reporting	X	X	X[b]
Withdrawal criteria	X	X	X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; ECG=electrocardiogram; IXRS=interactive voice/web response system; TT=Transition Telephone Contact; TV=Transition Visit; VNS=vagus nerve stimulation

[a] Transition Visit 2 will also serve as Visit 1 for EP0034.

[b] The designated procedures will serve as the point of data for both TV2 in SP0967 and Visit 1 for EP0034.

[c] Vagus nerve stimulation setting will be assessed as applicable.

[d] Orthostatic assessments of BP and pulse rate will be assessed if it is feasible according to investigator judgment.

[e] A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recording. The second recording will be conducted approximately 20 to 30 minutes after the first recording.

[f] Dosing instructions will be provided to the caregiver(s) during the telephone contacts. See Section 7.2.3 for additional details on dosing options.

Table 5–3: Schedule of study assessments (Taper and Safety Follow-Up Periods)

Assessments	Taper Period (8 to 16 days)		Safety Follow-Up Period (30 days)[a]	
Visit	**T4**[b]	**Taper Visit**[c]	**Safety Follow-Up Clinic Visit Days in Study: FSM+14 (±2)**	**Safety Follow-Up Telephone Contact Days in Study: FSM+30 (-1/+3)**
Study Day	**32**[d]	**36/40/44**[c,d]	**50/54/58**[d]	**66/70/74/93**[d]
Concomitant medications	X	X	X	X
Concomitant AEDs	X	X	X	X
VNS assessment[e]		X	X	
Physical examination (brief)		X		
Physical examination (complete)			X	
Vital signs[f] (including BP and pulse rate)		X	X	
Body weight		X	X	
Neurological examination (brief)		X		
Neurological examination (complete)			X	
ECG (12-lead)[g]		X[h]	X[h]	
Clinical chemistry/hematology		X[h]	X[h]	
Contact IXRS		X		
Dosing instructions[i]		X		
Return study medication		X		
AE reporting	X	X	X	X
Withdrawal criteria	X	X		

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; ECG=electrocardiogram; FSM=Final Study Medication; IXRS=interactive voice/web response system; T=Telephone Contact; VNS=vagus nerve stimulation

[a] The Safety Follow-Up Clinic Visit will be scheduled 14 days (±2 days) after the final dose of study medication. The Safety Follow-Up Telephone Contact will occur 30 days (-1/+3 days) after the final dose of study medication.

[b] A telephone contact (T4) will be conducted at the end of the first taper step of the Taper Period.

[c] Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Day 36, 40, or 44), depending on dose level achieved (see Table 7-3).

[d] The study day numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study day numbers provided do not apply to subjects who enter the Taper Period at other times. Day 66, 70, or 74 result from the administration of final study medication during the Taper Period whereas Day 93 would result from a subject progressing to the end of the Transition Period, but then not entering EP0034 and instead entering the Transition Period followed by the Taper Period.

[e] VNS setting will be assessed as applicable.

[f] Orthostatic assessments of BP and pulse rate will be assessed where it is feasible according to investigator

Table 5–3: Schedule of study assessments (Taper and Safety Follow-Up Periods)

Assessments	Taper Period (8 to 16 days)		Safety Follow-Up Period (30 days)[a]	
Visit	**T4**[b]	**Taper Visit**[c]	**Safety Follow-Up Clinic Visit Days in Study: FSM+14 (±2)**	**Safety Follow-Up Telephone Contact Days in Study: FSM+30 (-1/+3)**
Study Day	**32**[d]	**36/40/44**[c,d]	**50/54/58**[d]	**66/70/74/93**[d]

judgment.

[g] A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recording. The recordings should be made approximately 20 to 30 minutes apart.

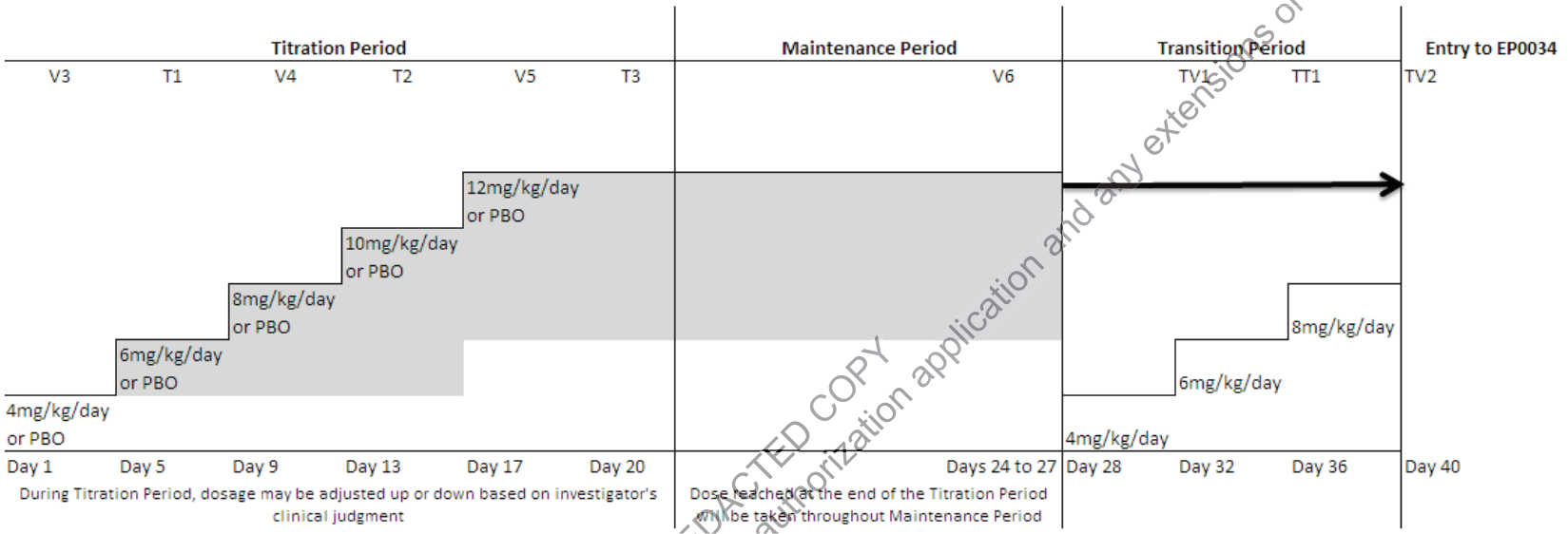
[h] The assessment will be required for subjects with a clinically significant abnormal value (clinical chemistry or hematology) or reading (ECG) at the previous clinic visit. For non-clinically significant abnormalities, repeat of these assessments is at the discretion of the investigator.

[i] Dosing instructions will be provided to the caregiver(s). See Section 7.2.3 for additional details on dosing options.

5.3 Schematic diagram

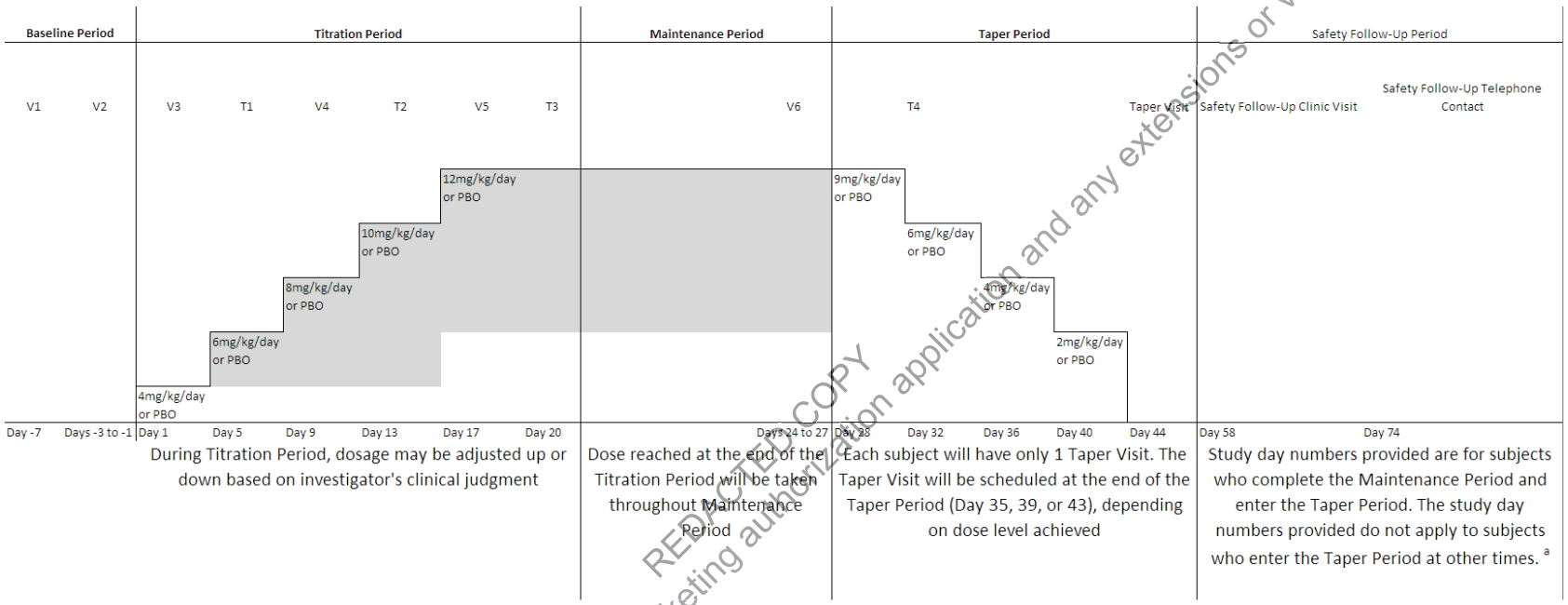
An overall schematic diagram for subjects entering EP0034 is provided in Figure 5–1. An overall schematic diagram for subjects not entering EP0034 is provided in Figure 5–2.

Figure 5–1: Subjects entering EP0034 open-label extension study



PBO=placebo; T=Telephone Contact; TT=Transition Telephone Contact; TV=Transition Visit; V=Visit

Figure 5–2: Subjects not entering EP0034 open-label extension study



[a] Subjects progressing to the end of the Transition Period, but then not entering EP0034 and instead entering the Transition Period followed by the Taper Period would complete the Safety Follow-Up Period at Day 93.

PBO=placebo; T=Telephone Contact; V=Visit

5.4 Rationale for study design and selection of dose

Epilepsy is a condition for which an improved benefit/risk ratio for medicinal products remains a challenge; this is especially true for pediatric patients. Based on the demonstrated efficacy and safety of LCM as adjunctive treatment in subjects aged ≥16 years of age, and the experience with other AEDs in pediatric subjects, it is likely that LCM will be an efficacious and safe treatment in the pediatric population with uncontrolled partial-onset seizures.

SP0967 is a Phase 3, multicenter, double-blind, randomized, PBO-controlled, parallel-group study to evaluate the efficacy and safety of LCM as adjunctive therapy in subjects ≥1 month to <4 years of age with epilepsy who have uncontrolled partial-onset seizures.

Based on the currently available LCM pediatric PK, safety, and tolerability data from SP847 and SP1047, as well as on information available in the medical literature, the recommendations for SP0967 are as follows:

- Subjects must weigh ≥4kg to <30kg at Visit 1.
- Feeding tube administration is permitted for subjects who are unable to swallow the oral solution.
- Titration should occur over a 20-day period; with LCM dose increased by 2mg/kg/day every 4 days until the target dose (LCM 8mg/kg/day to 12mg/kg/day, or matching PBO) is achieved. All subjects will start on a dose of LCM 4mg/kg/day or matching PBO at the start of the Titration Period.
- During the Titration Period, step-back titration by LCM 1mg/kg/day or LCM 2mg/kg/day will be permitted to allow subjects with reduced tolerability to remain in the study depending on tolerability (ie, based on investigator judgment and legal representative[s]/caregiver[s] feedback). If study medication is back titrated, the dose must never be lower than LCM 4mg/kg/day (or matching PBO) and must be maintained for ≥3 days (in order to reach steady state) before subsequent titration to a higher dose.
- During the Titration Period, subjects may also have the dose of study medication held steady or titrated to a higher dose. If study medication is titrated to a higher dose, the subject must remain on that dose for ≥4 days unless a step-back titration based on tolerability is required.
- The LCM dose should remain fixed over the Maintenance Period.

Based on US FDA and EMA requirements, 2 (co-) primary efficacy variables have been defined for this study based on electrographic partial-onset seizures with or without clinical correlate depending upon subject age. The primary efficacy variable will be the change in ADF of electrographic partial-onset seizures (US) or proportion of subjects experiencing ≥50% reduction in their ADF of electrographic partial-onset seizures (EU) as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG. At the request of FDA, a contingent primary efficacy variable has also been defined based on the percentage of subjects who discontinue early from the study prior to completing the End-of-Maintenance Period video-EEG. Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy parameter for the US will become identical to the primary efficacy parameter for the EU.

The endpoint not designated as primary will still be summarized as a secondary efficacy parameter.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and date by the parent(s) or legal representative(s)/caregiver(s) (in accordance with local regulation).
2. Subject's parent(s) or legal representative(s)/caregiver(s) is considered reliable and capable of adhering to the protocol visit schedule or medication intake according to the judgment of the investigator.
3. Subject is male or female from ≥1 month (ie, 4 weeks after full term [37 weeks gestational age]) to <4 years of age. For preterm infants <1 year old, the corrected gestational age should be used when determining eligibility. The generally accepted definition of corrected gestational age, which is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age, will be used for this study.
4. Subject has a diagnosis of epilepsy with partial-onset seizures. The results of ≥1 prior EEG and ≥1 magnetic resonance imaging/computerized tomography scan should be consistent with this diagnosis.
5. Subject weighs ≥4kg to <30kg at Visit 1.

7. Subject has experienced ≥2 partial-onset seizures with or without secondary generalization during each consecutive 7-day period during the 2 weeks prior to Visit 1.

8a. Subject has ≥2 partial-onset seizures with or without secondary generalization during the End-of-Baseline video-EEG. Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.

9. Subject is on a stable (concurrently or sequentially) dosage regimen of 1 to 3 AEDs. The dosage regimen of concomitant AED therapy must be kept constant for a period of ≥2 weeks prior to Visit 1. A stable daily dosage regimen of a concomitant benzodiazepine (BZD) will be considered as a concomitant AED.
10. Vagus nerve stimulation is allowed and will not be counted as a concomitant AED. The VNS device must have been implanted for ≥6 months prior to Visit 1; device settings must be kept stable for ≥2 weeks prior to Visit 1 and kept stable during the Baseline, Treatment, and Transition Periods. Use of the VNS device magnet is allowed.
11. Subject is an acceptable candidate for venipuncture.

6.2 Exclusion criteria

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

1a. Subject has been previously randomized in this study (re-screening for screen-failed subjects is only allowed with prior consultation and permission of the medical monitor).

2. Subject has participated in another study of an investigational medicinal product (IMP) or a medical device during the 2 months immediately prior to Visit 1 or is currently participating in another study of an IMP or a medical device.

3. 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.

4a. Subject has been previously treated with LCM and the LCM treatment was stopped due to lack of efficacy or adverse event(s).

5. Subject has a known hypersensitivity to any component of the study medication.

6. Subject has a medical condition that could be expected, in the opinion of the investigator, to interfere with study medication absorption, distribution, metabolism, or excretion.

7. Subject has experienced febrile seizures exclusively. The occurrence of febrile seizures in addition to partial-onset seizures is not exclusionary.

8a. Subject is on a ketogenic diet that has either changed within the 4 weeks prior to Visit 1 or is expected to change during the study.

9a. Subject has creatinine clearance <30mL/minute.

10. Subject has a clinically relevant ECG abnormality, in the opinion of the investigator (eg, second or third degree heart block at rest or a corrected QT interval [QTc] ≥450ms).

11. Subject has a hemodynamically significant congenital heart disease.

12. Subject has an arrhythmic heart condition requiring medical therapy.

13. Subject has a known history of severe anaphylactic reaction secondary to medication intake or serious blood dyscrasias.

14. Subject has nonepileptic events that could be confused with seizures. Subjects may be included if epileptic events can be clearly distinguished and the frequency meets the study inclusion criteria.

15a. Subject has a current diagnosis of Lennox-Gastaut syndrome, epilepsia partialis continua, primary generalized epilepsy, Dravet Syndrome, or seizures that are not of partial-onset origin.

16a. Subject has a history of generalized convulsive status epilepticus ≤2 months prior to Screening (Visit 1).

19. Subject has been treated with felbamate and has experienced any serious toxicity issues (defined as liver failure, aplastic anemia) with this treatment. Subjects treated with felbamate for <12 months are excluded. Subjects treated with felbamate for ≥12 months prior to Visit 1 and who have not experienced serious toxicity issues are eligible.

20. Subject has an acute or subacutely progressive central nervous system disease. Subject has epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease (malignant brain tumor or Rasmussen Syndrome).

21a. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.

22. 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.

6.3 Withdrawal criteria

Parent(s)/legal representative(s) are free to withdraw the subject from the study at any time, without prejudice to their continued care. The following criteria for subject withdrawal from SP0967 are outlined below. Additional discontinuation criteria for potential drug-induced liver injury (PDILI) are presented in Section 6.3.1.

Subjects **must** be withdrawn from the study if any of the following events occur:

1. Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study.

    Subjects who are unable to tolerate study medication will be withdrawn from the study as follows:

- Subjects unable to achieve or maintain target dose for the final 3 days of the Titration Period

2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject has QTc interval of ≥500ms that is confirmed by a cardiologist over-read on any ECG.
4. Subject develops a second or third degree atrioventricular (AV) block.
5. Subject is unwilling or unable to continue, or the parent(s)/legal representative(s)/caregiver(s) is unwilling or unable to allow the subject to continue in the study.
6. Investigator's decision that withdrawal from further participation would be in the subject's best interest.
7. Subject experiences generalized convulsive status epilepticus.

Subjects **may** be withdrawn from the study if any of the following events occur:

1. Subject has any clinically relevant change in medical or psychiatric condition and 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's legal representative(s)/caregiver(s) (in accordance with local regulation) is noncompliant with study procedures or medication, in the opinion of the investigator.
5. Subject uses BZDs within 24 hours prior to or during video-EEG for any reason other than a stable daily dosage regimen as a concomitant AED. The Medical Monitor should be contacted if withdrawal is being considered. Use of a stable daily dosage regimen of a concomitant BZD (ie, 1 of the Baseline concomitant AED[s]) should be maintained for the video-EEG procedures.

Investigators should attempt to obtain information for subjects who withdraw. For subjects considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the parent[s] or legal representative[s]/caregiver[s]), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the 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.

Subjects withdrawn from the study will proceed to the blinded Taper Period described in Section 7.2.4 and the assessments described in Table 5–3 will be performed.

Subjects who are withdrawn from the study will not be replaced.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury 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 11.6.1. 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.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

Investigational medicinal product will be provided as LCM oral solution (LCM 10mg/mL) and matching PBO. The LCM 10mg/mL oral solution and matching PBO oral solution are colorless to pale yellow in appearance. Both oral solutions will be packaged in amber polyethylene terephthalate (PET) bottles.

Study medication will be measured and administered via a dosing syringe. If a subject is unable to swallow the oral solution, administration by feeding tube will be permitted.

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.

7.2 Treatment(s) to be administered

At Visit 3, subjects will be randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or PBO in a 1:1 ratio. Randomization will occur after completion of the End-of-Baseline video-EEG and after confirmation that the subject has met selection criteria. Randomization will be stratified by age category (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age).

At the end of Visit 3, subjects should take the first dose of study medication while in the clinic. At each subsequent clinic visit, subjects should take study medication (and any concomitant AEDs) at the regular time(s). Study medication will be administered orally bid (at approximately 12-hour intervals in the morning and in the evening).

SP0967 will target Maintenance Period doses of LCM 8mg/kg/day to 12mg/kg/day or matching PBO.

7.2.1 Titration Period

Subjects will be dispensed study medication and will begin treatment with LCM oral solution at a dose of LCM 4mg/kg/day or matching PBO. Table 7–1 provides the recommended LCM (or matching PBO) dosing schedule during the Titration Period for subjects to reach the target doses for the Maintenance Period.

Table 7–1: Recommended dosing schedule for LCM (or matching PBO) during the Titration Period

Target LCM (or matching PBO) doses for the Titration Period				
Day 1 to Day 4	**Day 5 to Day 8**	**Day 9 to Day 12**	**Day 13 to Day 16**	**Day 17 to Day 20**
4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/day	12mg/kg/day

LCM=lacosamide; PBO=placebo

Dosing flexibility during the Titration Period based on tolerability is allowed in SP0967. After completion of Day 4, investigators will assess whether a subject would tolerate a further dose increase or whether a subject should hold the dose for a longer duration. In addition to holds, subjects may have the study medication titrated to a higher dose or back titrated by LCM 1mg/kg/day or 2mg/kg/day (or matching PBO) steps. If study medication is titrated to a higher dose, the subject should remain on the higher dose for ≥4 days unless a back-titration step based on tolerability is required.

If study medication is back titrated, the back titrated dose must never be lower than LCM 4mg/kg/day (or matching PBO) and be maintained for ≥3 days before a subsequent dose increase. After study medication is back titrated, if a subject returns to a higher dose previously administered, the dose must be maintained for ≥3 days (in order to reach steady state) before subsequent titration to a higher dose. After study medication is back titrated, if a subject subsequently receives a higher dose not previously administered, that dose should be maintained for ≥4 days unless tolerability concerns require a back titration.

There is no limit to the number of titration steps or dose holds allowed and all are at the investigator's discretion; however, subjects must achieve at least the minimum target dose of study medication (LCM 8mg/kg/day or matching PBO) for the final 3 days of the Titration Period. If it becomes apparent that the subject will not be able to reach the minimum target dose, then the subject should be withdrawn from the Titration Period and enter the Taper Period.

No adjustments in dose of study medication will be permitted after Day 20. Subjects who are not able to tolerate the study medication at an earlier time point during the Titration Period or who are not able to tolerate the reduced dose at the end of the Titration Period will be withdrawn from the study and enter the blinded Taper Period. Subjects who withdraw during the Transition Period will also enter the blinded Taper Period.

7.2.2 Maintenance Period

Subjects who achieve at least the minimum target dose of study medication (LCM 8mg/kg/day or matching PBO) for the final 3 days of the Titration Period will enter the 7-day blinded Maintenance Period on the dose achieved at the end of the Titration Period and will continue to receive this dose for the duration of the Maintenance Period. No adjustments to study medication dose will be allowed during the Maintenance Period.

Subjects who complete the Maintenance Period will be offered the opportunity to enroll in an open-label extension study (EP0034). Eligible subjects who choose to enroll in EP0034 will proceed to a blinded 12-day Transition Period.

7.2.3 Transition Period

During the Transition Period, subjects randomized to PBO will be transitioned in a double-blind manner from PBO to LCM 8mg/kg/day over a 12-day period. Transition dosing will be administered according to Table 7–2. Subjects randomized to LCM will remain on their Maintenance Period dose during the Transition Period.

Table 7–2: Transition Period LCM dosing schedule for subjects randomized to PBO

Maintenance Period	LCM doses for the Transition Period		
	Day 28 to Day 31	Day 32 to Day 35	Day 36 to 39
PBO	4mg/kg/day	6mg/kg/day	8mg/kg/day

LCM=lacosamide; PBO=placebo

At Visit 1 of EP0034, all subjects will transition to a dose of LCM 10mg/kg/day. The SP0967 final Transition Visit is the same as Visit 1 of EP0034.

7.2.4 Taper Period

Subjects who are not eligible for or who choose not to enter EP0034, or subjects who do not complete the Maintenance Period, will proceed to a blinded Taper Period of 8 to 16 days during which treatment with study medication will be withdrawn. The taper steps will be based on the dose of LCM (or matching PBO) achieved during the Maintenance Period according to Table 7-3. A slower taper is permitted if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

Subjects who are withdrawn during either the Titration Period or the Transition Period will also proceed to the Taper Period, and study medication will be tapered starting at the respective dose achieved during the Titration Period or the Transition Period. At the discretion of the investigator, AEDs may be added or adjusted and VNS adjustments may be made once the subject enters the Taper Period.

Table 7-3: Dosing of LCM (or matching PBO) during the Taper Period

LCM (or matching PBO) dose achieved	LCM (or matching PBO) doses for the Taper Period			
	Day 28 to Day 31	Day 32 to Day 35	Day 36 to Day 39	Day 40 to Day 43
11 or 12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9 or 10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7 or 8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day
5 or 6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day	NA
4mg/kg/day	2mg/kg/day	2mg/kg/day	NA	NA

LCM=lacosamide; NA=not applicable; PBO=placebo
Note: The study day numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study day numbers provided do not apply to subjects who enter the Taper Period at other times.

Subjects who enter the Taper Period will return for the Taper Visit at the end of the Taper Period.

Taper of LCM may not be required for some subjects who are on the lowest dose of study medication or who need to discontinue study medication abruptly, depending on the treatment option selected by the investigator in consultation with the medical monitor.

7.3 Packaging

Lacosamide and matching PBO are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

Lacosamide 10mg/mL oral solution and matching PBO will be packaged in amber PET bottles, and will be measured and administered via a dosing syringe.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product 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 or 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‘s legal representative(s)/caregiver(s) (in accordance with local regulation) to store the IMP following the instructions on the label.

7.6 Drug accountability

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

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 IMP 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 IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB's designee. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

At each visit after IMP is dispensed, subjects must return all used, unused, IMP and empty IMP containers. Drug accountability must be done in the presence of the subject's parent(s)/legal representative(s)/caregiver(s) in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant (defined as <75% or >125% compliant with the dosage schedule), the sponsor, in conjunction with the investigator, will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant medications/treatments

7.8.1 Permitted and prohibited concomitant treatments (medications and therapies)

Subjects must have been maintained on a stable dosage regimen of 1 to 3 marketed AEDs for ≥2 weeks prior to Visit 1.

Vagus nerve stimulation is allowed and will not be counted as concomitant AED use. The VNS device must have been implanted for ≥6 months prior to Visit 1, kept at a stable setting for ≥2 weeks prior to Visit 1, and kept stable during the Baseline, Treatment, and Transition Periods. Use of the VNS device magnet is allowed.

For subjects who enter the Taper Period, AEDs may be added or adjusted and VNS adjustments may be made at the discretion of the investigator.

The following concomitant medications are prohibited during the study:

- Clozapine
- Monoamine oxidase-A inhibitors
- Barbiturates (except as AEDs)
- Cannabidiols (not approved or indicated for epilepsy by local health authority)

Neuroleptics (except for clozapine) are allowed during the study but the investigator should make every effort to keep the dose stable.

Subjects who have been treated with felbamate and have experienced any serious toxicity issues are excluded from the study. Any subject who is currently treated with felbamate, and has received felbamate for a period of less than 12 months, is excluded from the study. Subjects treated with felbamate for ≥12 months prior to Visit 1 and who have not experienced serious toxicity issues are eligible.

The following medications are not allowed unless used as described:

- Amphetamines: stable use only.

A stable daily dosage regimen of concomitant BZDs will be considered as a concomitant AED. Such use is permitted throughout the study and should be maintained for the video-EEG procedures. Use of BZDs as rescue medications (ie, not as part of a stable daily dosing regimen) is permitted. However, use of BZDs for any reason other than a stable daily dosage regimen as concomitant AED within 24 hours prior to or during the video-EEG is not permitted and may lead to the subject being withdrawn from the study (**May** Withdrawal Criterion 5; Section 6.3).

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. In cases where this occurs but withdrawal criteria have not been met, the advisability of the subject's continuation in the study must be discussed between the Medical Monitor and the investigator. Other medications are permitted according to current clinical standards (eg, topical anesthetic).

7.8.2 Rescue medication

Use of BZDs as rescue medications (ie, not as part of a daily regimen) is permitted. However, use of BZDs for rescue within 24 hours prior to or during video-EEG recording is not permitted.

7.9 Blinding

Subjects, investigators, and all site personnel are blinded to study medication.

Lacosamide and PBO oral solutions are colorless to pale yellow solutions packaged in amber PET bottles. The blind is maintained as the accompanying packaging is identical in appearance so that neither the investigator/investigator's designee nor the subject is able to tell whether the subject is receiving LCM or PBO.

An interactive voice/web response system (IXRS) will be used to assign a treatment to subjects who meet eligibility criteria at Visit 3, based on a predetermined randomization schedule. The IXRS is used to control all drug distribution and inventory for this study.

The IXRS will be responsible for subsequent issue of treatment kits, as appropriate to the visit schedule.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the IXRS.

7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to treatment arm and dose the subject has been allocated by contacting the IXRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The Clinical Project Manager will be informed immediately via the IXRS when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the investigator must be recorded in the source documents and on the Study Termination

eCRF page. Subjects whose treatment is unblinded will be discontinued from the study and tapered off of LCM as noted in Table 7-3.

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined randomization schedule provided by UCB or its designee.

To enroll a subject (Visit 1), the investigator will contact the IXRS and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at Screening which serves as the subject identifier throughout the study. The subject number will be required in all communication between the investigator/investigator's designee and the IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

To randomize a subject (Visit 3), the investigator (or designee) will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will allocate kit numbers to the subject based on the subject number during the course of the study.

Randomization will be stratified by age category (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age).

8 STUDY PROCEDURES BY VISIT

Detailed tabular schedules of study procedures are provided in Section 5.2. The subject should take concomitant AEDs at the usual time(s) on the morning of each clinic visit.

At all visits and telephone contacts, subjects will be instructed to call the investigator if any intolerable and/or serious AEs (SAEs) occur before the next visit or contact. After subjects begin study medication, if any AEs necessitate a subject's withdrawal from the study, the subject should come in for a clinic visit as soon as possible after the occurrence of the AE.

Planned clinic visits should be scheduled as indicated in Section 5.2 with a window of ±2 days relative to Visit 3 (Baseline Period), with the exception of the Safety Follow-Up Clinic Visit, which should be scheduled 14 days (±2 days) after the final dose of study medication, and the Safety Follow-Up Telephone Contact, which should be scheduled 30 days (-1/+3 days) after the final dose of study medication.

8.1 Baseline Period: Visit 1 (Day -7) to Visit 2 (Day -3 to Day -1)

At Visit 1 (Day -7), subjects who meet the selection criteria will begin a 7-day Baseline Period (Day -7 to Day -1). Visit 1 may occur over more than 1 day; however, all results of Visit 1 assessments should be available before Visit 3. In the event that additional time is needed to access inpatient facilities to perform the video-EEG, a maximum of 7 days may be added to the period between Visit 1 and 2. During the Baseline Period, study visits are scheduled on Days -7, -3, -2, and -1.

8.1.1 Baseline Period: Visit 1 (Day -7)

At Visit 1, subjects will be evaluated for their suitability for enrollment. It is acceptable for this visit to be conducted on more than 1 day; however, all results of Visit 1 assessments should be available prior to randomization. Prior to the conduct of any study-related procedures, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the subject's parent(s)/legal representative(s) by the investigator (or designee). The

parent(s)/legal representative(s) of the subject is required to sign and date the IRB/IEC-approved informed consent if he/she decides to participate in the study.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature of an informed consent prior to any study-related procedures or evaluations, and the results of the following pretreatment assessments (for further details of the assessments and the required procedures and methods, refer to Section 9, Section 10, and Section 11 of this protocol):

- Informed consent
- Demographics (date of birth [where permitted], age group category, age in months and years, race, ethnicity, and gender)
- Inclusion/exclusion criteria
- Medical history
- Seizure history/count
- Concomitant medications (including any current medication intake as well as any medications taken ≤30 days prior to Visit 1)
- Concomitant AEDs (including any current medication intake as well as any previous AED taken prior to Visit 1)
- VNS assessment (if applicable)
- Physical examination (complete)
- Vital signs (including BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Height
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings [approximately 20 to 30 minutes apart] to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry/hematology
- Contact IXRS
- AE reporting

8.1.2 Baseline Period: Visit 2 (Day -3 to Day -1)

From Visit 2 (Day -3 to Day -1) to Visit 3 (Day 1), an End-of-Baseline video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) will be performed. The Day -3 assessments should be conducted prior to the start of video-EEG monitoring. The video-EEG will be conducted in an inpatient setting. Upon

completion of the End-of-Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the End-of-Baseline video-EEG data, the subject may be randomized at Visit 3. Assessment of the video-EEG seizure count will also be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of study analyses; however, completion of this review is not required prior to randomization.

During Visit 2, the following assessments will be performed:

- Inclusion/exclusion criteria (Day -3 only)
- Concomitant medications
- Concomitant AEDs
- VNS assessment (Day -3 only and only if applicable)
- Physical examination (brief) (Day -3 only)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment; Day -3 only)
- Body weight (Day -3 only)
- Neurological examination (brief) (Day -3 only)
- Video-EEG
- Rescue medication assessment
- AE reporting
- Review withdrawal criteria

8.2 Titration Period: Visit 3 (Day 1) to Telephone Contact 3 (Day 20)

Beginning with Visit 3 at Day 1 and continuing up to Telephone Contact 3 at Day 20, telephone contacts and clinic visits will be conducted during the Titration Period.

Subjects will be randomized into a treatment arm and study medication will be dispensed. The subject will take the first dose of study medication in the clinic. The subject will be instructed to call the investigator if any intolerable and/or SAEs occur. If any change in the study medication is required, the subject should come in for a clinic visit as soon as possible.

During the Titration Period, visits are scheduled on Days 1, 9, and 17, and telephone contacts are scheduled on Days 5, 13, and 20.

8.2.1 Titration Period: Visit 3 (Day 1)

Randomization and initial dispensing of study medication will occur at Visit 3 and after the completion of the video-EEG and confirmation that the subject has met selection criteria.

During Visit 3, the following assessments will be performed:

- Inclusion/exclusion criteria

- Concomitant medications
- Concomitant AEDs
- 12-lead ECG will be at the discretion of the investigator. The ECG (2 interpretable recordings [approximately 20 to 30 minutes apart] to be performed, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Video-EEG (End-of-Baseline video-EEG)
- Rescue medication assessment
- Contact IXRS
- Randomization
- Dispense study medication and administer first dose of study medication before the conclusion of visit
- AE reporting
- Review withdrawal criteria
- Healthcare resource use
- Investigators must make every attempt to administer the Bayley-III scales (for subjects who are <18 months of age who originate in English-speaking countries)
- BRIEF-P score
- PedsQL score
- Achenbach CBCL (the CBCL/1½-5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at Visit 3)

8.2.2 Titration Period: Telephone Contact 1 (Day 5), Telephone Contact 2 (Day 13), and Telephone Contact 3 (Day 20)

During the Titration Period telephone contacts (Telephone Contact 1, Telephone Contact 2, and Telephone Contact 3), the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- AE reporting
- Review withdrawal criteria
- Dosing instructions

At Telephone Contact 3, in addition to the procedures noted, the investigator or designee will confirm that the subject has tolerated study medication. After Day 20, the dose must remain stable.

8.2.3 Titration Period: Visit 4 (Day 9)

At Visit 4, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Neurological examination (brief)
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Review withdrawal criteria

8.2.4 Titration Period: Visit 5 (Day 17)

During Visit 5, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Neurological examination (brief)
- 12-lead ECG (2 interpretable recordings [approximately 20 to 30 minutes apart] to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Blood sample for clinical chemistry/hematology
- Blood sample for determination of LCM plasma concentration
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Review withdrawal criteria

8.3 Maintenance Period: Visit 6/Early Termination (Day 24 to Day 27)

Subjects completing the Titration Period will enter the Maintenance Period and continue on the final dose of LCM achieved during the Titration Period. Dose reduction or escalation during the Maintenance Period is not permitted. Subjects who are withdrawn will enter the Taper Period (see Section 7.2.4). Subjects who complete the Maintenance Period may be eligible to participate in the open-label extension study (EP0034).

During the Maintenance Period, study visits are scheduled on Days 24 to 27. The subject should take concomitant AEDs and study medication at the usual time(s) on the morning of each clinic visit.

8.3.1 Maintenance Period: Visit 6/Early Termination (Day 24, Day 25, and Day 26)

The Day 24 assessments should be conducted prior to the start of the End-of Maintenance Period video-EEG monitoring (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording). Assessment of video-EEG seizure count will be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of the study analyses. The following assessments will be performed on Day 24 for all subjects:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Neurological examination (brief)
- Video-EEG
- Rescue medication assessment
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Review withdrawal criteria

The following assessments will be performed on Day 25 and Day 26 during the video-EEG:

- Concomitant medications
- Concomitant AEDs
- Rescue medication assessment

- AE reporting
- Review withdrawal criteria

8.3.2 Maintenance Period: Visit 6/Early Termination (Day 27)

On the final day of the Maintenance Period, the following assessments will be performed after the completion of the End of Maintenance Period video-EEG:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Height
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings [approximately 20 to 30 minutes apart] to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Blood sample for clinical chemistry/hematology
- Blood sample for determination of LCM plasma concentration
- Clinical Global Impression of Change
- Caregiver's Global Impressions of Change
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Rescue medication assessment
- Review withdrawal criteria
- Healthcare resource use
- PedsQL (same version used at Visit 3)

8.4 Transition Period: Transition Visit 1 (Day 32) to Transition Visit 2 (Day 40)

Eligible subjects who choose to enter EP0034 will enter a 12-day Transition Period upon completion of the Maintenance Period.

During the Transition Period, subjects assigned to PBO will be transitioned in a double-blind manner from PBO to LCM 8mg/kg/day over a 12-day period according to the schedule shown in Table 7–2. Subjects assigned to LCM 8mg/kg/day to 12mg/kg/day will remain at the dose achieved during the Maintenance Period. At the entry visit of EP0034, all subjects will transition to a dose of LCM 10mg/kg/day.

During the Transition Period, study visits will be scheduled on Days 32 and 40, and a telephone contact will be conducted on Day 36.

8.4.1 Transition Period: Transition Visit 1 (Day 32)

During Transition Visit 1, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Neurological examination (brief)
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Review withdrawal criteria

8.4.2 Transition Period: Transition Telephone Contact 1 (Day 36)

During Transition Telephone Contact 1, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- AE reporting
- Review withdrawal criteria
- Dosing instructions

8.4.3 Transition Period: Transition Visit 2 (Day 40)

Transition Visit 2 will also serve as Visit 1 for EP0034.

During Transition Visit 2, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings [approximately 20 to 30 minutes apart] to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Blood sample for clinical chemistry/hematology
- Contact IXRS
- Return study medication
- AE reporting
- Review withdrawal criteria

8.5 Taper Period: Telephone Contact 4 (Day 32) and Taper Visit (Day 36, Day 40, or Day 44)

A blinded Taper Period (8 to 16 days, depending on the dose level achieved) will be required for subjects who discontinue study medication prematurely and for subjects who complete the Maintenance Period but will not enroll in EP0034. Study medication will be tapered as described in Table 7-3.

During the Taper Period, a telephone contact will be conducted on Day 32 and a Taper Visit will be scheduled at the end of the Taper Period, on Day 36, 40, or 44. Note that the study day numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period; the study day numbers provided do not apply to subjects who enter the Taper Period at other times.

8.5.1 Taper Period: Telephone Contact 4 (Day 32)

During Telephone Contact 4, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- AE reporting

- Review withdrawal criteria

8.5.2 Taper Period: Taper Visit (Day 36, Day 40, or Day 44)

A Taper Visit will be scheduled at the end of the Taper Period (Day 36, 40, or 44), depending on dose level achieved.

During the Taper Visit, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Neurological examination (brief)
- 12-lead ECG will be required for subjects with a clinically significant abnormal reading at the previous clinic visit. For non-clinically significant abnormalities, repeat of this assessment is at the discretion of the investigator. The ECGs (2 interpretable recordings [approximately 20 to 30 minutes apart] is to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Blood sample for clinical chemistry/hematology collection will be required for subjects with a clinically significant abnormal value at the previous clinic visit. For non-clinically significant abnormalities, repeat of these assessments are at the discretion of the investigator.
- Contact IXRS
- Dosing instructions
- Return study medication
- AE reporting
- Review withdrawal criteria

8.6 Safety Follow-Up Period

There will be a 30-day Safety Follow-Up Period for all subjects who will not be entering EP0034.

8.6.1 Safety Follow-Up Period: Safety Follow-Up Clinic Visit (Day 50, Day 54, or Day 58)

The Safety Follow-Up Clinic Visit will occur 14 days (±2 days) after the final dose of study medication and will include the following assessments:

- Concomitant medications

- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Neurological examination (complete)
- 12-lead ECG will be required for subjects with a clinically significant abnormal reading at the previous clinic visit. For non-clinically significant abnormalities, repeat of this assessment is at the discretion of the investigator.
- Blood sample for clinical chemistry/hematology collection will be required for subjects with a clinically significant abnormal value at the previous clinic visit. For non-clinically significant abnormalities, repeat of these assessments are at the discretion of the investigator.
- AE reporting

8.6.2 Safety Follow-Up Period: Safety Follow-Up Telephone Contact (Day 66, Day 70, Day 74, or Day 93)

The Safety Follow-Up Telephone Contact will occur 30 days (-1/+3 days) after the final dose of study medication and will include the following assessments:

- Concomitant medications
- Concomitant AEDs
- AE reporting

8.7 Unscheduled Visit

Unscheduled visits can be conducted at the discretion of the investigator (eg, due to an AE). During the Unscheduled Visit, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- AE reporting
- Review withdrawal criteria

In addition to the required assessments listed above, additional assessments may be performed at the investigator's discretion.

9 ASSESSMENT OF EFFICACY

9.1 Primary and secondary efficacy variables

The primary and secondary efficacy variables are based on the ADF of partial-onset seizures as measured on video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording).

Partial-onset seizure count will be based on electrographic seizures with or without clinical correlate depending upon age as specified below.

Partial-onset seizure frequency for infants aged ≥1 month to ≤6 months will be based on electrographic seizures. Partial-onset seizure frequency for children aged >6 months to <4 years will be based on electrographic seizures with an accompanying clinical correlate.

Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.

The video-EEG recordings will be evaluated for seizure counts locally by the investigator, subinvestigator, or qualified designated reader.

Calculation of the Baseline Period ADF of electrographic partial-onset seizures and the Maintenance Period ADF of electrographic partial-onset seizures will be based on results from a video-EEG during each period. Subjects are expected to have at least 48 hours of interpretable video-EEG during each period. For subjects who drop out during the End-of-Maintenance Period video-EEG, the number of hours from the start of the End-of-Maintenance Period video-EEG to the time of withdrawal (in hours) will be considered for analysis. Subjects who discontinue on or before Day 20 will not require a video-EEG.

9.2 Other efficacy assessments

9.2.1 Global Impression of Change

The Clinical and Caregiver's Global Impression of Change will be administered according to the tabular schedules of study procedures (Section 5.2).

The Clinical Global Impression of Change is a 7-point categorical rating scale in which the investigator assesses the subject's change from Baseline in clinical status, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status.

The Caregiver's Global Impression of Change is a 7-point categorical rating scale in which the caregiver(s) assesses the subject's change from Baseline in clinical status, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status.

9.2.2 PedsQL

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). The PedsQL will be administered only in countries where a translated version is available. The

version of the PedsQL used at Visit 3 (Baseline) should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Section 5.2).

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. Parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≤4 years of age.

The multidimensional PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. The PedsQL assessment is retrospective to the prior 4 weeks, and individual items are scored using a 5-point Likert scale (never, almost never, sometimes, often, or almost always). A total health summary score ranging between 0 and 100 is calculated from the sum of the raw scores, with higher scores indicating higher HRQoL.

9.2.3 Healthcare resource use

For healthcare resource use, the following will be evaluated: concomitant medications and AEDs, medical procedures, and healthcare provider consultations including hospitalizations not foreseen by the protocol.

10 ASSESSMENT OF PHARMACOKINETIC AND PHARMACODYNAMIC VARIABLES

Blood samples for the determination of LCM plasma concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). In each case, the time the subject took the most recent dose of study medication and the time of blood sampling must be recorded. Actual sampling times will be recorded in the eCRF to the minute.

Details of plasma sample collection and processing, sample labeling, and shipment will be provided in the laboratory manual.

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that 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 the signing of the Informed Consent form), 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. This includes all AEs not present prior to the initial visit and all AEs that 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.

11.1.1.1 Signs and symptoms of depression

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, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Each subject's parent(s)/legal representative(s)/caregiver(s) (in accordance with local regulation) should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

11.1.2 Procedures for reporting and recording adverse events

The subject's parent(s) and/or legal representative(s)/caregiver(s) will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about the subject's health (since your last visit)?"

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

11.1.3 Description of adverse events

When recording an AE, the investigator should use the 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 and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to study medication) are described in the eCRF Completion Guidelines.

11.1.4 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

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

11.1.5 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

11.1.6 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.

11.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

11.1.8 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP 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 representative.

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

11.2 Serious adverse events

11.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An 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 1 of the other outcomes listed in the definition of serious

(Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.3], 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 he/she is 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 1 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 criteria. 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.)

11.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, 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.

An Investigator SAE report form will be provided to the investigator. The Investigator SAE Report form must be completed in English.

It is important for the investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

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 investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), 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 SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

11.2.3 Follow up of serious adverse events

An 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 11.6.1.4.

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

11.3 Adverse events of special interest

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

The following are LCM's 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 (<45bpm)
- 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 US FDA

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

  Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
    - Eosinophils % ≥10%
    - Eosinophils absolute ≥0.5G/L
    - Neutrophils absolute <1.5G/L
    - Platelets ≤100G/L
    - ALT ≥2×ULN
    - AST ≥2×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.

11.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 11.3)

11.5 Anticipated serious adverse events

The following list of Anticipated SAEs (Table 11–1) 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 11.2.2.

Table 11–1: Anticipated SAEs for the pediatric epilepsy population

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

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

[a] Convulsion if consistent with the seizure type known for the subject.

11.6 Laboratory measurements

Blood specimens for routine assay of hematology and clinical chemistry testing will be collected according to the tabular schedule of study procedures (Section 5.2). A central laboratory will perform the routine analysis of blood specimens. The procedures for handling and shipping these specimens will be provided to the sites. In exceptional circumstances, local laboratory analysis may be performed. The medical monitor should be contacted beforehand to discuss these circumstances.

The laboratory tests to be performed are presented in Table 11–2 as follows:

Table 11–2: Laboratory measurements

Hematology	Clinical chemistry
Hematocrit	Calcium
Hemoglobin	Phosphorus
Platelet count	Serum electrolytes (sodium, potassium, chloride, bicarbonate)
RBC count	Creatinine
WBC count	BUN
Differential count	AST
	ALT
	Total bilirubin
	ALP
	GGT
	Glucose
	Albumin
	Total serum protein
	Uric acid
	Total cholesterol
	Triglycerides

ALP= alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyltransferase; RBC=red blood cell; WBC=white blood cell

Creatinine clearance will be estimated using the updated Schwartz bedside formula (Schwartz and Work, 2009).

11.6.1 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1 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 11.3), and, if applicable, also reported as an SAE (see Section 11.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). 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 11.6.1.4).

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 6.3.1), 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 11–3: 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 11.6.1.3); 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 11.6.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Table 11–3: 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 11.6.1.3)	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 11.6.1.1. 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.

11.6.1.1 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 11.6.1.3) and SAE report (if applicable).

11.6.1.2 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 6.3.1 and Table 11–3 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.

11.6.1.3 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 11–4 (laboratory measurements) and Table 11–5 (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 11–4: 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
	Differential count
Urinalysis	Toxicology screen
Chemistry	Amylase
	Bilirubin (If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin)
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
	AST
	ALT
	ALP
	GGT
	Albumin
Additional	Prothrombin time/INR[a]
	PK sample

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma-glutamyl transferase; 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 11–5: 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
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

11.6.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 11–3. 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.

11.7 Other safety measurements

11.7.1 Physical examination

Physical examinations will be performed according to the tabular schedule of study procedures (Section 5.2) by a medically qualified clinician licensed to perform the examination. Subsequent to Visit 1, clinically significant physical examination findings should be reported as AEs.

11.7.1.1 Complete physical examination

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

11.7.1.2 Brief physical examination

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

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

11.7.2 Neurological examination

Neurological examinations will be performed according to the tabular schedule of study procedures (Section 5.2) 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. Subsequent to Visit 1, clinically significant neurological examination findings should be reported as AEs.

11.7.2.1 Complete neurological examination

The complete neurological examination will include selected assessment of general neurological status (level of consciousness, mental status, speech), cranial nerves, reflexes, motor system (general motor status, muscle strength, muscle tone), coordination/cerebellar function, and sensation.

11.7.2.2 Brief neurological examination

The brief neurological examination will include selected assessment of general neurological status, reflexes, muscle strength, and coordination/cerebellar function.

11.7.3 Vital signs, body weight, and height

Noninvasive BP (systolic and diastolic) and pulse rate will be measured at clinic visits after at least 3 minutes at rest in a supine position, according to the tabular schedule of study procedures (Section 5.2). Assessment of orthostatic changes will be as follows: after the 3 minute measurement in a supine position, the subject is asked to stand up, and BP and pulse rate are taken 1 minute and 3 minutes after standing up, as feasible.

Body weight will be determined without shoes and wearing light clothing, and height will be measured without shoes. Body weight and height will be assessed according to the tabular schedule of study procedures (Section 5.2).

11.7.4 12-lead ECG

Standard 12-lead ECGs will be performed according to the tabular schedule of study assessments (Section 5.2). Care should be taken to assure proper lead placement and quality ECG recordings. Two interpretable recordings will be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding the ECG recording and the subject should be motionless during the recording. The second recording will be conducted approximately 20 to 30 minutes after the first recording.

11.7.5 Overall ECG interpretation

Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader and at a central ECG laboratory. If the reading identifies second or third degree AV block, a QTc ≥500ms, or another abnormal ECG finding that is assessed by the investigator to be clinically significant, then the ECG should be repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study (see Section 6.3). 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.

11.7.6 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)/caregiver(s). The CBCL/1½-5 checklist for children 18 months to 5 years and 11 months of age will be used in this study. The Achenbach CBCL/1½-5 will be completed by the parent(s)/legal representative(s)/caregiver(s) of subjects ≥18 months of age at Visit 3. The Achenbach CBCL will be administered only in countries where a translated version is available.

The scale will be completed in accordance with the tabular schedules of study procedures (Section 5.2) and should be completed by the same parent(s)/legal representative(s)/caregiver(s). The completion of the Achenbach CBCL will require approximately 45 minutes.

In the CBCL/1½-5 checklist, the occurrence of certain problems and behaviors at the time of administering the questionnaire or within the past 2 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.

Baseline assessment of the Achenbach CBCL will be performed at Visit 3; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.

11.7.7 BRIEF-P

The BRIEF-P is a validated tool that will be used for the evaluation of subjects ≥2 years of age and will be administered according to the tabular schedules of study procedures (Section 5.2). The BRIEF-P will be administered only in countries where a translated version is available.

The BRIEF-P includes rating forms used by parents to assess subjects' executive functioning within the context of the subject's everyday environment. It requires that the parent must have had recent and extensive contact with the child over the past 6 months. 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 overlapping indexes: Inhibitory Self-Control (Inhibit and Emotional Control), Flexibility (Shift and Emotional Control), and Emergent Metacognition (Working Memory and Plan/Organize) and 1 composite score (Global Executive Composite).

The BRIEF-P includes validity scales to measure negativity and inconsistency of responses.

Baseline assessment of the BRIEF-P will be performed at Visit 3; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.

11.7.8 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-III scales are a standardized, individually administered, adaptive assessment that measures the developmental functioning of infants and young pediatric subjects 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 (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.

The scales are validated as a tool for assessment of neurological development in young pediatric subjects and are therefore considered appropriate for SP0967.

The Bayley-III scales are an individually administered, adaptive assessment that presents pediatric subjects 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. It also has 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(s)/legal representative(s)/caregiver(s).

The completion of the Bayley-III scales will require approximately 50 minutes for pediatric subjects who are 12 months old or younger and 90 minutes for pediatric subjects aged 12 months to 18 months.

Investigators must make every attempt to administer the scale according to the tabular schedules of study procedures (Section 5.2). If needed, the investigators may utilize trained pediatric psychologists or other appropriately skilled individuals to administer the scale.

Due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor. After implementation of such measure, the investigator must notify the Clinical Project Manager (CPM) of the sponsor within 24 hours and follow any local regulatory requirements.

12.2 Monitoring

UCB (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 to a contract research organization (CRO) or a contract monitor.

The investigator and his/her staff are expected to cooperate with UCB (or designee) 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 inspection(s).

The investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authority(ies) regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments

(such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, 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 facilitate the process for enabling 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 electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

12.2.2 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, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 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 electronic eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

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. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. In the event that the 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.

12.3.3 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.

The subject's consent 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.

12.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused study medication and other material in accordance with UCB procedures for the study.

12.5 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [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.

12.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, 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).

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan (SAP).

13.1 Definition of analysis sets

The Safety Set (SS) will include all randomized subjects who took at least 1 dose of study medication. This is the primary analysis set for the safety variables.

The primary analysis set for the efficacy data will be the Full Analysis Set (FAS), which will include all subjects in the SS.

The secondary analysis set for the efficacy data will be the Per-Protocol Set (PPS), which includes all subjects in the FAS who did not have important protocol deviations related to efficacy.

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 visit with documented study medication intake times.

13.1.1 Analysis of the primary efficacy variable

Analyses of the primary efficacy variables are based on the ADF of electrographic partial-onset seizures.

Partial-onset seizure count will be based on electrographic seizures. Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds. The video-EEG recordings will be evaluated for seizure counts locally by the investigator, subinvestigator, or qualified designated reader. Subjects who discontinue on or before Day 20 will not require a video-EEG.

Partial-onset seizure frequency for infants aged ≥1 month to ≤6 months will be based on electrographic seizures. Partial-onset seizure frequency for children aged >6 months to <4 years will be based on electrographic seizures with an accompanying clinical correlate.

Calculation of the Baseline Period ADF of electrographic partial-onset seizures and the Maintenance Period ADF of electrographic partial-onset seizures will be based on results from a video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) during each period. Subjects are expected to have at least 48 hours of interpretable video-EEG during each period. For subjects who drop out during the End-of-Maintenance Period video-EEG, the number of hours from the start of the End-of-Maintenance Period video-EEG to the time of withdrawal (in hours) will be considered for analysis.

The ADF of electrographic partial-onset seizures will be calculated as (number of partial-onset seizures recorded on the video-EEG divided by the number of interpretable hours recorded) multiplied by 24.

13.1.1.1 Analysis of the primary efficacy variable for the US

Contingent upon ≤10% of subjects discontinuing early from the study, the primary efficacy parameter for the US is the change in ADF of electrographic partial-onset seizures during the Maintenance Period compared to the end of the Baseline Period. Seizure ADF will be analyzed using analysis of covariance with terms for treatment, age category (4 age stratification categories, pooled as appropriate), and center (properly pooled), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF. Log-transformed Baseline seizure ADF will be used as a covariate. The seizure ADF between LCM and PBO will be compared using least squares means (LSMs). The percent reduction over PBO will be estimated as 100 x (1 – exp [LSM Treatment {TRT} - LSMPBO]). The analysis of this efficacy variable will consist of all subjects in the FAS who have at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using the Baseline observation-carried-forward approach. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced by the overall mean ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG from the subject's respective treatment arm. This will be applied for all subjects who discontinued early from the study.

- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment arm and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using monotone regression. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis using the FAS for all subjects who have at least 24 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy parameter for the US is identical to the primary efficacy parameter for the EU, described below. The endpoint not designated as primary will still be summarized as a secondary efficacy parameter.

13.1.1.2 Analysis of the primary efficacy variable for the EU

The primary efficacy parameter for the EU is the proportion of responders during the Maintenance Period. Subjects with a 50% or more reduction in seizure ADF will be categorized as responders; this classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG. The proportion of responders between LCM and PBO will be analyzed using logistic regression with age category (4 age stratification categories, pooled as appropriate) and center (properly pooled) as factors. Subjects who withdraw or drop out before the first 48 hours of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non responders; all other subjects will be missing for this analysis. The number and percentage of subjects with a 50% or more reduction in seizure ADF will be presented by treatment group.

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except subjects who discontinued from the study prior to performance of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non responders, and subjects who discontinued from the study early for any other reason will be considered responders.
- Repeat the primary analysis using the FAS, except all subjects who discontinued from the study early will be considered non responders.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment arm and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using monotone regression. This will be applied for all subjects who discontinued from the study early, and the imputed End-of-Maintenance Period ADF of partial-onset seizures will be used to determine whether a subject is a responder.

- Repeat the primary analysis using the FAS for all subjects who have at least 24 hours of interpretable recordings during both the end of Baseline Period video-EEG and the end of Maintenance Period video-EEG.

13.1.2 Analysis of secondary efficacy variables

The percent change in ADF of electrographic partial-onset seizures is calculated as the seizure ADF during the End-of-Maintenance Period video-EEG minus the seizure ADF during the End-of-Baseline Period video-EEG divided by the seizure ADF at Baseline and then multiplied by 100. Descriptive statistics for ADF of electrographic partial-onset seizures and its absolute and percentage change from Baseline will be summarized by treatment group.

For subjects who complete the Maintenance Period, the number and percentage of subjects who achieved "seizure-free" status from all seizure types, and from partial-onset seizure types only during the Maintenance Period will be tabulated and presented by treatment group.

The number and percentage of subjects experiencing a ≥25% to <50%, 50 to 75%, or >75% reduction in ADF of partial-onset seizures will also be presented by treatment group, as will the number and percentage experiencing no change, and the number and percentage experiencing an increase ≥25%.

13.1.3 Other efficacy analyses

The number and percentage of subjects with each Clinical Global Impression of Change, Caregiver's Global Impression of Change, and the PedsQL health summary score will be summarized by treatment group.

Descriptive statistics will be presented by treatment group for the number of medical resources used during the study, healthcare provider consultations not related to study, procedures, hospital stays, and length of hospital stays.

13.2 Planned safety and other analyses

Descriptive statistics will be used to provide an overview of the safety and PK results.

13.2.1 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and tabulated by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be defined as those events that start on or after the date of first study medication administration and within 30 days following the date of final study medication administration, or whose severity worsens within this time frame. The incidence of TEAEs will be presented by SOC and PT. Serious AEs and TEAEs leading to withdrawal will also be tabulated and listed.

Other variables assessing safety are ECG, measurements of laboratory parameters (hematology and clinical chemistry) and vital signs (body weight, height and BMI), and physical and neurological examination findings.

Measurement and change from Baseline in vital signs (BP and pulse rate), body weight, laboratory parameters (hematology and clinical chemistry), and 12-lead ECG measurements will be summarized using descriptive statistics. When analyzing categorical data, the number and

percentage of subjects in each category will be presented by treatment group. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different postbaseline status when compared to their baseline status.

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

Baseline assessment of the Bayley-III scales, Achenbach CBCL, and BRIEF-P will be performed; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study and analysis of these data will be conducted in EP0034.

13.2.2 Pharmacokinetics and pharmacodynamics

13.2.2.1 Descriptive statistics of LCM and AED plasma concentrations

The results of LCM plasma concentrations will be summarized using descriptive statistics: arithmetic mean, standard deviation, median, range, geometric mean, and geometric coefficient of variation.

13.2.2.2 Population pharmacokinetics

A population exposure-response model (PK/pharmacodynamics) between LCM plasma concentration and seizure counts will be developed using NONMEM. The methods will be described in the DAP (Data Analysis Plan) and the results will be reported in a modeling report.

13.3 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on either primary efficacy outcome or key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. To the extent feasible the rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Important protocol deviations will be reviewed as part of the blinded data cleaning meetings prior to database lock to confirm exclusion from analysis sets.

13.4 Handling of dropouts or missing data

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

As described in Section 13.1.1, subjects are expected to have at least 48 hours of interpretable video-EEG during each period. For subjects who drop out during the End-of-Maintenance Period video-EEG, the number of hours from the start of the End-of-Maintenance Period video-EEG to the time of withdrawal (in hours) will be considered for analysis. Subjects who discontinue prior to the End-of-Maintenance Period video-EEG will not be included in the analyses (ie, data will not be carried forward from the End-of-Baseline Period video-EEG).

The impact of missing data on the assessment of primary efficacy will be evaluated with sensitivity analyses with further details to be included in the SAP.

No imputation of missing values associated with an individual date or visit is planned for the primary safety analysis, with the exception of partial date information for AEs and concomitant medications in order to determine whether they are treatment emergent.

13.5 Planned interim analysis and data monitoring

No formal interim analysis for determination of efficacy is planned for this study. To ensure subject safety, interim reviews of safety data will be performed using an Independent Data Monitoring Committee (IDMC). Serious adverse events and other significant events are monitored and will be triaged by the Medical Monitor and UCB Patient Safety in real time. After this triage, events will be passed on to the IDMC as appropriate. In addition, 3 interim reviews of safety data by the IDMC are planned when 25%, 50%, and 75% of subjects have been randomized and at study completion. The objective, procedures, and timing of IDMC safety assessments to evaluate risk and benefit for subjects in SP0967 will be described in an IDMC Charter.

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study, and have data available for analysis to check the validity of these assumptions using interim data from the study. The sample size re-estimation with equal allocation in each arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011). An assessment of the observed dropout rate will also be made as part of this analysis, and the potential dropout rate of 14% used for calculation of the initial sample size (see Section 13.6) will be modified based on the observed rate. Additionally, an assessment of the observed difference of End-of-Baseline Period video-EEG interpretation rate will be made; the anticipated rate of 5% will be modified based on the observed rate (see Section 13.6).

The final sample size will be modified according to the sample size re-estimate and also the anticipated dropout rate and anticipated rate of difference of interpretation of the End-of-Baseline Period video-EEG; however, an upper bound will be applied to reach a maximum sample size based on practical and logistical considerations. The initial sample size re-estimate using Guenther adjustment will not be adjusted above 109 subjects per treatment arm, the original estimated overall study drop-out rate will not be adjusted above 24%, and the difference of End-of-Baseline Period video-EEG interpretation rate will not be adjusted above 10%.

13.6 Determination of sample size

Assuming an effect size of 0.402, in which the effect size was calculated using a PBO-subtracted difference of -0.249 and a common standard deviation of 0.62 on the log-transformed data, the difference of -0.249 on the log-transformed data is equivalent to approximately 22% reduction over PBO after exponentiation. With this effect size, power of 80%, and a 2-sided test at the 5% level of significance, a sample of 99 subjects in each treatment arm will be needed.

Assuming a responder rate of 20% and 40% for the PBO and LCM groups, respectively, a 2-sided continuity corrected Chi-square test at a significance level of 5% will provide approximately 83% power with 99 subjects in the PBO group and 99 subjects in the LCM group.

Subjects are randomized into the study based on the initial interpretation of the video-EEG to meet study entry requirements. However, the subsequent detailed assessment of seizure types and counts needed for the efficacy analyses could lead to a discrepancy in seizure counts (ie, a subject initially thought to be eligible is later found to have fewer than the required number of partial-onset seizures during the End-of-Baseline Period video-EEG). To account for an anticipated difference of interpretation of the End-of-Baseline Period video-EEG of 5% as well as the potential subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study, and have data available for analysis to check the validity of these assumptions as described in Section 13.5.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

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

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

If the Informed Consent form is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the US must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject's legal representative(s) may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when his/her legal representative(s) has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained written consent from his/her legal representative(s) in order to participate in the study.

14.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative(s) will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency

contact information. The investigator will instruct the subject's parent(s)/legal representative(s)/caregiver(s) to keep the card with him/her at all times.

14.3 Institutional Review Boards and Independent Ethics Committees

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 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 will forward copies of the protocol, Informed Consent form, Investigator's Brochure, investigator's curriculum vitae (if applicable), 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 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.

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 (based on IRB/IEC requirements), 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.

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

14.4 Subject privacy

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

The investigator agrees that representatives of UCB, 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).

14.5 Protocol amendments

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.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and/or CRO agreements, as applicable.

16 REFERENCES

Aicardi J. Syndromic classification in the management of childhood epilepsy. J Child Neurol. 1994;9(Suppl 2):14-18.

Appleton R, Fichtner K, LaMoreaux L, Alexander J, Halsall G, Murray G, et al. Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study: Gabapentin Pediatric Study Group. Epilepsia. 1999;40:1147-54.

Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio: Pearson Education Inc; 2006.

Bayley N. Bayley Scales of Infant Development. 2nd ed. San Antonio: The Psychological Corporation; 1993.

Bourgeois BF, Goodkin HP. Efficacy of antiepileptic drugs in adults vs children: does one size fit all? Neurology. 2012;79;1420-1.

CHMP/EWP/566/98 Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (EMA) Rev 2, 20 Jan 2010.

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.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Dichek B. Epilepsy: an ancient ailment that still eludes a cure. Scrip Magazine. 1999;Feb:9-11.

Duchowny M, Pellock JM, Graf WD, Billard C, Gilman J, Casale E, et al. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children: Lamictal Pediatric Partial Seizure Study Group. Neurology. 1999;53:1724-31.

Elterman RD, Glauser TA, Wylie E, Reife R, Wu SC, Pledger G. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children: Topiramate YP Study Group. Neurology. 1999;52:1338-44.

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.

Friede T, Kieser M. Blinded sample size recalculation for clinical trials with normal data and baseline adjusted analysis. Pharm Stat. 2011;10:8-13.

Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CB, Gauer LJ, et al. on behalf of the N159b Study Group. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology. 2006;66:1654-60.

Glauser TA, Nigro M, Sachdeo R, Pasteris LA, Weinstein S, Abou-Khalil B, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures: the Oxcarbazepine Pediatric Study Group. Neurology. 2000;54:2237-44.

Hadjiloizou SM, Bourgeois BF. Antiepileptic drug treatment in children. Expert Rev Neurother. 2007;7:179-193.

Herman ST, Pedley TA. New options for the treatment of epilepsy. JAMA. 1998;280:693-4.

Institute of Medicine. Epilepsy across the spectrum: promoting health and understanding. Washington, DC: The National Academies Press; 2012.

Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: A systematic review. Neurology. 2012;79;1482-9.

Perucca E. Established antiepileptic drugs. Baillieres Clin Neurol. 1996;5:693-722.

Rheims S, Ryvlin P. Profile of perampanel and its potential in the treatment of partial onset seizures. Neuropsychiatr Dis Treat. 2013;9:629-37.

Sander JW. New drugs for epilepsy. Curr Opin Neurol. 1998;11:141-8.

Sattler JM, Hoge RD. Assessment of children: behavioral, social, and clinical foundations. 5th ed. La Mesa: Jerome M Sattler; 2006.

Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4:1832-43.

Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life version 4.0 generic core scales in healthy and patient populations. Med Care. 2001; 39:800-12

17 APPENDICES

17.1 AMENDMENT 1

Rationale for the amendment

The primary purposes of this amendment are to implement the contingent primary efficacy variable for the US, include sensitivity analyses for the primary endpoint, to clarify the enrollment of subjects <2 years of age, and to provide additional detail regarding the sample size re-estimation at the request of FDA.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Contact details for the Clinical Project Manager have been updated
- The Sponsor Declaration has been updated for electronic signature
- The language of the percentage of subjects <2years of age to be included in the study has been clarified
- The contingent primary efficacy variable for the US has been defined
- The anticipated SAE table has been updated to include a footnote for convulsion
- Text for adherence to the protocol has been updated
- Text for healthcare resource use has been updated
- Rescue medication assessment has been added
- Analysis of the primary efficacy variable for the US and EU has been updated
- The sensitivity analysis has been described
- Sample size re-estimation text has been further detailed

Specific changes

Change #1

SPONSOR DECLARATION

The Clinical Project Manager has changed.

Clinical Project Manager

[redacted]

_____
Date/Signature

Clinical Trial Biostatistician

[redacted], MA

_____
Date/Signature

Study Physician

[redacted], MD

_____
Date/Signature

Clinical Program Director

[redacted], BS

_____
Date/Signature

Has been revised and moved to Section 19:

19 SPONSOR DECLARATION

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

Change #2

STUDY CONTACT INFORMATION

The Clinical Project Manager contact details have been updated.

Name:	[redacted]
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Change #3

Section 1 SUMMARY

Reference to the Food and Drug Administration has been clarified that it is for the US and the contingent primary efficacy variable has been defined, 5th paragraph.

Based on Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements, 2 (co-) primary efficacy variables have been defined for this study based on electrographic partial-onset seizures with or without clinical correlate depending upon subject age. The primary efficacy variable will be the change in average daily frequency (ADF) of electrographic partial-onset seizures (US) or proportion of subjects experiencing ≥50% reduction in their ADF of electrographic partial-onset seizures (EU) as measured on the 72-hour end-of-Maintenance Period video-electroencephalogram (EEG) compared to the 72-hour end-of-Baseline Period video-EEG. Partial-onset seizures will be counted by a central reader evaluating the characteristic ictal patterns of electrographic seizures.

Has been changed to:

Based on US Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements, 2 (co-) primary efficacy variables have been defined for this study based on electrographic partial-onset seizures with or without clinical correlate depending upon subject age. The primary efficacy variable will be the change in average daily frequency (ADF) of electrographic partial-onset seizures (US) or proportion of subjects experiencing ≥50% reduction in their ADF of electrographic partial-onset seizures (EU) as measured on the 72-hour End-of-Maintenance Period video-electroencephalogram (EEG) compared to the 72-hour End-of-Baseline Period video-EEG. Partial-onset seizures will be counted by a central reader evaluating the characteristic ictal patterns of electrographic seizures. At the request of FDA, a contingent primary efficacy variable has also been defined based on the percentage of subjects who discontinue early from the study prior to completing the End-of-Maintenance Period video-EEG. Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy parameter for the US will become identical to the primary efficacy parameter for the EU. The endpoint not designated as primary will still be summarized as a secondary efficacy parameter.

Change #4

Section 4.1.1 Primary efficacy variable

The contingent primary efficacy variable has been defined.

For the US:

The primary efficacy variable will be the change in ADF of electrographic partial-onset seizures as measured on the 72-hour end-of-Maintenance Period video-EEG compared to the 72-hour end-of-Baseline Period video-EEG.

Has been changed to:

For the US, the primary efficacy variable will be contingent on the percentage of subjects that discontinue from the study after the first dose of study medication but prior to performance of the 72-hour End-of-Maintenance Period video-EEG (ie, early discontinuation).

The following variable will be considered primary for the US given that ≤10% of subjects discontinue early from the study:

- The change in ADF of electrographic partial-onset seizures as measured on the 72-hour End-of-Maintenance Period video-EEG compared to the 72-hour End-of-Baseline Period video-EEG.

If >10% of subjects discontinue early from the study, the following contingency endpoint will be considered primary for the US (same as the primary efficacy variable for the EU):

The proportion of responders where a responder is a subject experiencing a 50% or greater reduction in their ADF of electrographic partial-onset seizures recorded on the 72-hour End-of-Maintenance Period video-EEG compared to the 72-hour end of Baseline Period video-EEG.

Change #5

Section 5.1.2 Planned number of subjects and sites

The language of the percentage of subjects <2 years of age to be included in the study has been clarified, 1st and 2nd paragraphs.

A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized.

Subjects will be enrolled in the following age categories as detailed below:

- ≥1 month to <6 months of age (≥25 subjects)
- ≥6 months to <1 year of age (≥25 subjects)
- ≥1 year to <2 years of age (≥25 subjects)
- ≥2 years to <4 years of age (≥20 subjects)

Approximately 175 sites are planned in order to recruit the required subjects; additional sites will be added if deemed necessary. A target of approximately 50% of the randomized subjects should consist of subjects <2 years of age. Of these subjects (122), a target of 20% will be enrolled in each of the 3 age categories <2 years of age.

Has been changed to:

A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized. Approximately 50% of the 244 randomized subjects should be <2 years of age. Of these (n=122), a minimum target of 20% (n=25) of subjects will be enrolled in each of the 3 age categories: ≥1 month to <6 months, ≥6 months to <1 year, and ≥1 year to <2 years.

Subjects will be enrolled in the following age categories as detailed below:

- ≥1 month to <6 months of age (≥25 subjects)
- ≥6 months to <1 year of age (≥25 subjects)
- ≥1 year to <2 years of age (≥25 subjects)
- ≥2 years to <4 years of age (≥20 subjects)

Approximately 175 sites are planned in order to recruit the required subjects; additional sites will be added if deemed necessary.

Change #6

Section 5.2 Schedule of study assessments

Schedule of study assessments Table 5-1 has been updated to include rescue medication assessment.

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
Informed consent	X														
Demographics[c]	X														
Inclusion/exclusion criteria	X	X			X										
Medical history	X														
Seizure history/count	X														
Concomitant medications	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VNS assessment[f]	X	X					X				X			X	X
Physical examination (complete)	X													X	
Physical examination (brief)		X					X		X		X				
Vital signs (including BP and pulse rate)[g]	X	X					X		X		X			X	X
Body weight	X	X					X		X					X	X
Height	X													X	
Head circumference	X													X	
Neurological examination (complete)	X													X	
Neurological examination (brief)		X					X		X		X				
ECG (12-lead)[h]	X				X				X					X	
Video-EEG[i]		X	X	X	X						X	X	X	X	

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
Clinical chemistry/hematology	X								X					X	
Concomitant AED plasma concentration	X								X					X	
LCM plasma concentration	X								X					X	
Clinical GIC														X	
Caregiver's GIC														X	
Contact IXRS	X				X		X		X		X			X	
Randomization					X[j]										
Dispense study medication					X[j]		X		X		X			X	
Return study medication							X		X		X			X	
Dosing instructions[k]						X		X		X					
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare resource use					X		X		X					X	
Bayley-III scales[l]					X										
BRIEF-P[m]					X									X	
PedsQL[n]					X									X	
Achenbach CBCL[o]					X									X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Childhood Behavior Checklist; ECG=electrocardiogram; EEG=electroencephalogram; ET=Early Termination; GIC=Global Impression of

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	V1	V2			V3	T1	V4	T2	V5	T3	V6/ET				UV[a]
Study Day	-7	-3[b]	-2	-1	1	5	9	13	17	20	24[b]	25	26	27	

Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; T=Telephone Contact; UV=Unscheduled Visit; V=Visit; VNS=vagus nerve stimulation.

a If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion.

b The Day -3 and Day 24 assessments should be conducted prior to the start of video-EEG monitoring. A maximum of 7 days may be added to the period between Visit 1 and 2 in the event that additional time is needed to access inpatient facilities to perform the video-EEG,

c Demographics: date of birth, age group category, age in months and years, race, ethnicity, and gender. In countries where recording of complete date of birth is not permitted, only permitted data will be collected.

d The concomitant medications recording will include any current medication intake as well as any medications taken ≤30 days prior to Visit 1.

e The concomitant AED recording will include any current medication intake as well as any previous AED taken prior to Visit 1.

f The VNS setting will be assessed as applicable.

g Orthostatic assessments of BP and pulse rate will be assessed where it is feasible according to investigator judgment.

h A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recording. The second recording will be conducted 20 to 30 minutes after the first recording. Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader and at a central ECG laboratory. The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality; however, 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.

i The video-EEG (72 hours of continuous recording) will be conducted in an inpatient setting. Upon completion of the Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the video-EEG data, the subject may be randomized at Visit 3. All video-EEG data recordings will be transmitted to a central reader for the purposes of data analysis. The End-of-Maintenance Period video-EEG will be done at Visit 6. Subjects who discontinue on or before Day 20 will not require a video-EEG.

j Randomization and initial dispensing of study medication will occur at Visit 3 and after the completion of the video-EEG and confirmation that the subject has met selection criteria.

k Dosing instructions will be provided to the caregiver(s) during the telephone contacts. At a minimum, AEs and tolerability should be discussed with the caregiver(s) in order to determine the next dose for the subject. See Section 7.2.1 for additional details on dosing options.

l The Bayley Scales of Infant and Toddler Development, Third Edition, will be completed by subjects who are <18 months of age who originate in English-speaking countries.

m The BRIEF-P will be used only for subjects who are ≥2 years of age at Visits 3 and 6. BRIEF-P will be used only in countries where a translated

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV[a]**
Study Day	**-7**	**-3[b]**	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24[b]**	**25**	**26**	**27**	

version is available.

[n] The version of the PedsQL used at Visit 3 should be consistent with the subject's age at Visit 3 and should be maintained for each subject for the duration of the study. The PedsQL will be used only in countries where a translated version is available.

[o] The Achenbach CBCL/1½-5 will be completed by the parent(s)/legal representative(s)/caregiver(s) of subjects ≥18 months of age at Visits 3 and 6. The Achenbach CBCL will be administered only in countries where a translated version is available.

Has been changed to:

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
Informed consent	X														
Demographics[c]	X														
Inclusion/exclusion criteria	X	X			X										
Medical history	X														
Seizure history/count	X														
Concomitant medications	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VNS assessment[f]	X	X					X				X			X	X
Physical examination (complete)	X													X	
Physical examination (brief)		X					X		X		X				
Vital signs (including BP and pulse rate)[g]	X	X					X		X		X			X	X
Body weight	X	X					X		X					X	X
Height	X													X	
Head circumference	X													X	
Neurological examination (complete)	X													X	
Neurological examination (brief)		X					X		X		X				

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
ECG (12-lead)[h]	X				X				X					X	
Video-EEG[i]		X	X	X	X						X	X	X	X	
Rescue medication[j]		X	X	X	X						X	X	X	X	
Clinical chemistry/hematology	X								X					X	
Concomitant AED plasma concentration	X								X					X	
LCM plasma concentration	X								X					X	
Clinical GIC														X	
Caregiver's GIC														X	
Contact IXRS	X				X		X		X		X			X	
Randomization					X[k]										
Dispense study medication					X[k]		X		X		X			X	
Return study medication							X		X		X			X	
Dosing instructions[l]						X		X		X					
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare resource use					X		X		X					X	
Bayley-III scales[m]					X										
BRIEF-P[n]					X									X	

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	
PedsQL[o]					X									X	
Achenbach CBCL[p]					X									X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Childhood Behavior Checklist; ECG=electrocardiogram; EEG=electroencephalogram; ET=Early Termination; GIC=Global Impression of Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; T=Telephone Contact; UV=Unscheduled Visit; V=Visit; VNS=vagus nerve stimulation.

[a] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion.

[b] The Day -3 and Day 24 assessments should be conducted prior to the start of video-EEG monitoring. A maximum of 7 days may be added to the period between Visit 1 and 2 in the event that additional time is needed to access inpatient facilities to perform the video-EEG.

[c] Demographics: date of birth, age group category, age in months and years, race, ethnicity, and gender. In countries where recording of complete date of birth is not permitted, only permitted data will be collected.

[d] The concomitant medications recording will include any current medication intake as well as any medications taken ≤30 days prior to Visit 1.

[e] The concomitant AED recording will include any current medication intake as well as any previous AED taken prior to Visit 1.

[f] The VNS setting will be assessed as applicable.

[g] Orthostatic assessments of BP and pulse rate will be assessed where it is feasible according to investigator judgment.

[h] A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recording. The second recording will be conducted 20 to 30 minutes after the first recording. Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader and at a central ECG laboratory. The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality; however, 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.

[i] The video-EEG (72 hours of continuous recording) will be conducted in an inpatient setting. Upon completion of the Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the video-EEG data, the subject may be randomized at Visit 3. All video-EEG data recordings will be transmitted to a central reader for the purposes of data analysis. The end-of-Maintenance Period video-EEG will be done at Visit 6. Subjects who discontinue on or before Day 20 will not require a video-EEG.

[j] Additional assessment for changes in VNS or rescue medication taken within 24 hours prior to and until the end of the video-EEG monitoring.

Table 5-1: Schedule of study assessments (Baseline and Treatment Periods)

Assessment	Baseline Period (7 days)				Treatment Period (27 days)										
					Titration Period (20 days)						Maintenance Period (7 days)				
Visit	**V1**	**V2**			**V3**	**T1**	**V4**	**T2**	**V5**	**T3**	**V6/ET**				**UV**[a]
Study Day	**-7**	**-3**[b]	**-2**	**-1**	**1**	**5**	**9**	**13**	**17**	**20**	**24**[b]	**25**	**26**	**27**	

[k] Randomization and initial dispensing of study medication will occur at Visit 3 and after the completion of the video-EEG and confirmation that the subject has met selection criteria.

[l] Dosing instructions will be provided to the caregiver(s) during the telephone contacts. At a minimum, AEs and tolerability should be discussed with the caregiver(s) in order to determine the next dose for the subject. See Section 7.2.1 for additional details on dosing options.

[m] The Bayley Scales of Infant and Toddler Development, Third Edition, will be completed by subjects who are <18 months of age who originate in English-speaking countries.

[n] The BRIEF-P will be used only for subjects who are ≥2 years of age at Visits 3 and 6. BRIEF-P will be used only in countries where a translated version is available.

[o] The version of the PedsQL used at Visit 3 should be consistent with the subject's age at Visit 3 and should be maintained for each subject for the duration of the study. The PedsQL will be used only in countries where a translated version is available.

[p] The Achenbach CBCL/1½-5 will be completed by the parent(s)/legal representative(s)/caregiver(s) of subjects ≥18 months of age at Visits 3 and 6. The Achenbach CBCL will be administered only in countries where a translated version is available.

Change #7

Section 5.4 Rationale for study design and selection of dose

Text defining the contingent primary efficacy variable has been added, 4th paragraph.

Based on US FDA and EMA requirements, 2 (co-) primary efficacy variables have been defined for this study based on electrographic partial-onset seizures with or without clinical correlate depending upon subject age. The primary efficacy variable will be the change in ADF of electrographic partial-onset seizures (US) or proportion of subjects experiencing ≥50% reduction in their ADF of electrographic partial-onset seizures (EU) as measured on the 72-hour End-of-Maintenance Period video-EEG compared to the 72-hour End-of-Baseline Period video-EEG. At the request of FDA, a contingent primary efficacy variable has also been defined based on the percentage of subjects who discontinue early from the study prior to completing the End-of-Maintenance Period video-EEG. Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy parameter for the US will become identical to the primary efficacy parameter for the EU.

The endpoint not designated as primary will still be summarized as a secondary efficacy parameter

Change #8

Section 8.1.2 Baseline Period: Visit 2 (Day -3 to Day -1)

Rescue medication has been added to the list of assessments.

- Inclusion/exclusion criteria (Day -3 only)
- Concomitant medications
- Concomitant AEDs
- VNS assessment (Day -3 only and only if applicable)
- Physical examination (brief) (Day -3 only)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment; Day -3 only)
- Body weight (Day -3 only)
- Neurological examination (brief) (Day -3 only)
- Video-EEG (72 hours of continuous recording)
- AE reporting
- Review withdrawal criteria

Has been changed to:

- Inclusion/exclusion criteria (Day -3 only)
- Concomitant medications
- Concomitant AEDs

- VNS assessment (Day -3 only and only if applicable)
- Physical examination (brief) (Day -3 only)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment; Day -3 only)
- Body weight (Day -3 only)
- Neurological examination (brief) (Day -3 only)
- Video-EEG (72 hours of continuous recording)
- Rescue medication assessment
- AE reporting
- Review withdrawal criteria

Change #9

Section 8.2.1 Titration Period: Visit 3 (Day 1)

Rescue medication has been added to the list of assessments.

Randomization and initial dispensing of study medication will occur at Visit 3 and after the completion of the video-EEG and confirmation that the subject has met selection criteria.

During Visit 3, the following assessments will be performed:

- Inclusion/exclusion criteria
- Concomitant medications
- Concomitant AEDs
- 12-lead ECG (2 interpretable recordings [20 to 30 minutes apart] to be performed, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Video-EEG (end-of-Baseline video-EEG)
- Contact IXRS
- Randomization
- Dispense study medication and administer first dose of study medication before the conclusion of visit
- AE reporting
- Review withdrawal criteria
- Healthcare resource use
- Bayley-III scales (for subjects who are <18 months of age who originate in English-speaking countries)
- BRIEF-P score
- PedsQL score

- Achenbach CBCL (the CBCL/1½-5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at Visit 3)

Has been changed to:

Randomization and initial dispensing of study medication will occur at Visit 3 and after the completion of the video-EEG and confirmation that the subject has met selection criteria.

During Visit 3, the following assessments will be performed:

- Inclusion/exclusion criteria
- Concomitant medications
- Concomitant AEDs
- 12-lead ECG (2 interpretable recordings [20 to 30 minutes apart] to be performed, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Video-EEG (End-of-Baseline video-EEG)
- Rescue medication assessment
- Contact IXRS
- Randomization
- Dispense study medication and administer first dose of study medication before the conclusion of visit
- AE reporting
- Review withdrawal criteria
- Healthcare resource use
- Bayley-III scales (for subjects who are <18 months of age who originate in English-speaking countries)
- BRIEF-P score
- PedsQL score

Achenbach CBCL (the CBCL/1½-5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at Visit 3)

Change #10

Section 8.3.1 Maintenance Period: Visit 6/Early Termination (Day 24, Day 25 and Day 26)

Rescue medication has been added to the list of assessments.

The Day 24 assessments should be conducted prior to the start of video-EEG monitoring. The following assessments will be performed on Day 24 for all subjects:

- Concomitant medications
- Concomitant AEDs

- VNS assessment (if applicable)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Neurological examination (brief)
- Video-EEG (72 hours of continuous recording)
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Review withdrawal criteria

The following assessments will be performed on Day 25 and Day 26 during the 72-hour video-EEG:

- Concomitant medications
- Concomitant AEDs
- AE reporting
- Review withdrawal criteria

Has been changed to:

The Day 24 assessments should be conducted prior to the start of video-EEG monitoring. The following assessments will be performed on Day 24 for all subjects:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Neurological examination (brief)
- Video-EEG (72 hours of continuous recording)
- Rescue medication assessment
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting

- Review withdrawal criteria

The following assessments will be performed on Day 25 and Day 26 during the 72-hour video-EEG:

- Concomitant medications
- Concomitant AEDs
- Rescue medication assessment
- AE reporting
- Review withdrawal criteria

Change #11

Section 8.3.2 Maintenance Period: Visit 6/Early Termination (Day 27)

Rescue medication has been added to the list of assessments.

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Height
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings [20 to 30 minutes apart] to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Blood sample for clinical chemistry/hematology
- Blood sample for determination of concomitant AED plasma concentration
- Blood sample for determination of LCM plasma concentration
- Clinical Global Impression of Change
- Caregiver's Global Impressions of Change
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting

- Review withdrawal criteria
- Healthcare resource use
- BRIEF-P
- PedsQL (same version used at Visit 3)
- Achenbach CBCL (the CBCL/1½-5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at Visit 6/ET)

Has been changed to:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (if applicable)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)
- Body weight
- Height
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings [20 to 30 minutes apart] to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in a supine position for 5 minutes preceding ECG recording)
- Blood sample for clinical chemistry/hematology
- Blood sample for determination of concomitant AED plasma concentration
- Blood sample for determination of LCM plasma concentration
- Clinical Global Impression of Change
- Caregiver's Global Impressions of Change
- Contact IXRS
- Dispense study medication
- Return study medication
- AE reporting
- Rescue medication assessment
- Review withdrawal criteria
- Healthcare resource use

- BRIEF-P
- PedsQL (same version used at Visit 3)
- Achenbach CBCL (the CBCL/1½-5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at Visit 6/ET)

Change #12

Section 9.2.3 Healthcare resource use

Healthcare resource use section has been updated, 1st paragraph.

For healthcare resource use, the following will be evaluated: concomitant medications and AEDs, medical procedures, healthcare provider consultations not related to study, and hospitalizations not related to study.

Has been changed to:

For healthcare resource use, the following will be evaluated: concomitant medications and AEDs, medical procedures, and healthcare provider consultations including hospitalizations not foreseen by the protocol.

Change #13

Section 11.1.4 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

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

Has been changed to:

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

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

Change #14

Section 11.5 Anticipated serious adverse events

The anticipated SAE table has been updated to include a footnote for convulsion.

Table 11-1: Anticipated SAEs for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administration site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion
	Incontinence
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behaviour
	Abnormal behaviour
	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

Has been changed to:

Table 11-1: Anticipated SAEs for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administration site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion[a]
	Incontinence
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behaviour
	Abnormal behaviour
	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

[a] Convulsion if consistent with the seizure type known for the subject.

Change #15

Section 12.1 Adherence to protocol

Text for adherence to the protocol has been updated.

The investigator should not deviate from the protocol. In medical emergencies, the investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

Has been changed to:

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor. After implementation of such measure, the investigator must notify the Clinical Project Manager (CPM) of the sponsor within 24 hours and follow any local regulatory requirements**.**

Change #16

Section 13.1 Definition of analysis sets

Definition of the analysis sets has been clarified, 1st paragraph.

The primary analysis set for the efficacy data will be the Full Analysis Set (FAS), and will include all subjects who were randomized, received at least 1 dose of study medication, and had an End-of-Maintenance Period video-EEG.

The secondary analysis set for the efficacy data will be the Per Protocol Set (PPS), which includes all subjects in the FAS who did not have important protocol deviations related to efficacy.

The Safety Set (SS) will include all randomized subjects who took at least 1 dose of study medication. This is the primary analysis set for the safety variables.

The Pharmacokinetic Per Protocol Set (PK-PPS) will consist of all subjects having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 visit with documented study medication intake times.

Has been changed to:

The Safety Set (SS) will include all randomized subjects who took at least 1 dose of study medication. This is the primary analysis set for the safety variables.

The primary analysis set for the efficacy data will be the Full Analysis Set (FAS), which will include all subjects in the SS.

The secondary analysis set for the efficacy data will be the Per-Protocol Set (PPS), which includes all subjects in the FAS who did not have important protocol deviations related to efficacy.

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 visit with documented study medication intake times.

Change #17

Section 13.1.1.1 Analysis of the primary efficacy variable for the US

This section has been added.

Contingent upon ≤10% of subjects discontinuing early from the study, the primary efficacy parameter for the US is the change in ADF of electrographic partial-onset seizures during the Maintenance Period compared to the end of the Baseline Period. Seizure ADF will be analyzed using analysis of covariance with terms for treatment and center (properly pooled), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF. Log-transformed Baseline seizure ADF will be used as a covariate. The seizure ADF between LCM and PBO will be compared using least squares means (LSMs). The percent reduction over PBO will be estimated as 100 x (1 – exp [LSM Treatment {TRT} - LSMPBO]). The analysis of this efficacy variable will consist of all subjects in the FAS who have at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using the Baseline observation-carried-forward approach. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced by the overall mean ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG from the subject's respective treatment arm. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment arm and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using a Markov chain Monte Carlo method assuming a log-normal distribution. This will be applied for all subjects who discontinued early from the study.
- Repeat the primary analysis using the FAS for all subjects who have at least 24 hours of interpretable recordings during both the End-of Baseline Period video-EEG and the End-of-Maintenance Period video-EEG.

Contingent upon >10% of subjects discontinuing early from the study, the primary efficacy parameter for the US is identical to the primary efficacy parameter for the EU, described below. The endpoint not designated as primary will still be summarized as a secondary efficacy parameter.

Change #18

Section 13.1.1.2 Analysis of the primary efficacy variable for the EU

This section has been added.

The primary efficacy parameter for the EU is the proportion of responders during the Maintenance Period. Subjects with a 50% or more reduction in seizure ADF will be categorized as responders; this classification requires at least 48 hours of interpretable recordings during both the End-of-Baseline Period video-EEG and the End-of-Maintenance Period video-EEG. The proportion of responders between LCM and PBO will be analyzed using logistic regression with center (properly pooled) as a factor. Subjects who withdraw or drop out before the first 48 hours of the End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non responders; all other subjects will be missing for this analysis. The number and percentage of subjects with a 50% or more reduction in seizure ADF will be presented by treatment group.

The following additional sensitivity analyses on this primary efficacy variable will be conducted in order to assess the effect of early discontinuations, protocol deviations, and operational bias on this primary endpoint:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except subjects who discontinued from the study prior to performance of the 72-hour End-of-Maintenance Period video-EEG with reasons related to lack of efficacy will be considered non responders, and subjects who discontinued from the study early for any other reason will be considered responders.
- Repeat the primary analysis using the FAS, except all subjects who discontinued from the study early will be considered non responders.
- Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment arm and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using a Markov chain Monte Carlo method assuming a log-normal distribution. This will be applied for all subjects who discontinued from the study early, and the imputed End-of-Maintenance Period ADF of partial-onset seizures will be used to determine whether a subject is a responder.
- Repeat the primary analysis using the FAS for all subjects who have at least 24 hours of interpretable recordings during both the end of Baseline Period video-EEG and the end of Maintenance Period video-EEG.

Change #19

Section 13.2.1 Planned efficacy analyses

This section has been removed.

Subjects evaluable for the EEG-based efficacy endpoints will consist of all subjects in the FAS who have at least 48 hours of interpretable recordings during both the end of Baseline Period video-EEG and the end of Maintenance Period video-EEG.

Change #20

Section 13.5 Planned interim analysis and data monitoring

The sample size re-estimation has been further detailed, 2nd and 3rd paragraphs.

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study, and have data available for analysis to check the validity of these assumptions using interim data from the study. The sample size re-estimation with equal allocation in each arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011). An assessment of the observed dropout rate will also be made as part of this analysis, and the anticipated dropout rate of 14% will be modified based on the observed rate. Additionally, an assessment of the observed difference of interpretation rate will be made; the anticipated rate of 5% will be modified based on the observed rate.

The final sample size will be modified according to the sample size re-estimate and also the anticipated dropout rate and anticipated rate of difference of interpretation of the end-of-Baseline Period video-EEG; however, an upper bound may be applied to reach a maximum sample size based on practical and logistical considerations.

Has been changed to:

A blinded sample size re-estimation will be performed when 50% of subjects have been randomized, completed the study, and have data available for analysis to check the validity of these assumptions using interim data from the study. The sample size re-estimation with equal allocation in each arm will be performed using the related residual variance combined with Guenther adjustment (Friede and Kieser, 2011). An assessment of the observed dropout rate will also be made as part of this analysis, and the potential dropout rate of 14% used for calculation of the initial sample size (see Section 13.6) will be modified based on the observed rate. Additionally, an assessment of the observed difference of End-of-Baseline Period EEG interpretation rate will be made; the anticipated rate of 5% will be modified based on the observed rate.

The final sample size will be modified according to the sample size re-estimate and also the anticipated dropout rate and anticipated rate of difference of interpretation of the End-of-Baseline Period video-EEG; however, an upper bound will be applied to reach a maximum sample size based on practical and logistical considerations. The initial sample size re-estimate using Guenther adjustment will not be adjusted above 109 subjects per treatment arm, the original estimated overall study drop out rate will not be adjusted above 24%, and the difference of End-of-Baseline Period EEG interpretation rate will not be adjusted above 10%.

Change #21

Section 13.6 Determination of sample size

Text for third paragraph has been updated.

Subjects are randomized into the study based on the investigator's interpretation of the video-EEG to meet study entry requirements; however, there may be a difference of interpretation of the number of seizures counted on the end-of-Baseline Period video-EEG between the central reader and the investigator. To account for an anticipated difference of interpretation of the

end-of-Baseline Period video-EEG of 5% as well as an anticipated subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.

Has been changed to:

Subjects are randomized into the study based on the investigator's interpretation of the video-EEG to meet study entry requirements; however, there may be a difference of interpretation of the number of seizures counted on the End-of-Baseline Period video-EEG between the central reader and the investigator. To account for an anticipated difference of interpretation of the End-of-Baseline Period video-EEG of 5% as well as the potential subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.

Change #22:

The following section has been added for electronic signature:

Section 19 SPONSOR DECLARATION

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

17.2 AMENDMENT 2

Rationale for the amendment

The primary purposes of this substantial amendment are to clarify elements of the study design including inclusion and exclusion criteria, withdrawal criteria, permitted and prohibited concomitant medication, and study procedures to make the protocol more patient-friendly and enhance enrollment. The protocol was also updated according to the new UCB protocol template, for example, with the addition of text regarding PDILI.

The following table summarizes each change with the associated rationale.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 1	Lacosamide is being evaluated in pediatric subjects 1 month to 17 years of age in 3 studies: SP847 (open label, Phase 2, safety, tolerability, and PK study), SP848 (open label long term safety study), and SP1047 (PK study for subjects prescribed LCM). In SP847 and SP848, subjects with uncontrolled partial onset seizures receive LCM oral solution at doses up to 12mg/kg/day based on tolerability.	Lacosamide is being evaluated in pediatric subjects 1 month to 17 years of age with partial-onset seizures in completed and ongoing studies. The completed pediatric studies include: SP847 (open-label, safety, tolerability, and PK study) and SP1047 (PK study for subjects prescribed LCM). The ongoing pediatric studies include: SP848 and EP0034 (open-label, long-term safety studies). In SP847 SP848, and EP0034 subjects with uncontrolled partial onset seizures have received LCM oral solution at doses up to 12mg/kg/day based on tolerability.	Updated text according to pediatric studies that have been completed.
Section 1 Section 5.1.2	A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized at approximately 175 sites in North America, Europe, Asia Pacific, and Latin America, with possible extension to other countries and regions.	A total of approximately 244 subjects (122 subjects per treatment arm) are planned to be randomized at approximately 140 sites in North America, Europe, Asia Pacific, and Latin America, with possible extension to other countries and regions.	Revised number of sites.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 1 Section 5.1.1	• The maximum duration of study medication administration in SP0967 is 55 days, and the maximum study duration is 93 days (not withstanding visit windows). • For each subject, the total study duration can be up to 93 days (not withstanding visit windows), including the 30 day Safety Follow-Up Period. Each subject's participation in the study begins with a 7-day Baseline Period (no administration of study medication). Each subject's total duration of study medication administration in SP0967 is up to 55 days. This includes a 20-day Titration Period, a 7-day Maintenance Period, and a 12-day Transition Period (for subjects who plan to enter the open label extension study [EP0034]) or up to a 16-day Taper Period (for subjects who will not be entering EP0034).	• The maximum duration of study medication administration in SP0967 is 55 days (this includes a 20-day Titration Period, a 7-day Maintenance Period, a 12-day Transition Period, and/or up to a 16-day Taper Period), and the maximum study duration is 93 days (not withstanding visit windows). • For each subject, the maximum total study duration can be up to 93 days (not withstanding visit windows), including the 30 day Safety Follow-Up Period. Each subject's participation in the study begins with a 7-day Baseline Period (no administration of study medication). Each subject's maximum total duration of study medication administration in SP0967 can be up to 55 days. This includes a 20-day Titration Period, a 7-day Maintenance Period, a 12-day Transition Period (for subjects who plan to enter the open label extension study [EP0034]) and/or up to a 16-day Taper Period (for subjects who will not be entering EP0034).	Clarify that the duration of study medication administration (55 days) and total study duration (93 days) are maximum durations for a subject who enters the Transition Period end up also going through the Taper Period.
Section 2	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).	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).	Updated introductory text with newer reference.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 4.2 Table 5-1 Section 8.1.1 Section 8.2.4 Section 8.3.2 Section 10 Section 13.2.2.1 Section 13.2.2.3	Collection of blood at V1, V5, and V6 (Day 27) to investigate the effect of LCM on the steady-state plasma concentrations of concomitant AEDs	Global change: • Remove variable. Collection of blood samples at V1, Visit 5, and V6 (Day 27) for analysis of concomitant AEDs will not be performed.	• No clinically significant impact of concomitant AEDs on LCM plasma concentrations or LCM efficacy – as shown by PK analyses in adults and children. • Additional blood collected for this analysis is unnecessary in this vulnerable patient population.
Table 5-1 Section 8.1.1	Collection of blood sample for analysis of LCM plasma concentrations at V1.	Removed from V1.	• There is no need to collect blood to evaluate LCM plasma concentrations prior to subject randomization. • Collection of blood for this analysis puts undue burden on this vulnerable patient population.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Table 5-1 Table 5-2 Table 5-3 Section 8.1.1 Section 8.2.1 Section 8.2.4 Section 8.3.2 Section 8.4.3 Section 8.5.2 Section 11.7.4	A 12-lead ECG (2 interpretable recordings) will be performed at V1, V3, V5, V6 (Day 27), TV2, Taper Visit, and Safety Follow-up Visit (at investigator's discretion) prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recording. The second recording will be conducted 20 to 30 minutes after the first recording.	Global changes: • Insert "approximately" as follows: The second recording will be conducted approximately 20 to 30 minutes after the first recording. • ECG performed at V3 will be at the discretion of the investigator. • ECG at V1 will serve as Baseline for the evaluation of change in ECG measurements. • The ECG at the Taper Visit and Safety Follow-up Visit will be required for subjects with a clinically significant abnormal or reading at the previous clinic visit. For non-clinically significant abnormalities, repeat of this assessment is at the discretion of the investigator.	• Allow some flexibility for the timing of the second ECG recording. • ECG is performed at V1, which will be at most 7 days prior to V3. Therefore, ECG at V3 is unnecessary. • No changes in concomitant AEDs are allowed during the Baseline Period. Thus, there is no need to repeat the ECG unless medically necessary. • If the ECG is normal at End of Maintenance, there is no need to repeat as early as 4 days later at the Taper Visit when the study drug is being tapered.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 1 Section 4.1 Section 4.1.1 Section 5.1 Table 5-1 Section 5.4 Section 8.1.2 Section 8.2.1 Section 8.3.1 Section 9.1 Section 13.1.1 Section 13.1.1.2	• Video-EEG (72 hours of continuous recording) performed at V2, V3, and V6 serves to evaluate both the primary and secondary efficacy variables. • The ADF of electrographic partial-onset seizures will be calculated as (number of partial-onset seizures recorded on the 72-hour video-EEG divided by 72 [or number of interpretable hours recorded]) multiplied by 24.	Global changes: • Revise duration of video-EEG to be up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording. • Localize definition of video-EEG duration to Sections 4.1, 5.1, 8.1.2, 8.3.1, 9.1, and 13.1.1, and Table 5-1. Text revised: • The ADF of electrographic partial-onset seizures will be calculated as (number of partial-onset seizures recorded on the video-EEG divided by the number of interpretable hours recorded) multiplied by 24.	• Clarify duration of video-EEG requirements with every attempt to obtain at least 48 hours of interpretable recording. • Completion of a full 72-hour EEG is an impediment to patient enrollment based on site feedback. • Seizure data are normalized to 24 hours. • There would be no changes to the analyses that would affect the validity of the data.
Section 5.1.3	A target of approximately 30% of the randomized subjects should consist of subjects originating from sites in North America and the EU.	A target of approximately 30% of the randomized subjects should consist of subjects originating from sites in North America and Europe.	Inclusion of non-EU countries into the 30% randomization target.
Table 5-1 Table 5-2 Table 5-3 Section 8.2.3 Section 8.2.4 Section 8.4.1 Section 8.4.3 Section 8.5.2 Section 8.6.1	Assessments of healthcare resource use on Visit 3, Visit 4, Visit 5, Visit 6, TV1, TV2, Taper Visit, and Safety Follow-up Visit.	Global change: • Remove assessments for healthcare resource use on Visit 4, Visit 5, TV1, TV2, Taper Visit, and Safety Follow-up Visit.	Duration of the study is too short to administer the questionnaire on multiple occasions.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Table 5-1 Section 8.2.1 Section 11.7.8 Section 13.2.1	The Bayley Scales of Infant and Toddler Development, Third Edition is to be completed by subjects who are <18 months of age who originate in English-speaking countries.	Text revised: • Investigators must make every attempt to administer the Bayley Scales of Infant and Toddler Development, Third Edition, for subjects who are <18 months of age who originate in English-speaking countries. • The investigators may utilize trained pediatric psychologists or other appropriately skilled individuals to administer the scale. • Investigators must make every attempt to administer Baseline assessment of the Bayley-III scales; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study and analysis of these data will be conducted in EP0034.	The administration of Bayley Scales is complicated and requires trained individuals. The revised wording provides additional instructions to the investigators.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 1 Section 4.3.2 Table 5-1 Section 8.3.2 Section 11.7.7 Section 13.2.1	• The BRIEF-P will be used only for subjects who are ≥2 years of age at V3 and V6. • The BRIEF P includes 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 P includes validity scales to measure negativity and inconsistency of responses.	• The BRIEF-P will be used only for subjects who are ≥2 years of age at V3 and this will serve as the baseline for assessment in EP0034 (open-label extension study). • The Other Safety Variable for change from Baseline to end of Maintenance Period in the BRIEF-P score for subjects ≥2 years was removed. • The BRIEF P includes rating forms used by parents to assess subjects' executive functioning within the context of the subject's everyday environment. It requires that the parent must have had recent and extensive contact with the child over the past 6 months. • The clinical scales form 3 broad overlapping indexes: Inhibitory Self-Control (Inhibit and Emotional Control), Flexibility (Shift and Emotional Control), and Emergent Metacognition (Working Memory and Plan/Organize) and 1 composite score (Global Executive Composite). • Baseline assessment of the BRIEF-P will be performed at Visit 3; however, due to the study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study. Thus, the analysis of these data will be conducted in EP0034.	• Recall period for BRIEF-P is 6 months. In a study of approximately 1-month treatment duration, the recall period at V3 would overlap that at V6/ET. Therefore, it is not possible to reliably detect any change from Baseline. • V3 measures of BRIEF-P will still serve as Baseline for subjects in EP0034. • Because the V6 assessment was removed, the analysis of change from baseline will occur in EP0034; therefore, the variable was removed from SP0967.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 1 Section 4.3.2 Table 5-1 Section 8.3.2 Section 11.7.6 Section 13.2.1	• Achenbach CBCL (the CBCL/1½ 5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at V3 and V6/ET) • 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	• Achenbach CBCL (the CBCL/1½ 5 will be completed by parent[s]/legal representative[s]/caregiver[s] of subjects ≥18 months of age at V3 and this will serve as the baseline for assessment in EP0034 (open-label extension study)) • The Other Safety Variable for change from Baseline to the end of the Maintenance Period in the Achenbach CBCL/1½-5 for subjects ≥18 months was removed. • Baseline assessment of Achenbach CBCL will be performed; however, due to the short study duration of SP0967, the next assessment will be collected in subjects entering into the EP0034 study and analysis of these data will be conducted in EP0034. • In both questionnaires, the occurrence of certain problems and behaviors at the time of administering the questionnaire or within the past 2 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	• Recall period for Achenbach CBCL is 2 months. In a study of approximately 1-month treatment duration, the recall period at V3 would overlap that at V6/ET. Therefore, it is not possible to reliably detect any change from Baseline. • V3 measures of Achenbach CBCL will still serve as Baseline for subjects in EP0034. • Because the V6 assessment was removed, the analysis of change from baseline will occur in EP0034; therefore, the variable was removed from SP0967.
Table 5-2 Section 8.4.3	Height and head circumference will be measured at TV2.	Removed from TV2	Height and head circumference are measured at V6 (Day 27). There is no need to repeat 2 weeks later.
Table 5-3	No dosing instructions provided to the caregiver at the Taper Visit.	At the Taper Visit, dosing instructions will be provided to the caregiver(s).	Provide the caregiver with dosing instructions.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Table 5-3 Section 8.5.2	• Blood sample for clinical chemistry/hematology drawn at Taper Visit and Safety Follow-up Visit. • At the Safety Follow-up Visit, the assessment will be required only for subjects with an abnormal value (clinical chemistry or hematology) or reading (ECG) at the previous clinic visit.	• Blood sample for clinical chemistry/hematology drawn at Taper Visit and Safety Follow-up Visit. • For both the Taper Visit and Safety Follow-up Visit: blood sample for clinical chemistry/hematology collection will be required for subjects with a clinically significant abnormal value at the previous clinic visit. For non-clinically significant abnormalities, repeat of these assessments are at the discretion of the investigator.	If the laboratory values are normal at End of Maintenance, there is no need to repeat as early as 4 days later at the Taper Visit when the study drug is being tapered.
Section 6.1	Inclusion Criterion 6: • Subject has uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with ≥2 AEDs (concurrently or sequentially).	Remove Inclusion Criterion 6	• Inclusion Criterion 9 targets the population of interest with regard to concomitant AEDs. • Requiring subjects to fail 2 or more AEDs is an impediment for recruiting younger subjects.
Section 6.1	Inclusion Criterion 8: • Subject has ≥2 partial-onset seizures with or without secondary generalization during the 72-hour Baseline video-EEG.	Revise Inclusion Criterion 8a: • Subject has ≥2 partial-onset seizures with or without secondary generalization during the End-of-Baseline video-EEG.	Duration of End-of-Baseline video-EEG is explained elsewhere.
Section 6.2	Exclusion Criterion 1: • Subject has previously participated in this study.	Revise Exclusion Criterion 1a: • Subject has been previously randomized in this study (re-screening for screen-failed subjects is only allowed with prior consultation and permission of the medical monitor).	Clarify that re-screening is allowed for screen failed subjects who have not been previously randomized in SP0967 (see Exclusion Criterion 4a).
Section 6.2	Exclusion Criterion 4: • Subject has been previously treated with LCM.	Revise Exclusion Criterion 4a: • Subject has been previously treated with LCM and the LCM treatment was stopped due to lack of efficacy or adverse event(s).	Clarify exclusion of subjects previously treated with LCM

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 6.2	Exclusion Criterion 8: • Subject is on a ketogenic or other specialized diet for the treatment of epilepsy. If the subject was on a ketogenic or other specialized diet in the past, they must be off this diet for ≥2 months prior to Visit 1.	Revise Exclusion Criterion 8a: • Subject is on a ketogenic diet that has either changed within the 4 weeks prior to Visit 1 or is expected to change during the study.	• As long as a ketogenic diet is stable, the subject should be allowed into the study. • Treatment of ketogenic diet eligibility should be similar to VNS use eligibility (Inclusion Criterion 10).
Section 6.2	Exclusion Criterion 9: • Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level ≥2 times the upper limit of normal (ULN), or creatinine clearance <30mL/minute.	Revised Exclusion Criterion 9a: • Subject has creatinine clearance <30mL/minute.	• Update to UCB protocol template text. • Exclusion of subjects with abnormal ALT, AST, or bilirubin now covered by new Exclusion Criterion 22.
Section 6.2	Exclusion Criterion 15: • Subject has a current diagnosis of Lennox-Gastaut syndrome, epilepsia partialis continua, primary generalized epilepsy, or seizures that are not of partial-onset origin.	Revise Exclusion Criterion 15a: • Subject has a current diagnosis of Lennox-Gastaut syndrome, epilepsia partialis continua, primary generalized epilepsy, Dravet Syndrome, or seizures that are not of partial-onset origin.	A subject could have partial-onset seizures but also have generalized seizures. LCM can exacerbate generalized seizures in subjects with Dravet Syndrome in this age category.
Section 6.2	Exclusion Criterion 16: • Subject has a history of status epilepticus ≤2 months prior to Screening (Visit 1).	Revise Exclusion Criterion 16a: • Subject has a history of generalized convulsive status epilepticus ≤2 months prior to Screening (Visit 1).	• Clarify type of status epilepticus history that would be excluded • Generalized convulsive status epilepticus has the highest associated morbidity and mortality; therefore, only subjects with a history of this type of status epilepticus will be excluded.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 6.2	Exclusion Criterion 17: • Subject has been treated with ethosuximide.	Remove Exclusion Criterion 17	• Subjects with IGE are excluded per Exclusion Criterion 15. • Ethosuximide is generally only used for treatment of generalized seizures.
Section 6.2	Exclusion Criterion 18: • Subject is currently being treated with vigabatrin or has discontinued use <12 months prior to Visit 1. Subjects who were previously treated with vigabatrin and have discontinued use >12 months prior to Visit 1 are eligible.	Remove Exclusion Criterion 18.	• The risks with vigabatrin use are higher with long-term treatment. SP0967 is only 27 days of LCM treatment. • This criterion was removed from long-term, open-label extension to SP0967 (EP0034).
Section 6.2	Exclusion Criterion 21: • Subject has a known sodium channelopathy, such as Brugada syndrome	Revise Exclusion Criterion 21a: • Subject has a known cardiac sodium channelopathy, such as Brugada syndrome	Clarification of the exclusion criterion.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 6.2	NA	New Exclusion Criterion 22: • 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.	Provide more detailed eligibility criteria to align with FDA guidance regarding PDILI.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 6.3 Section 7.2.2 Section 8.3	**Must** Withdrawal Criterion 1: • Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study. • Subjects who are unable to tolerate study medication will be withdrawn from the study as follows: – Subjects unable to achieve or maintain target dose for the final 3 days of the Titration Period – Subjects who require dose reduction during the Maintenance Period Section 7.2.2 and Section 8.3: • Subjects who require dose reduction during the Maintenance Period will be withdrawn from the study and enter the blinded Taper Period.	Revise **must** Withdrawal Criterion 1: • Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study. • Subjects who are unable to tolerate study medication will be withdrawn from the study as follows: – Subjects unable to achieve or maintain target dose for the final 3 days of the Titration Period • Text removed from Section 7.2.2 and Section 8.3	• The patient can still contribute valuable efficacy and safety data even if they need a dose reduction. • This patient will be included the Full Analysis Set but not included in the Per-Protocol set.
Section 6.3	• **Must** Withdrawal Criterion 8: – Subject has liver function test (LFT) results for transaminases (AST, ALT, or both) ≥3xULN to <5xULN and total bilirubin ≥2xULN, or transaminases (AST, ALT, or both) ≥5xULN. In such instances, 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. • **May** Withdrawal Criterion 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.	• Remove **must** Withdrawal Criterion 8. • Remove **may** Withdrawal Criterion 4.	• Withdrawal criteria related to liver function tests now covered in new Section 6.3.1.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 6.3	**Must** Withdrawal Criterion 9: • Subject requires a change in concomitant AED daily dose or a change in VNS setting.	Remove **must** Withdrawal Criterion 9.	• The patient can still contribute valuable efficacy and safety data even if they need a change in dose or VNS setting. • This patient will be included the Full Analysis Set but not included in the Per-Protocol set.
Section 6.3	**Must** Withdrawal Criterion 10: • Subject initiates a ketogenic diet.	Remove **must** Withdrawal Criterion 10.	• Per Exclusion Criterion 8, a patient's ketogenic diet must remain stable. • Due to the short duration of this study, it is unlikely that a subject would initiate a ketogenic diet. • Should a ketogenic diet be initiated in violation of the exclusion criterion, the patient will be included in the Full Analysis Set but not included in the Per-Protocol set.
Section 7.8.1	However, use of BZDs for any reason other than a stable daily dosage regimen as concomitant AED within 24 hours prior to or during the video-EEG is not permitted and may lead to the subject being withdrawn from the study (Withdrawal Criterion 15; Section 6.3).	Text revised: • However, use of BZDs for any reason other than a stable daily dosage regimen as concomitant AED within 24 hours prior to or during the video-EEG is not permitted and may lead to the subject being withdrawn from the study (**MAY** Withdrawal Criterion 5; Section 6.3).	Correct Withdrawal Criterion cross reference number.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 6.3	• Investigators should attempt to obtain information for subjects who withdraw or discontinue. • The Case Report form (CRF) must document the primary reason for withdrawal or discontinuation.	Text revised: • Investigators should attempt to obtain information for subjects who withdraw. • The eCRF must document the primary reason for withdrawal.	Update to UCB protocol template text.
New Section 6.3.1	NA	**New Section 6.3.1: 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	• Update to UCB protocol template text. • 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.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
New Section 6.3.1 (continued)	NA	**New Section 6.3.1: Potential drug-induced liver injury IMP discontinuation criteria (continued)** ● 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).	(continued)

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
New Section 6.3.1 (continued)	NA	**New Section 6.3.1: Potential drug-induced liver injury IMP discontinuation criteria (continued)** • 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.	(continued)
Section 7.2.4	NA	• Text added: • Taper of LCM may not be required for some subjects who are on the lowest dose of study medication or who need to discontinue study medication abruptly, depending on the treatment option selected by the investigator in consultation with the medical monitor.	• If a subject received study medication at a dose of 2mg/kg/day and discontinued, a taper would not be required. • In case there is a need to immediately switch the subject to a different AED, the protocol would allow immediate discontinuation from LCM.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 7.5	• Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access. • Appropriate storage conditions must be ensured either by controlled room temperature or 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 communicated in accordance with the pharmacy manual.	Text revised: • Investigational medicinal product 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 or 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.	Update to UCB protocol template text.
Section 7.6	• Details of any IMP lost (due to breakage or wastage), not used, or returned to the sponsor or designee must also be recorded on the appropriate forms. • Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB's designee, preferably in their original package.	Text revised: • Details of any IMP 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. • Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers/partially used), unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB's designee.	Update to UCB protocol template text.
Section 7.8.1	Subjects must have been maintained on a stable dosage regimen of 1 to 3 marketed AEDs for ≥2 weeks prior to Visit 1 (ie, prior to entry into the Baseline Period).	Text revised: • Subjects must have been maintained on a stable dosage regimen of 1 to 3 marketed AEDs for ≥2 weeks prior to Visit 1 (ie, prior to initiation of Baseline video-EEG monitoring)	Timing of stable AED dosing clarified.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 7.8.1	• The following concomitant medications are prohibited during the study: – Neuroleptics – Monoamine oxidase inhibitors – Barbiturates (except as AEDs) – Narcotic analgesics	Text revised: • The following concomitant medications are prohibited during the study: – Clozapine – Monoamine-A oxidase inhibitors – Barbiturates (except as AEDs) – Cannabidiols (not approved or indicated for epilepsy by local health authority) • Neuroleptics (except for clozapine) are allowed during the study but the investigator should make every effort to keep the dose stable. • Other medications are permitted according to current clinical standards (eg, topical anesthetic).	• Clozapine is the only neuroleptic that lowers seizure threshold. • Clarification made to note that prohibited medication refers to MAO-A inhibitors. • Majority of narcotic analgesics do not lower seizure threshold and, therefore, should not interfere with efficacy evaluations. In the rare instance they are used in association with an AE, the reason for use would be recorded. • Cannibidiols that are approved or indicated will count as a concomitant AED. • Revisions in prohibited medications to allow use of medications to those patients who may need it.
Section 7.8.1 (continued)	• The following medications are not allowed unless used as described: – Amphetamines and sedative antihistamines: stable use only.	Text revised: • The following medications are not allowed unless used as described: – Amphetamines: stable use only.	• Antihistamines should be allowed for treatment of URTI. • They are not expected to have an effect on efficacy or safety evaluations.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 7.8.1	Subjects who have been treated with ethosuximide are excluded from the study. Subjects who are currently being treated with vigabatrin or have discontinued vigabatrin use <12 months prior to Visit 1 are excluded from the study. Subjects who were previously treated with vigabatrin and have discontinued use >12 months prior to Visit 1 are eligible. Concomitant use of either vigabatrin or ethosuximide during the course of the study is prohibited.	Text removed.	Text removed for consistency with changes to Exclusion Criteria 17 and 18.
New Section 11.1.6	NA	**New Section 11.1.6: 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. • Subsequent Sections 11.1.7 and 11.1.8 renumbered.	Update to UCB protocol template text.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 11.2.1	(Important medical events may include 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.)	Text revised: • (Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.3], 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.)	• Update to UCB protocol template text. • 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.
Section 11.2.3	An 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.	Text revised: An 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 11.6.1.4.	• Update to UCB protocol template text.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 11.3	NA	New text: • 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.	• Update to UCB protocol template text. • 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.
Section 11.5	• 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 (Table 11–1) will remain in effect for the duration of the protocol. • Pregnancy, puerperium and perinatal disorders: Abortion spontaneous • Reproductive system and breast disorders: Menstrual disorder	Text revised: • The following list of Anticipated SAEs (Table 11–1) is anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. • Removal of pregnancy, puerperium and perinatal disorders: Abortion spontaneous • Removal of reproductive system and breast disorders: Menstrual disorder	• Update to UCB protocol template text. • Updated based on patient population of this study
Section 14.1	Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject's legal representative(s), and by the person who conducted the informed consent discussion (investigator or designee).	Text revised: • Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject's legal representative(s), and by the person who conducted the informed consent discussion (investigator or designee).	Update to UCB protocol template text.

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 11.6.1 (formerly Section 11.7)	**Section 11.7 Liver function tests** • Refer to Section 6.3 for LFT withdrawal criteria. • Transaminases (AST, ALT, or both) ≥3×ULN but <5×ULN, in the presence of total bilirubin ≥2×ULN, or transaminases (AST, ALT, or both) ≥5×ULN will result in immediate discontinuation of 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 1 week later. • 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.	**Section 11.6.1 Liver function tests and evaluation of PDILI** • Original text removed and replaced with more detailed text about the evaluation of PDILI: – Table 11–1: Required investigations and follow up of PDILI – Section 11.6.1.1 Consultation with Medical Monitor and local hepatologist – Section 11.6.1.2 Immediate action: determination of IMP discontinuation – Section 11.6.1.3 Testing: identification/exclusion of alternative etiology – Table 11–2: PDILI laboratory measurements – Table 11–3: PDILI information to be collected – Section 11.6.1.4 Follow-up evaluation • Subsequent sections renumbered.	• Update to UCB protocol template text. • 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.
Administrative updates	• CRF • Drug Safety • ICH=International Conference on Harmonisation • More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999).	Text revised: • eCRF • Patient Safety • ICH=International Council for Harmonisation • Updated list of abbreviations • Updated list of references • It is estimated that almost 70 million people suffer from epilepsy (Ngugi et al, 2011).	NA

17.3 AMENDMENT 3

Rationale for the amendment

The primary purpose of this substantial amendment is to address the high variability in video-EEG seizure counts between the site and central reader by removing the central reader. This change was proposed by the FDA as part of a Type C meeting written response obtained on 25 January 2018.

Additional changes in Protocol Amendment 3 included the following:

- Update clinical trial biostatistician contact
- Update of the regulatory status of LCM in the US and EU
- Clarify the planned number of subjects per age group to reflect UCB's commitment to make every attempt to enroll subjects <2 years of age while recognizing the difficulty of enrolling this age group
- Prevent ineligibility of an otherwise eligible subject who has undergone the baseline EEG due to the narrow visit window for central laboratory measurements
- Clarify that "seizure-free" status during the Maintenance Period will be summarized by (1) all seizure types and (2) partial-onset seizure types only
- Update hematology and chemistry measurements for the assessment of PDILI events
- Replace Markov chain Monte Carlo multiple imputation method with a more appropriate monotone regression method
- Add age group to the analysis of the primary efficacy variable since randomization is stratified by age group

The following table summarizes each change with the associated rationale.

Appendix Table 2: Summary of changes in SP0967 Amendment 3

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
STUDY CONTACT INFORMATION	Clinical Trial Biostatistician [redacted], MA UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES [redacted]	Clinical Trial Biostatistician [redacted] UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES [redacted]	Update clinical trial biostatistician contact
Section 1.0 Section 5.1 Table 5-1 Section 9.1 Section 13.1.1	a central reader	locally by the investigator, subinvestigator, or qualified designated reader	Address the high variability in video-EEG seizure counts between the site and the central reader; clarify who is responsible for the assessment of the video-EEG seizure count
Section 2.0	Lacosamide has been approved as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the US (tablets, oral solution, and solution for intravenous [iv] infusion) and 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 in the EU (tablets, oral solution, and solution for iv infusion).	In the US, LCM has been approved as monotherapy and adjunctive therapy in the treatment of partial-onset seizures in patients 4 years of age and older for tablets and oral solution, and 17 years of age and older for intravenous [iv] infusion. In the EU, LCM has been approved as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 4 years of age with epilepsy (tablets, oral solution, and solution for iv infusion).	Update of the regulatory status of LCM in the US and EU
Section 4.1.2	• Proportion of subjects who achieved "seizure-free" status (yes/no) for subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG	• Proportion of subjects who achieved "seizure-free" status (yes/no) from all seizure types, and from partial-onset seizure types only for subjects who completed at least 48 hours of interpretable video-EEG recording during the End-of-Maintenance Period video-EEG	Clarify that "seizure-free" status during the Maintenance Period will be summarized by (1) all seizures types and (2) partial-onset seizures only

Appendix Table 2: Summary of changes in SP0967 Amendment 3

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 5.1	Assessment of video-EEG seizure count for verification of selection criteria will be performed by the investigator, but for the purpose of study analyses will be performed by a central EEG reader.	Assessment of video-EEG seizure count will be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of both assessment of eligibility and study analyses.	Address the high variability in video-EEG seizure counts between the site and the central reader; clarify who is responsible for the assessment of the video-EEG seizure count
Section 5.1.2	Of these (n=122), a minimum target of 20% (n=25) of subjects will be enrolled in each of the 3 age categories: ≥1 month to <6 months, ≥6 months to <1 year, and ≥1 year to <2 years. Subjects will be enrolled in the following age categories as detailed below:	Of these (n=122), every attempt will be made to enroll a minimum target of 20% (n=25) of subjects in each of the 3 age categories: ≥1 month to <6 months, ≥6 months to <1 year, and ≥1 year to <2 years. Every attempt will be made to enroll subjects in the following age categories as detailed below:	Clarify the planned number of subjects per age group to reflect UCB's commitment to make every attempt to enroll subjects <2 years of age while recognizing the difficulty of enrolling this age group
Table 5-1 (footnote i)	The video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) will be conducted in an inpatient setting. Upon completion of the End-of-Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the video-EEG data, the subject may be randomized at Visit 3. All video EEG data recordings will be transmitted to a central reader for the purposes of data analysis. The End-of-Maintenance Period video-EEG will be done at Visit 6. Subjects who discontinue on or before Day 20 will not require a video-EEG.	The video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) will be conducted in an inpatient setting. Upon completion of the End-of-Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the video-EEG data, the subject may be randomized at Visit 3. Assessment of video-EEG seizure count will be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of both assessment of eligibility and study analyses. The End-of-Maintenance Period video-EEG will be done at Visit 6. Subjects who discontinue on or before Day 20 will not require a video-EEG.	Address the high variability in video-EEG seizure counts between the site and the central reader; clarify who is responsible for the assessment of the video-EEG seizure count

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Section 6.1 (IC 8a)	Subject has ≥2 partial-onset seizures with or without secondary generalization during the End-of-Baseline video-EEG.	Subject has ≥2 partial-onset seizures with or without secondary generalization during the End-of-Baseline video-EEG. Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.	Provide clarity by including the definition of electrographic seizures
Section 8.1.2	From Visit 2 (Day -3 to Day -1) to Visit 3 (Day 1), an End-of-Baseline video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) will be performed. The Day -3 assessments should be conducted prior to the start of video-EEG monitoring. The video-EEG will be conducted in an inpatient setting. Upon completion of the End-of-Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the End-of-Baseline video-EEG data, the subject may be randomized at Visit 3.	From Visit 2 (Day -3 to Day -1) to Visit 3 (Day 1), an End-of-Baseline video-EEG (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording) will be performed. The Day -3 assessments should be conducted prior to the start of video-EEG monitoring. The video-EEG will be conducted in an inpatient setting. Upon completion of the End-of-Baseline video-EEG (Visits 2 and 3), the investigator will assess the electrographic seizure count and confirm the selection criteria have been met. If the subject meets all selection criteria, including the requisite number of seizures based on the End-of-Baseline video-EEG data, the subject may be randomized at Visit 3. Assessment of the video-EEG seizure count will also be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of study analyses; however, completion of this review is not required prior to randomization.	Address the high variability in video-EEG seizure counts between the site and the central reader; clarify who is responsible for the assessment of the video-EEG seizure count

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Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 8.3.1	The Day 24 assessments should be conducted prior to the start of the End-of Maintenance Period video-EEG monitoring (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording). The following assessments will be performed on Day 24 for all subjects:	The Day 24 assessments should be conducted prior to the start of the End-of Maintenance Period video-EEG monitoring (up to 72 hours of continuous recording with every attempt to obtain at least 48 hours of interpretable recording). Assessment of video-EEG seizure count will be performed locally by the investigator, subinvestigator, or qualified designated reader for the purpose of the study analyses. The following assessments will be performed on Day 24 for all subjects:	Address the high variability in video-EEG seizure counts between the site and the central reader; clarify who is responsible for the assessment of the video-EEG seizure count
Section 9.1 Section 13.1.1	The video-EEG recordings will be evaluated by a central reader.	The video-EEG recordings will be evaluated for seizure counts locally by the investigator, subinvestigator, or qualified designated reader.	Address the high variability in video-EEG seizure counts between the site and the central reader; clarify who is responsible for the assessment of the video-EEG seizure count
Section 11.6	Blood specimens for routine assay of hematology and clinical chemistry testing will be collected according to the tabular schedule of study procedures (Section 5.2). A central laboratory will perform the routine analysis of blood specimens. The procedures for handling and shipping these specimens will be provided to the sites.	Blood specimens for routine assay of hematology and clinical chemistry testing will be collected according to the tabular schedule of study procedures (Section 5.2). A central laboratory will perform the routine analysis of blood specimens. The procedures for handling and shipping these specimens will be provided to the sites. In exceptional circumstances, local laboratory analysis may be performed. The medical monitor should be contacted beforehand to discuss these circumstances.	Prevent ineligibility of an otherwise eligible subject who has undergone the baseline EEG due to the narrow visit window for central laboratory measurements
Table 11-4	Hematology measurements: Eosinophil count	Hematology measurements: Hematocrit, Hemoglobin, Platelet count, RBC count, WBC count, and Differential count	Update hematology measurements for the assessment of PDILI events

Appendix Table 2: Summary of changes in SP0967 Amendment 3

Protocol Section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Table 11-4	Chemistry measurements: Amylase, If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin, and Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation	Chemistry measurements: Amylase, Bilirubin (if total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin), Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation, AST, ALT, ALP, GGT, and Albumin	Clarify and add chemistry measurements for the assessment of PDILI events
Section 13.1.1.1	Seizure ADF will be analyzed using analysis of covariance with terms for treatment and center (properly pooled), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF.	Seizure ADF will be analyzed using analysis of covariance with terms for treatment, age category (4 age stratification categories, pooled as appropriate), center (properly pooled), on log-transformed seizure ADF using the transformation of ln (X+1), where X is the seizure ADF.	Add age group to the analysis of the primary efficacy variable since randomization is stratified by age group
Section 13.1.1.1 Section 13.1.1.2	• Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment arm and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using a Markov chain Monte Carlo method assuming a log-normal distribution.	• Repeat the primary analysis using the FAS, except missing ADF of partial-onset seizures from the End-of-Maintenance Period video-EEG will be replaced using multiple imputation by treatment arm and age group (≥1 month to <6 months of age, ≥6 months to <1 year of age, ≥1 year to <2 years of age, and ≥2 years to <4 years of age) using monotone regression.	Replaced Markov chain Monte Carlo multiple imputation method with a more appropriate monotone regression method; further details to be described in the statistical analysis plan
Section 13.1.1.2	The proportion of responders between LCM and PBO will be analyzed using logistic regression with center (properly pooled) as a factor.	The proportion of responders between LCM and PBO will be analyzed using logistic regression with age category (4 age stratification categories, pooled as appropriate) and center (properly pooled) as factors.	Add age group to the analysis of the primary efficacy variable since randomization is stratified by age group
Section 13.1.2	For subjects who complete the Maintenance Period, the number and percentage of subjects who achieved "seizure-free" status during the Maintenance Period will be tabulated and presented by treatment group.	For subjects who complete the Maintenance Period, the number and percentage of subjects who achieved "seizure-free" status from all seizure types, and from partial-onset seizure types only during the Maintenance Period will be tabulated and presented by treatment group.	Clarify that "seizure-free" status during the Maintenance Period will be summarized by (1) all seizures types and (2) partial-onset seizures only

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Section 13.6	Subjects are randomized into the study based on the investigator's interpretation of the video EEG to meet study entry requirements; however, there may be a difference of interpretation of the number of seizures counted on the End-of-Baseline Period video-EEG between the central reader and the investigator.	Subjects are randomized into the study based on the initial interpretation of the video-EEG to meet study entry requirements. However, the subsequent detailed assessment of seizure types and counts needed for the efficacy analyses could lead to a discrepancy in seizure counts (ie, a subject initially thought to be eligible is later found to have fewer than the required number of partial-onset seizures during the End-of-Baseline Period video-EEG). To account for an anticipated difference of interpretation of the End of Baseline Period video-EEG of 5% as well as the potential subject dropout rate of approximately 14%, the planned number of subjects to enroll is 122 subjects per treatment arm.	To address removal of the central reader

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 have received and 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.

All rights of publication of the results reside with UCB, 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 understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

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Document Approvals	
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