PROTOCOL SP0969 AMENDMENT 1

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 ≥4 YEARS TO <17 YEARS OF AGE WITH PARTIAL-ONSET SEIZURES

PHASE 3

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Confidential Material

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SERIOUS ADVERSE EVENT REPORTING

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AV	atrioventricular
bid	twice daily
BP	blood pressure
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
CBCL	Child Behavior Checklist
CDMS	clinical data management system
CPM	Clinical Project Manager
CRF	Case Report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DAP	Data Analysis Plan
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
EI-AED	enzyme-inducing antiepileptic drug
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	high density polyethylene
HRQoL	health-related quality of life
ICH	International Conference on 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 squares mean
MedDRA®	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
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
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SS	Safety Set
TAD	time after dose
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
VNS	vagus nerve stimulation

1 SUMMARY

SP0969 is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lacosamide (LCM) as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial-onset seizures.

A total of approximately 300 subjects with uncontrolled partial-onset seizures will be enrolled at approximately 149 sites in [redacted] and other regions as deemed necessary. The maximum duration of a subject's study participation is up to 36 weeks. The maximum duration of study medication administration is 24 weeks.

The study is comprised of the following: an 8-week Baseline Period; a 6-week Titration Period (with study medication dosing flexibility allowed based on tolerability) to achieve a target dose for the Maintenance Period (LCM 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for subjects weighing ≥50kg, or matching placebo); a 10-week Maintenance Period at the dose of study medication achieved on the final day of the Titration Period; and then a 4-week blinded Transition Period (for subjects who plan to enter the open-label extension study [EP0034]) or a blinded Taper Period (2 to 4 weeks) followed by a 30-day Safety Follow-Up Period (for subjects who will not be entering EP0034).

The assessment of efficacy is based on partial-onset seizure frequency. The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period. Secondary and other efficacy variables will allow further exploration of the effect of LCM on partial-onset seizure frequency, global impressions of changes, quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]), and health care resource use. Plasma concentrations of LCM and concomitant antiepileptic drugs (AEDs) 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 will be evaluated based on the occurrence of adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator; subject withdrawals due to AEs; the results of periodic clinical laboratory, electrocardiogram (ECG), and vital sign monitoring; physical and neurological examinations; behavioral assessments (Achenbach Child Behavior Checklist [CBCL]); and cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]/BRIEF®-Preschool Version [BRIEF®-P]).

2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). 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 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (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 (VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the United States (tablets, oral solution, and solution for intravenous [iv] infusion) and in patients 16 years of age and older in the European Union (partial-onset seizures with or without secondary generalization) (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, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in 1308 adult subjects, aged 16 to 70 years, established the efficacy of oral LCM as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with difficult to control partial-onset seizures. In these studies, LCM was initiated at a dose of 100mg/day (in 2 divided doses) and escalated to the randomized dose (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, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent adverse events (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, nausea, and diplopia. The nature and frequency of 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 placebo for the adjunctive treatment of partial-onset seizures in adult clinical studies were also shown to be superior to placebo 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 twice-daily 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 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. In SP1047, subjects with epilepsy receive LCM oral tablets (50mg, 100mg, 150mg, or 200mg), or LCM oral solution (LCM 10mg/mL) that they had been prescribed for epilepsy and brought with them to the clinic for dosing. Preliminary data have not demonstrated any clinically relevant changes in vital signs, in ECGs, or in clinical laboratory values; or evidence of cardiac-related treatment-emergent AEs or body weight changes. Preliminary PK data suggest that exposure-response in pediatric subjects 2 years to 17 years of age and adult subjects treated with LCM will be similar.

SP0969 is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for subjects weighing ≥50kg,

or matching placebo) as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled partial-onset seizures.

3 STUDY OBJECTIVES

The primary objective of this study is to evaluate the efficacy of LCM administered concomitantly with 1 to ≤3 AEDs in subjects with epilepsy ≥4 years to <17 years of age who currently have uncontrolled partial-onset seizures.

The secondary objective is to evaluate the safety and tolerability of LCM in subjects ≥4 years to <17 years of age.

An additional objective is to evaluate the PK of LCM in subjects ≥4 years to <17 years of age.

4 STUDY VARIABLES

4.1 Efficacy variables

The assessment of efficacy is based on partial-onset seizure frequency.

4.1.1 Primary efficacy variable

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period.

4.1.2 Secondary efficacy variables

The secondary efficacy variables are described below:

- Proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in partial-onset seizure frequency from Baseline to the Maintenance Period
- Proportion of subjects experiencing a ≥25% to <50%, 50% to 75%, or >75% reduction in partial-onset seizure frequency from Baseline to the end of Maintenance Period
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing a ≥25% to <50%, 50% to 75%, or >75% reduction in partial-onset seizure frequency from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing no change in partial-onset seizure frequency (between <25% reduction and <25% increase) from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing an increase in partial-onset seizure frequency of ≥25% from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods) by seizure type
- Proportion of seizure-free days during the Maintenance Period for subjects who entered the Maintenance Period

- Proportion of subjects who achieved "seizure-free" status (yes/no) for subjects who completed the Maintenance Period

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
- Quality of life assessments (PedsQL)
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol)

4.2 Safety variables

4.2.1 Primary safety variables

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

- Adverse events reported spontaneously by the subject and/or caregiver (including parent/legal guardian) or observed by the investigator
- Subject withdrawals due to AEs

4.2.2 Other safety variables

- Changes in hematology, clinical chemistry, and endocrinology parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate)
- Physical and neurological examination findings
- Changes in body weight, height, and calculated body mass index
- Behavioral assessments (Achenbach CBCL/1½-5 or CBCL/6-18)
- Cognitive function assessments (BRIEF-P/BRIEF)

4.3 Pharmacokinetic and pharmacodynamic variables

Plasma concentrations of LCM and concomitant AEDs will be obtained in order to:

- Develop a population PK model of LCM
- Investigate the effect of LCM on the steady-state plasma concentrations of concomitant AEDs
- Investigate the correlation between LCM plasma concentrations and efficacy or safety

5 STUDY DESIGN

5.1 Study description

SP0969 is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day [oral solution] for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day [oral solution] for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day [tablets] for subjects weighing ≥50kg, or matching placebo) as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled partial-onset seizures. Subjects weighing ≥50kg who are unable or unwilling to swallow tablets may receive LCM oral solution; however, they are not permitted to exceed the maximum dose of LCM 400mg/day.

The study consists of the following periods:

Baseline Period

Subjects with uncontrolled partial-onset seizures will be enrolled into an 8-week Baseline Period. At the end of the Baseline Period, subjects will be randomized in a double-blind manner to 1 of 2 parallel treatment arms: LCM or placebo in a 1:1 ratio.

Titration Period

Eligible subjects will enter a 6-week Titration Period (with study medication dosing flexibility allowed based on tolerability) to achieve the target Maintenance Period dose (LCM 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for subjects weighing ≥50kg, or matching placebo). For subjects who require study medication dosing flexibility based on tolerability, there is no limit to the number of back titration steps or dose holds allowed and all are at the investigator's discretion; however, subjects must remain on the back-titrated dose for ≥3 days before the dose may be increased. Subjects must achieve the minimum target dose for their body weight category for the final 3 days of the Titration Period to be eligible for entry into the Maintenance Period. If it becomes apparent that a subject will not be able to reach the minimum target dose, then the subject should be withdrawn from the study and enter the Taper Period.

The recommended LCM (or matching placebo) dosing during the Titration Period to achieve the target doses for the Maintenance Period is provided in Table 7–1; subjects are required to comply with Week 1 dosing as shown. Subsequent to Week 1, dosing flexibility based on tolerability is permitted as described in Table 7–2.

Maintenance Period

Subjects who achieved at least the minimum target study medication (LCM or matching placebo) dose for the final 3 days of the Titration Period will enter a 10-week Maintenance Period on the study medication dose achieved on the final day of the Titration Period. Lacosamide dose (or matching placebo) will remain stable throughout the Maintenance Period. Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will enter the blinded Transition Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn and enter the

blinded Taper Period. Subjects who choose not to participate in EP0034 will also enter the Taper Period.

Transition Period

Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will enter a 4-week blinded Transition Period. Subjects randomized to LCM will maintain their Maintenance Period dose during the Transition Period. Subjects randomized to placebo will transition to LCM in a double-blind fashion in accordance with the schedule provided in Table 7–4.

Taper Period

The blinded Taper Period (2 to 4 weeks, depending on dose level achieved) is for subjects who will not be entering the open-label extension study (EP0034) for any of the following reasons:

- Subject does not complete the Titration Period, the Maintenance Period, or the Transition Period.
- Subject does not choose to enroll in the open-label extension study (EP0034) after completing the Maintenance Period or the Transition Period.

Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

The dosing of study medication for the Taper Period is provided in Table 7–5.

Safety Follow-Up Period

There will be a 30-day Safety Follow-Up Period for subjects not entering the open-label extension study (EP0034).

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

Each subject's participation in the study begins with an 8-week Baseline Period. Each subject's total duration of study medication administration is up to 24 weeks; this includes a 6-week Titration Period, a 10-week Maintenance Period, and a 4-week Transition Period (for subjects who plan to enter the open-label extension study [EP0034]) and a Taper Period (2 to 4 weeks, depending on dose level achieved for subjects who will not be entering EP0034). The total study duration can be up to 36 weeks, including the 30-day Safety Follow-Up Period. Both the total duration of study medication and the total study duration include the possibility of a subject who completes the Transition Period choosing not to participate in EP0034 and having to enter the Taper Period.

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 300 subjects are planned to be randomized.

Stratification of subjects by age category is planned to ensure that an appropriate number of subjects will be included in each age range. The age categories are as follows:

- At least 100 subjects ≥4 years to <12 years of age
- At least 100 subjects ≥12 years to <17 years of age

Approximately 149 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 the [redacted], and the [redacted] with the possibility to expand the study to other countries and regions if deemed necessary.

5.2 Schedule of study assessments

Table 5-1, Table 5-2, and Table 5-3 present the tabular schedules of study procedures.

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, Early Termination Visit, and Unscheduled Visits)

Assessments	Baseline Period (8 weeks)			Treatment Period (16 weeks)												
				Titration Period (6 weeks)						Maintenance Period (10 weeks)						
Visit	V1[a]	T1	V2	T2	V3	T3	V4	T4	V5	V6	T5	V7	T6	V8[b]	ET	Unscheduled Visit[c]
Week in study	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16		
Informed consent	X															
Inclusion/exclusion criteria	X	X	X													
Medical history[d]	X															
Seizure history	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VNS assessment[e]	X		X		X		X		X	X		X		X	X	X
Physical examination (complete)	X		X											X	X	
Physical examination (brief)					X		X		X	X		X				
Tanner Stage[f]	X													X	X	
Vital signs (BP and pulse rate, including orthostatic assessments)	X		X		X		X		X	X		X		X	X	X
Body weight[g]	X		X[g]		X		X		X	X		X		X	X	X
Height	X		X											X	X	
Head circumference	X													X	X	
Neurological examination (complete)	X		X											X	X	
Neurological examination (brief)					X		X		X	X		X				
ECG (12-lead)[h]	X		X		X		X		X	X		X		X	X	

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, Early Termination Visit, and Unscheduled Visits)

Assessments	Baseline Period (8 weeks)			Treatment Period (16 weeks)												
				Titration Period (6 weeks)						Maintenance Period (10 weeks)						
Visit	V1[a]	T1	V2	T2	V3	T3	V4	T4	V5	V6	T5	V7	T6	V8[b]	ET	Unscheduled Visit[c]
Week in study	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16		
Clinical chemistry/hematology	X		X				X		X			X		X	X	
Endocrinology			X											X	X	
Urinalysis[i]	X		X				X		X			X		X	X	
Serum pregnancy test[j]	X						X		X			X		X	X	
Urine pregnancy test[j]			X		X					X						
Concomitant AED plasma concentrations[k]	X								X					X	X	
LCM plasma concentration[k]	X								X					X	X	
C-SSRS[l]	X		X		X		X		X	X		X		X	X	X
Clinical Global Impression of Change														X	X	
Caregiver's Global Impression of Change														X	X	
Achenbach CBCL[m]			X						X					X	X	
BRIEF-P/BRIEF[n]			X											X	X	
PedsQL[o]			X											X	X	
Contact IXRS	X		X		X		X		X	X		X		X	X	
Randomization[p]			X													
Dispense study medication			X[t]		X		X		X	X		X		X	X	
Study medication return					X		X		X	X		X		X	X	
Subject diary[q]	X	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

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, Early Termination Visit, and Unscheduled Visits)

Assessments	Baseline Period (8 weeks)			Treatment Period (16 weeks)												
				Titration Period (6 weeks)						Maintenance Period (10 weeks)						
Visit	V1[a]	T1	V2	T2	V3	T3	V4	T4	V5	V6	T5	V7	T6	V8[b]	ET	Unscheduled Visit[c]
Week in study	-8	-4	0	1	2	3	4	5	6	8	10	12	14	16		
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments of epilepsy surgery/VNS	X															
Health care resource use	X		X		X		X		X	X		X		X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Early Termination Visit; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; T=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

Note: For all visits shown in Table 5-1, a time window of ±2 days relative to Visit 2 (Baseline Period) is applicable. During the Treatment Period, each visit should occur at the end of the week indicated in accordance with this time window.

[a] Visit 1 (V1) may occur over more than 1 day; however, all results of Baseline/Visit 1 assessments should be available before randomization on Visit 2.

[b] At the end of Visit 8, subjects who complete the Maintenance Period may be eligible to participate in an open-label extension study (EP0034). Subjects who plan to enroll in the open-label extension study will proceed to a 4-week blinded Transition Period. Subjects who choose not to enter the open-label extension study or who do not complete the Maintenance Period will proceed to a blinded Taper Period (2 to 4 weeks, depending on dose level achieved). Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

[c] If an Unscheduled Visit is needed (eg, due to AE), then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion. The C-SSRS will be completed at an Unscheduled Visit only if the visit is related to an AE.

[d] Medical history to include demographics (date of birth [where permitted], age group category, age in months and years, race, ethnicity, and gender).

[e] Only applicable for subjects with an implanted VNS device.

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

[g] The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

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

[i] Urinalysis will be performed for subjects ≥5 years of age only.

[j] Pregnancy tests will be performed for female subjects of childbearing potential only.
[k] Blood samples for analysis of concomitant AED plasma concentrations and/or LCM will be drawn along with clinical chemistry, hematology, and endocrinology samples, as applicable.
[l] The C-SSRS will be completed for all subjects ≥6 years of age. The C-SSRS will be completed at an Unscheduled Visit only if the visit related to an AE.
[m] The Achenbach CBCL: CBCL/1½ -5 for children 18 months to 5 years and 11 months of age, and CBCL/6-18 for children ≥6 years to <17 years of age at Screening; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each subject, the same version of the scale that was completed at Visit 2 (CBCL/1½ -5 or CBCL/6-18) should be maintained for the duration of the study and should be completed by the same parent/legal representative. The Achenbach CBCL will be used only in countries where a translated version is available.
[n] The BRIEF-P should be used for subjects who are ≥2 years to <5 years of age at Visit 2, and the BRIEF should be used for subjects who are ≥5 years of age at Visit 2. The same version of the scale that was completed at Visit 2 (BRIEF-P or BRIEF) should be maintained for each subject for the duration of the study. The BRIEF-P and BRIEF will be used only in countries where a translated version is available.
[o] The version of the PedsQL used at Visit 2 should be consistent with the subject's age at Visit 2 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] At the end of Visit 2, subjects should take the first dose of study medication in the clinic.
[q] The subject diary will be dispensed at Visit 1. At all subsequent visits, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis.

Table 5-2 Schedule of study assessments (Transition Period)

Assessment	Transition Period (4 weeks)[a]			
Visit	TV1	TV2	TV3	TV4
Week in study	17[a]	18	19	20
Concomitant medications	X	X	X	X
Concomitant AEDs	X	X	X	X
VNS assessments[b]	X	X	X	X
Physical examination (complete)				X
Physical examination (brief)	X	X	X	
Vital signs (BP and pulse rate, including orthostatic assessment)	X	X	X	X
Body weight	X	X	X	X
Neurological examination (complete)				X
Neurological examination (brief)	X	X	X	
12-lead ECG[c]				X
Clinical chemistry/hematology				X
Urinalysis[d]				X
Urine pregnancy test[e]				X
Concomitant AED plasma[f] concentrations				X
LCM plasma concentration[f]				X
C-SSRS[g]	X	X	X	X
Contact IXRS	X	X	X	X
Dispense study medication	X	X	X	
Study medication return	X	X	X	X
Subject diary[h]	X	X	X	X
Withdrawal criteria	X	X	X	X
AE reporting	X	X	X	X
Health care resource use	X	X	X	X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IXRS=interactive voice/web response system; LCM=lacosamide; TV=Transition Visit; VNS=vagus nerve stimulation

Note: For all visits shown in Table 5-2, a window of ±2 days relative to Visit 2 (Baseline Period) is applicable. Each visit should occur at the end of the week indicated in accordance with this time window.

[a] At the end of Visit 8, (Maintenance Period), subjects may be eligible to participate in an open-label extension study (EP0034). Subjects who plan to enroll in the open-label extension study will enter a 4-week blinded Transition Period.

[b] Only applicable for subjects with an implanted VNS device.

[c] A 12-lead ECG (2 interpretable recordings) will be performed prior to any blood draws and vital signs

Table 5-2 Schedule of study assessments (Transition Period)

Assessment	Transition Period (4 weeks)[a]			
Visit	TV1	TV2	TV3	TV4
Week in study	17[a]	18	19	20

assessment. The subject should rest in the supine position for approximately 5 minutes before the ECG recording and during the recordings if possible. The recordings should be made 20 to 30 minutes apart.

[d] Urinalysis will be performed for subjects ≥5 years of age only.

[e] Pregnancy tests will be performed for female subjects of childbearing potential only.

[f] Blood samples for analysis of concomitant AED plasma concentrations and/or LCM will be drawn along with clinical chemistry, hematology, and endocrinology samples, as applicable.

[g] The C-SSRS will be completed for all subjects ≥6 years of age.

[h] The subject diary will be returned at TV4. At all other visits, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis.

Table 5-3 Schedule of study assessments (Taper Period and Safety Follow-Up Period)

	Taper Period[a] (2 to 4 weeks)		Safety Follow-Up Period[b] (30 days)	
Assessment				
Visit	T7[c]	Taper Visit[d]	Safety Follow-Up Visit	Safety Follow-Up Telephone Contact
Week in study	17	18, 19, or 20	20, 21, or 22	22, 23, or 24
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 (BP and pulse rate, including orthostatic assessment)		X	X	
Body weight		X	X	
Neurological examination (brief)		X		
Neurological examination (complete)			X	
ECG (12-lead)[f]		X	X[g]	
Clinical chemistry/hematology		X	X[g]	
Endocrinology		X	X[g]	
Urinalysis[h]		X	X	
Serum pregnancy test		X	X[i]	

Table 5-3 Schedule of study assessments (Taper Period and Safety Follow-Up Period)

	Taper Period[a] (2 to 4 weeks)		Safety Follow-Up Period[b] (30 days)	
Assessment				
Visit	T7[c]	Taper Visit[d]	Safety Follow-Up Visit	Safety Follow-Up Telephone Contact
Week in study	17	18, 19, or 20	20, 21, or 22	22, 23, or 24
Urine pregnancy test			X[i]	
C-SSRS[j]		X	X	
Contact IXRS		X		
Study medication return		X		
Subject diary[k]	X	X		
Withdrawal criteria	X	X		
AE reporting	X	X	X	X
Health care resource use		X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IXRS=interactive voice/web response system; LCM=lacosamide; T=Telephone Contact; VNS=vagus nerve stimulation

Note: The study week numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study week numbers provided do not apply to subjects who enter the Taper Period at other times.

[a] A blinded Taper Period (2 to 4 weeks, depending on dose achieved) will be required for subjects who discontinue study medication prematurely and for subjects who complete the Maintenance Period but choose not to enter the open-label extension study (EP0034). Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and or parent/legal representative.

[b] The Safety Follow-Up Visit will occur 2 weeks (±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.

[c] A telephone contact (T7) will be conducted at the end of the first week of the Taper Period.

[d] Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Week 18, Week 19, or Week 20, depending on dose level achieved; see Table 7–5). A time window of ±2 days relative to Visit 2 (Baseline Period) is applicable.

[e] Only applicable for subjects with an implanted VNS device.

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

[g] The assessment will only be required for subjects with an abnormal value (clinical chemistry, hematology, or endocrinology) or reading (ECG) at the previous clinic visit.

[h] Urinalysis will be performed for subjects ≥5 years of age only.

[i] Pregnancy tests will be performed for female subjects of childbearing potential only. A serum pregnancy test will be performed at the Safety Follow-Up Visit only if blood is collected for other laboratory tests. If no blood is collected for other assessments, then a urine pregnancy test will be performed.

[j] The C-SSRS will be completed for all subjects ≥6 years of age.

Table 5-3 Schedule of study assessments (Taper Period and Safety Follow-Up Period)

	Taper Period[a] (2 to 4 weeks)		Safety Follow-Up Period[b] (30 days)	
Assessment				
Visit	**T7[c]**	**Taper Visit[d]**	**Safety Follow-Up Visit**	**Safety Follow-Up Telephone Contact**
Week in study	**17**	**18, 19, or 20**	**20, 21, or 22**	**22, 23, or 24**

[a] At T7, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis. The subject diary will be returned at the Taper Visit.

5.3 Schematic diagram

An overall schematic diagram with successive panels for each body weight category (<30kg, ≥30kg to <50kg, and ≥50kg) is provided in Figure 5–1. The schematic diagram for the Transition Period is provided in Figure 5–2.

Figure 5–1: SP0969 overall schematic diagram

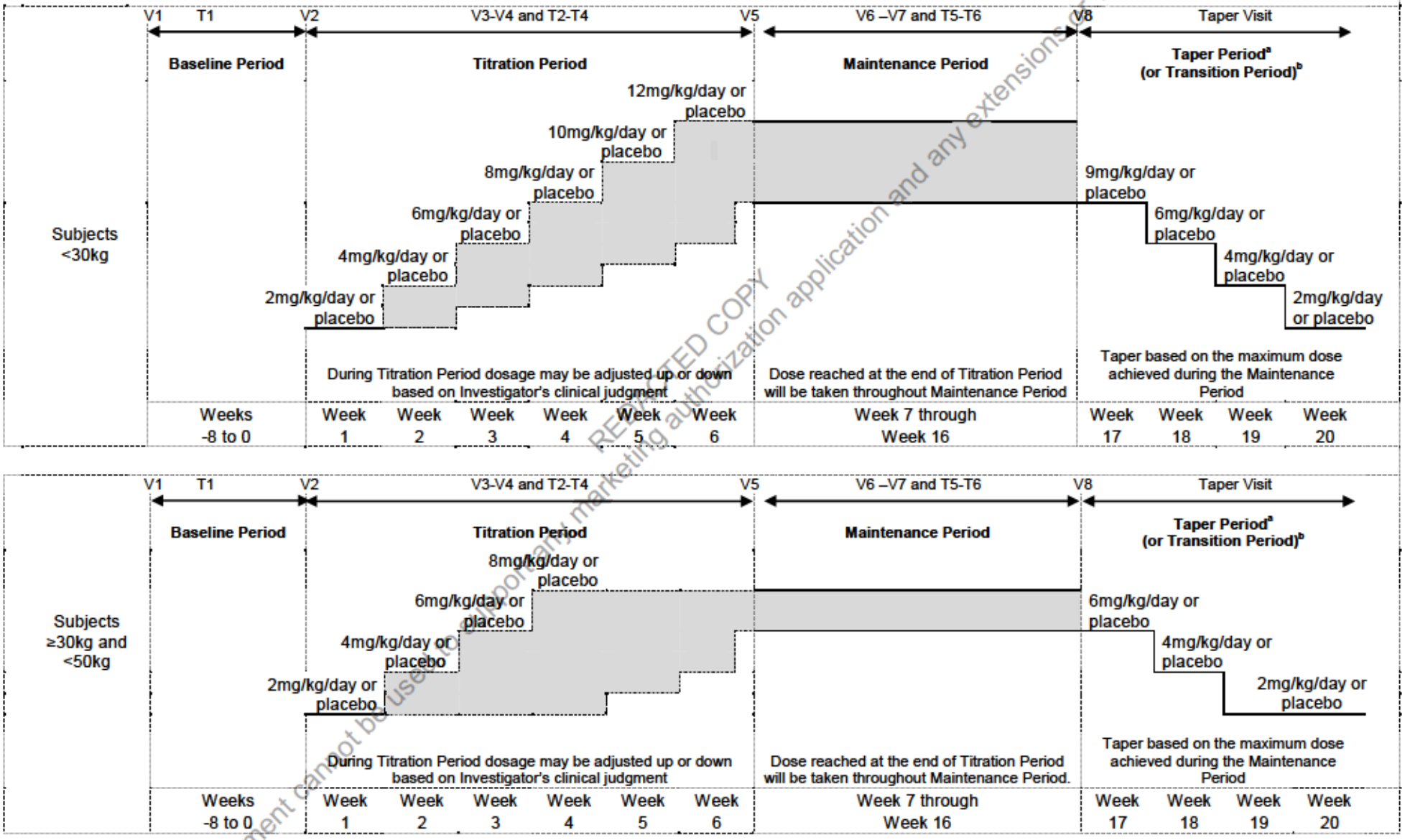
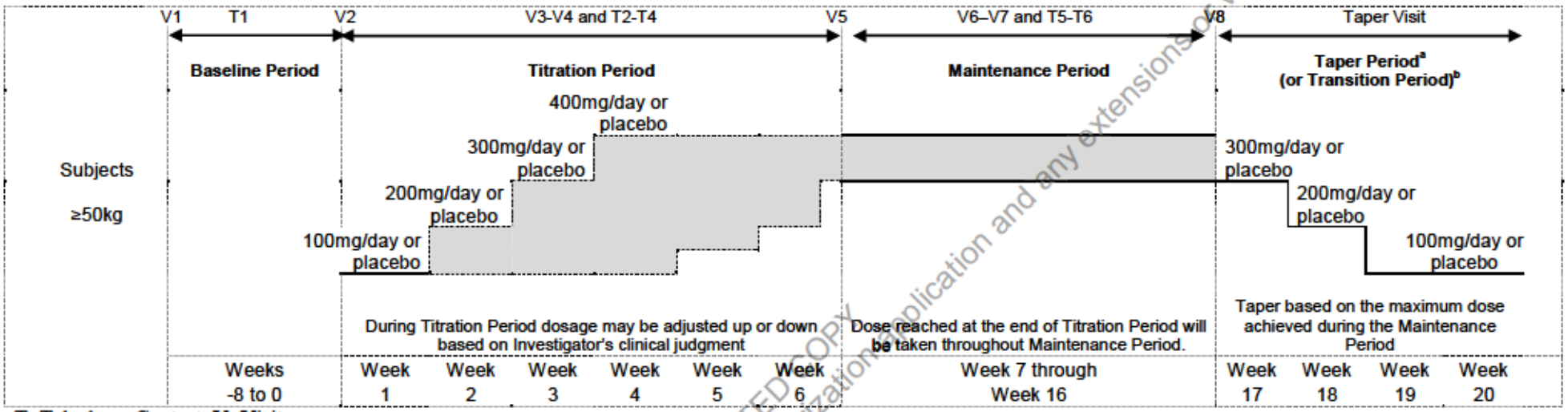


Figure 5-1: SP0969 overall schematic diagram



T=Telephone Contact; V=Visit

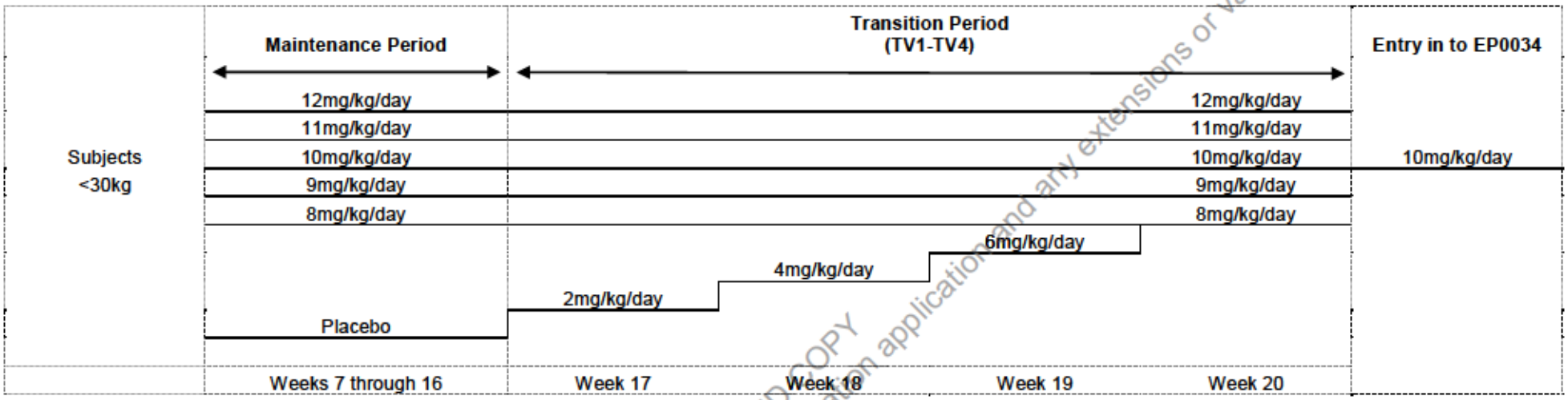
Note: LCM dosing is designated as "mg/kg/day" (oral solution) and "mg/day" (tablets), and matching placebo is shown as "placebo."

Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

[a] The study week numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study week numbers provided do not apply to subjects who enter the Taper Period at other times. The highest possible dose for each week of taper for each body weight category is shown; complete dosing information for the Taper Period is provided in Table 7–5. Taper of LCM may not be required for some subjects who discontinue study medication prematurely depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative. There will be a 30-day Safety Follow-Up Period (see Table 5-3) for subjects not entering EP0034.

[b] Subjects who complete the Maintenance Period and plan to participate in the open-label extension study (EP0034) will participate in a 4-week blinded Transition Period with dosing as shown in Figure 5–2.

Figure 5–2: SP0969 schematic diagram (Transition Period)



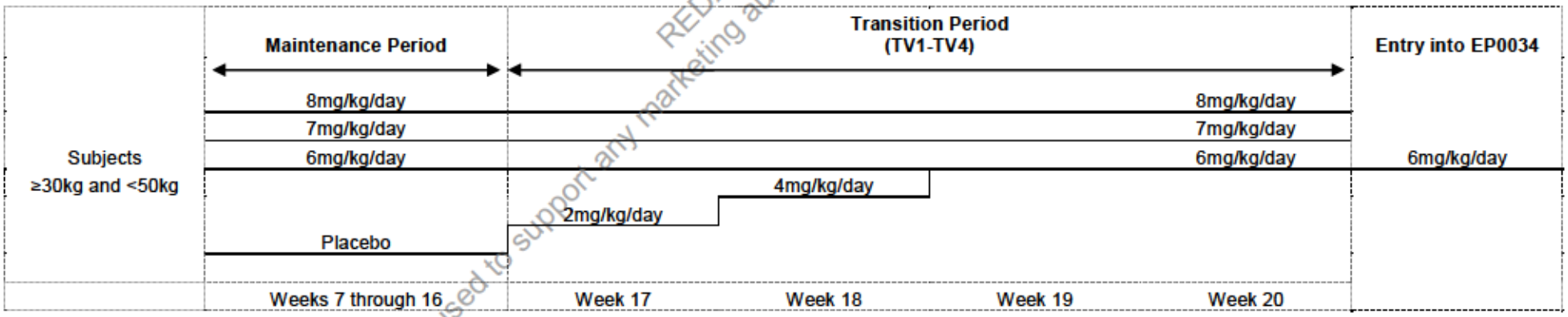
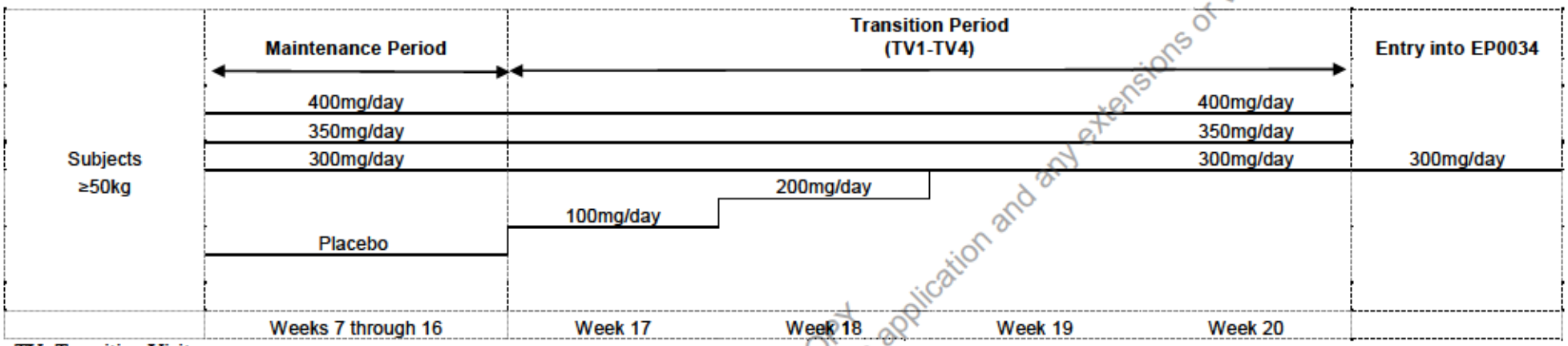


Figure 5-2: SP0969 schematic diagram (Transition Period)



TV=Transition Visit
Note: LCM dosing is designated as "mg/kg/day" (oral solution) and "mg/day" (tablets), and matching placebo is shown as "placebo."
Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

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 with epilepsy ≥16 years of age with partial-onset seizures, 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 partial-onset seizures.

SP0969 is a Phase 3 multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial-onset seizures. A Phase 3 study (SP0967) investigating the use of LCM in subjects with epilepsy ≥1 month to <4 years of age with partial-onset seizures is planned.

Based on the currently available LCM pediatric safety and PK data from SP847 and SP1047, as well as on information available in the medical literature, the dosing recommendations for SP0969 are as follows to achieve LCM plasma concentrations corresponding to the average steady-state LCM plasma concentration (C_{ss}) reached after a LCM 400mg/day dose administration in adult studies, which is approximately 8µg/mL:

- A weight-based dosing scheme is recommended for the Maintenance Period:
  - Subjects <30kg: LCM 8mg/kg/day to 12mg/kg/day
  - Subjects ≥30kg to <50kg: LCM 6mg/kg/day to 8mg/kg/day
  - Subjects ≥50kg: LCM 300mg/day to 400mg/day
- The LCM (or matching placebo) dose should otherwise remain fixed over the Maintenance Period.
- To provide dosing flexibility and optimize tolerability for each subject during titration, flexible study medication dosing to achieve a minimum target dose for entry into the Maintenance Period. The dosing flexibility during the Titration Period includes 4 key elements:
  - A Titration Period of 6 weeks to allow sufficient time to achieve the minimum target dose for entry into the Maintenance Period for subjects who require study medication dosing flexibility based on tolerability.
  - Allowing investigators to hold a subject's study medication dose constant at any time during the Titration Period and allowing for multiple holds if needed.
  - Allowing investigators to back titrate a subject's study medication dose by full-step or half-step increments, with asymmetric dosing as needed for tablets.
  - Allowing flexibility in the duration a subject must remain on a back-titrated study medication dose before a subsequent increase.

- Administration of oral solution by feeding tube is permitted for subjects who are unable to swallow the oral solution; however, they are not permitted to exceed the maximum dose of LCM 400mg/day.
- Dosing with oral solution is permitted for subjects weighing ≥50kg who are unable or unwilling to swallow tablets.

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 dated by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female from ≥4 years to <17 years of age.
4. Subject has a diagnosis of epilepsy with partial-onset seizures. The results of ≥1 prior electroencephalogram (EEG) AND 1 prior magnetic resonance imaging/computerized tomography scan should be consistent with the above diagnosis.
5. Subject has been observed to have uncontrolled partial-onset seizures after an adequate course of treatment (in the opinion of the investigator) with ≥2 AEDs (concurrently or sequentially).
6. Subject must have been observed to have on average ≥2 partial-onset seizures per 28 days with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the Baseline Period. During this study, subjects must have reported ≥2 partial-onset seizures during the 8-week prospective Baseline Period to be eligible for randomization at Visit 2. (Note: In the case of simple partial-onset seizures, only those seizures with motor signs will be counted towards meeting the inclusion criterion.)
7. Subject is on a stable dosage regimen of 1 to ≤3 AEDs. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of ≥4 weeks prior to the Baseline Period.
8. Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. The VNS device must be implanted for ≥6 months before Visit 1, and the device settings must be stable for ≥4 weeks before Visit 1 and be kept stable during the Baseline Period. Use of the VNS device magnet is allowed.

6.2 Exclusion criteria

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

1. Subject has previously participated in this study or subject has been assigned to LCM in a previous LCM study.
2. Subject has participated in another study of an investigational medicinal product (IMP) or a medical device within ≤2 months of 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.
4. Subject ≥6 years of age has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.
5. Subject has a known hypersensitivity to any component of the IMP or has ever received LCM.
6. Female subject who is pregnant or nursing, and/or a female subject of childbearing potential who is not surgically sterile or does not practice 1 highly effective method of contraception (according to International Conference on Harmonisation [ICH] guidance defined as those that result in a failure rate of less than 1% per year when used consistently and correctly), unless sexually abstinent, for the duration of the study. Female subject of childbearing potential taking enzyme-inducing antiepileptic drugs (EI-AEDs: carbamazepine, phenytoin, barbiturates, primidone, topiramate, oxcarbazepine) who is not surgically sterile or does not practice 1 highly effective method of contraception according to the WHO recommendation (ie, depot medroxyprogesterone acetate, norethisterone enantate, intrauterine devices, combined injectables, and progestogen implants) with administration of EI-AEDs OR does not practice 2 combined methods of contraception (ie, combined hormonal contraception plus barrier method with spermicidal agent), unless sexually abstinent, for the duration of the study.
7. Subject has a medical condition that could be expected in the opinion of the investigator to interfere with drug absorption, distribution, metabolism, or excretion.
8. Subject has experienced febrile seizures exclusively. The occurrence of febrile seizures in addition to other unprovoked seizures is not exclusionary.
9. Subject is on a ketogenic or other specialized diet. If the subject was on a specialized diet in the past, they must be off the diet for ≥2 months prior to the Baseline Period.
10. Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level ≥2 times the upper limit of normal (ULN), or creatinine clearance less than 30mL/min.
11. 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] greater than 450ms).

12. Subject has hemodynamically significant congenital heart disease.
13. Subject has an arrhythmic heart condition requiring medical therapy.
14. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
15. Subject has nonepileptic events that could be confused with seizures.
16. Subject has a current diagnosis of Lennox-Gastaut syndrome, primary generalized epilepsy, mixed seizure disorder (partial and primarily generalized seizures), or purely nocturnal seizures.
17. Subject has a history of convulsive status epilepticus ≤2 months prior to the Baseline Period.
18. Subject has been treated with vigabatrin and experienced any vision loss. Subjects who have received vigabatrin in the past must have documentation of an assessment for vision loss prior to study entry or documentation of why visual field testing cannot be performed.
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. Note: any subject who has been treated with felbamate for ≥12 months and has not experienced serious toxicity issues is eligible.
21. Subject has a medically documented history of alcohol or drug abuse.
22. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.
23. Subject has an acute or sub-acutely 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).

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects **must** be withdrawn from this 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.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject has QTc interval ≥500ms that is confirmed by a cardiologist overread on any ECG.
4. Subject develops a second degree atrioventricular (AV) block while awake or develops a third degree AV block.
5. For subjects ≥6 years of age, subject has actual suicidal ideation since last visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

6. Subject is unwilling or unable to continue, or the parent/legal representative is unwilling or unable to allow the subject to continue in the study.
7. Investigator decides that withdrawal from further participation would be in the subject's best interest.
8. Subject experiences convulsive status epilepticus.
9. Subject uses rescue medication in excess of that permitted by the protocol.
10. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x ULN to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST, ALT, or both) ≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case >1 week later.
11. Female subject who achieves menarche and does not practice contraception as provided in Exclusion Criteria 6 unless sexually abstinent. Subject becomes pregnant, as evidenced by a positive pregnancy test.
12. Subject needs any alteration in AED daily dose or VNS settings.

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

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

Investigators should attempt to obtain information on subjects, in the case of withdrawal or discontinuation. For subjects considered as lost to follow-up, the investigator should make every effort (≥1 phone call and 1 written message to the parent[s] or legal representative), 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 Case Report form (CRF) must document the primary reason for withdrawal or discontinuation.

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

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

The IMP will be provided as LCM oral solution (syrup) (LCM 10mg/mL), LCM tablets (LCM 50mg and LCM 100mg), and matching placebos.

The LCM 10mg/mL oral solution and matching placebo oral solution are colorless to pale yellow in appearance. Both oral solutions will be packaged in amber polyethylene terephthalate (PET) bottles. Oral solution doses will be measured and administered via a dosing syringe.

The LCM 50mg tablets and matching placebo are pinkish, oval tablets debossed with "SP" on one side and "50" on the other side. The LCM 100mg tablets and matching placebo are dark yellow, oval tablets debossed with "SP" on one side and "100" on the other side. Tablets will be packaged in high density polyethylene (HDPE) bottles.

7.2 Treatments to be administered

Study medication will be administered orally bid (at approximately 12-hour intervals in the morning and in the evening).

At Visit 2, subjects will be randomized to receive either LCM (oral solution for subjects weighing <50kg or tablets for subjects weighing ≥50kg), or matching placebo. Oral solution will be allowed for subjects weighing ≥50kg who are unwilling or unable to swallow tablets; however, they are not permitted to exceed the maximum dose of LCM 400mg/day. Administration of oral solution by feeding tube is permitted for subjects who are unable to swallow the oral solution.

At the end of Visit 2, 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). The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

SP0969 will target Maintenance Period doses of LCM 8mg/kg/day to 12mg/kg/day for subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for subjects weighing ≥50kg, or matching placebo.

7.2.1 Titration Period

Table 7–1 provides the recommended LCM (or matching placebo) dosing during the Titration Period for subjects to reach the target doses for the Maintenance Period. All subjects are required to complete Week 1 study medication dosing before dosing flexibility is allowed based on tolerability.

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

Body weight category (formulation)	Target LCM (or matching placebo) doses for the Titration Period					
	Week 1[a]	Week 2	Week 3	Week 4	Week 5	Week 6
<30kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/day	12mg/kg/day
≥30kg to <50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	8mg/kg/day	8mg/kg/day
≥50kg (tablets)	100mg/day	200mg/day	300mg/day	400mg/day	400mg/day	400mg/day

LCM=lacosamide
Note: Subjects may not receive doses higher than LCM 12mg/kg/day (body weight <30kg), LCM 8mg/kg/day (body weight ≥30kg to <50kg), or LCM 400mg/day (body weight ≥50kg), or matching placebo.
Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.
[a] All subjects are required to complete Week 1 study medication dosing before dosing flexibility is allowed based on tolerability. Subjects who are unable to complete the Titration Period or subjects who will not be able to attain at least the minimum Maintenance Period target dose, should be withdrawn and enter the Taper Period.

After completion of Week 1, investigators will assess whether a subject would tolerate a further dose increase or whether a subject should hold the Week 1 dose for a longer duration. This hold will be at the investigator's discretion.

Table 7–2 provides LCM (or matching placebo) dosing with flexibility based on tolerability during the Titration Period.

Table 7–2: Dosing of LCM (or matching placebo) with flexibility based on tolerability during the Titration Period

Body weight category (formulation)	Target LCM (or matching placebo) dose increase/week[a] (titration)	LCM (or matching placebo) dose decrease per back titration step		Subsequent LCM (or matching placebo) dose increase[b] (dose increase after back titration step)	
		Min	Max	Min	Max
<30kg (oral solution)	2mg/kg/day	1mg/kg/day	2mg/kg/day	1mg/kg/day	2mg/kg/day
≥30kg to <50kg (oral solution)					
≥50kg (tablets)	100mg/day	50mg/day	100mg/day	50mg/day	100mg/day

LCM=lacosamide; Max=maximum; Min=minimum
Note: Asymmetrical dosing with no more than 50mg difference between morning and evening doses will be allowed for subjects taking tablets who require back titration in a 50mg increment (ie, only 50mg and 100mg tablets are available).
Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.
[a] Titration step to achieve a dose not previously administered
[b] Titration step subsequent to a back titration

There is no limit to the number of back titration steps or dose holds allowed and all are at the investigator's discretion; however, subjects must achieve the minimum LCM (or matching placebo) target dose for their body weight category by the end of the Titration Period. If it becomes apparent that a 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.

Subjects who have their study medication titrated to a higher dose not previously administered should remain at that dose for ≥7 days unless a back titration step is required based on tolerability. Subjects who have their study medication back titrated must remain on the lower dose for ≥3 days (in order to reach steady state) before a subsequent dose increase. After back titration, subjects who return to a higher dose previously administered must maintain that dose for ≥3 days before subsequent titration to a higher dose.

As outlined in Table 7–3, subjects will be required to achieve and maintain at least a minimum LCM (or matching placebo) dose for at least the final 3 days of Week 6 to be eligible for entry into the Maintenance Period. Subjects may have a back titration step as late as the last day of Week 6, as long as the minimum target dose is maintained.

Table 7–3: Required LCM (or matching placebo) dose for at least the final 3 days of Week 6

Body weight category (formulation)	LCM (or matching placebo) dose for at least the final 3 days of Week 6	
	Min	Max
<30kg (oral solution)	8mg/kg/day	12mg/kg/day
≥30kg to <50kg (oral solution)	6mg/kg/day	8mg/kg/day
≥50kg (tablets)	300mg/day	400mg/day

LCM=lacosamide; Max=maximum; Min=minimum
Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

7.2.2 Maintenance Period

Subjects who reach and maintain at least the minimum study medication dose for at least the final 3 days of the Titration Period, will enter a 10-week Maintenance Period at the dose they received on the final day of the Titration Period (Table 7–3). Lacosamide (or matching placebo) doses will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the Maintenance Period and enter the Taper Period. Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

7.2.3 Transition Period (for subjects who plan to enter EP0034)

At the end of the Maintenance Period (Visit 8), all subjects who complete the Maintenance Period will be offered the opportunity to enroll in an open-label extension study (EP0034). Subjects who plan to enroll in EP0034 will proceed to a 4-week blinded Transition Period.

Subjects randomized to LCM will maintain their Maintenance Period dose throughout the Transition Period. Subjects randomized to placebo will transition in a double-blind fashion to LCM dosing as described Table 7–4. At the completion of the Transition Period, subjects eligible to enter EP0034 will be placed on a common dose (see Figure 5–2) based on body weight category at EP0034 entry.

Table 7–4: Transition Period LCM dosing schedule for subjects randomized to placebo

Body weight category (formulation)	LCM doses for the Transition Period			
	Week 17	Week 18	Week 19	Week 20
<30kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day
≥30kg to <50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	6mg/kg/day
≥50kg (tablets)	100mg/day	200mg/day	300mg/day	300mg/day

LCM=lacosamide
Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

7.2.4 Taper Period (for subjects not entering EP0034)

A blinded Taper Period (2 to 4 weeks, depending on dose achieved) will be required for subjects who discontinue study medication prematurely and for subjects who complete the Maintenance Period but choose not to enter the open-label extension study (EP0034). Table 7–5 provides the taper steps based on the dose of LCM (or matching placebo) achieved. A slow taper is permitted if medically necessary. Whenever possible, these cases should be discussed with the medical monitor prior to withdrawing the subject from the study, especially in cases in which withdrawal criteria have been met. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible. Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative.

Table 7–5: Taper Period dosing of LCM (or matching placebo)

LCM (or matching placebo) dose achieved	LCM (or matching placebo) doses for the Taper Period			
	Week 17	Week 18	Week 19	Week 20
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
3 or 4mg/kg/day	2mg/kg/day	2mg/kg/day	NA	NA
2mg/kg/day	NA	NA	NA	NA
350 or 400mg/day	300mg/day	200mg/day	100mg/day	100mg/day
250 or 300 mg/day	200mg/day	100mg/day	100mg/day	NA
150 or 200mg/day	100mg/day	100mg/day	NA	NA
100mg/day	NA	NA	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: The oral solution is dosed as mg/kg/day and tablets are dosed as mg/day.
Note: Subjects not requiring taper will enter directly into the Safety Follow-Up Period and not attend any Taper Period visits.
Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.
Note: The study week numbers provided are for subjects who complete the Maintenance Period and enter the Taper Period. The study week numbers provided do not apply to subjects who enter the Taper Period at other times.

7.3 Packaging

Lacosamide (tablets and oral solution) and matching placebos 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 tablets and matching placebos will be packaged in HDPE bottles.

Lacosamide 10mg/mL oral solution and matching placebo 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 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. The IMP stored by the investigator is to be kept in a secured area with limited access.

The IMP is to be stored according to the instructions on the label. Appropriate storage conditions must be ensured either by controlled room temperature, or by completion of a temperature log (showing minimum and maximum temperatures reached over the time interval) in accordance with local requirements on a regular basis.

In case an out-of-range temperature is noted, it must be immediately communicated to the sponsor's designee in accordance with the pharmacy manual.

The investigator (or designee) will instruct the subject 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 (due to breakage or wastage), not used, disposed of at the study site, or returned to the sponsor's 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) and unused IMP containers must be reconciled and returned to UCB's designee, preferably in their original package. The IMP 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, and empty IMP containers. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability Form.

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

Timely completion of the subject diary is essential for evaluation of safety and efficacy. Subject diary use will be confirmed at each visit and telephone contact.

7.8 Concomitant medications/treatments

7.8.1 Permitted and prohibited concomitant treatments (medications and therapies)

Subject must have been maintained on a stable dose regimen of 1 to ≤3 marketed AEDs for ≥4 weeks prior to Visit 1 (ie, prior to entry into the Baseline Period); the dose regimen of the AEDs must be kept stable throughout study participation.

Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. The VNS device must implanted for ≥6 months before Visit 1, and the device settings must be stable

for ≥4 weeks before Visit 1 and be kept stable during the Baseline Period, Treatment Period, and Transition Period. Use of the VNS device magnet is allowed.

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

- Neuroleptics
- Monoamine oxidase inhibitors
- Barbiturates (except as anti-epileptic medications)
- Narcotic analgesics

Subjects who have been treated with vigabatrin and experienced any vision loss are excluded from the study. Subjects who have received vigabatrin in the past must have documentation of an assessment for vision loss prior to study entry or documentation of why visual field testing cannot be performed.

Subjects who have been treated with felbamate and have experienced any serious toxicity issues (defined as liver failure, aplastic anemia) with this treatment are excluded from the study. Subjects treated with felbamate for <12 months are also excluded. Any subject who has been treated with felbamate for ≥12 months and has not experienced serious toxicity issues is eligible for the study.

The following medications are not allowed unless used as described:

- Amphetamines and sedative antihistamines: stable use only.
- Anxiolytics or once-daily hypnotics: stable, low doses of for nonepilepsy indications only.

The chronic use of benzodiazepines is allowed for treatment of epilepsy. Benzodiazepines taken for treatment of epilepsy will be counted as 1 of the AEDs, and the dose regimen must be stable for ≥28 days prior to Visit 1. Intermittent use of benzodiazepines as rescue therapy for epilepsy is allowed if taken at a maximum frequency of 1 day per month (with up to 3 doses within 24 hours).

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.

7.8.2 Rescue medication

The use of benzodiazepines as rescue therapy for epilepsy is allowed if taken at a maximum frequency of one day per month (with ≤3 doses within 24 hours) during study participation; more frequent use precludes subjects from study participation.

7.9 Blinding

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

Lacosamide (tablets and oral solution) and matching placebos are tablets identical in shape, size, and color. The blind is maintained as the accompanying packaging is identical in appearance so that neither the investigator (or designee) nor the subject is able to tell whether the subject is receiving LCM or placebo.

An interactive voice/web response system (IXRS) will be used to assign a treatment to subjects who meet eligibility criteria at Visit 2, 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 which 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 CPM 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 CRF page.

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 BIOSCIENCES. The randomization schedule will be produced by a UCB BIOSCIENCES biostatistician who is otherwise not involved in this study. The IXRS is responsible for issuing subject kits of study medication, as appropriate, according to the visit schedule.

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 (or designee) and the IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

To randomize a subject (Visit 2), 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.

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 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 2 (Baseline Period), with the exception of the Safety Follow-Up Visit, which should be scheduled 14 days (-1/+3 days) after the final dose of study medication.

The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

8.1 Baseline Period: Week -8 to Week 0

8.1.1 Baseline Period: Visit 1 (Week -8) (Screening)

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 before T1. 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 by the investigator (or designee). The subject or parent/legal representative 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, please refer to Section 9, Section 10, and Section 11 of this protocol):

- Medical history
- Seizure history
- Concomitant medications
- Concomitant AEDs
- VNS assessment (for subjects with an implanted VNS device)
- Physical examination (complete)
- Tanner Stage assessment
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Height assessment
- 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 the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Serum pregnancy test (for females of childbearing potential)
- Blood sample for measurement of concomitant AED plasma concentrations
- Blood sample for measurement of LCM plasma concentration
- C-SSRS (for subjects ≥6 years of age)
- Contact IXRS to obtain unique subject identification number
- Dispense subject diary
- AE reporting
- Assessments of subject's candidacy for epilepsy surgery/VNS
- Health care resource use

The subject will be scheduled to return to the clinic as specified in Table 5-1. The morning of the next clinic visit, the subject should take concomitant AEDs at the usual time(s).

8.1.2 Baseline Period: Telephone Contact 1 (Week -4)

If the subject is eligible to continue in the study, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting

8.1.3 Baseline Period: Visit 2 (Week 0) (Randomization)

At the beginning of this visit, the investigator should assess the partial-onset seizure frequency over the 8-week Baseline Period as recorded in the subject diary. On the basis of the diary, the subject must have reported at least 2 partial-onset seizures per 28 days on average, with no more than 21 consecutive seizure-free days during the 8 weeks prior to entry into the Baseline Period. During this study, subjects must have reported at least 2 partial-onset seizures during the 8-week prospective Baseline Period to be eligible for randomization at Visit 2. If the subject is eligible to continue in the study, the following assessments will be performed:

- Concomitant medications

- Concomitant AEDs
- VNS assessments (for subjects with an implanted VNS device)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Height assessment
- 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 the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Urine pregnancy test (for females of childbearing potential)
- C-SSRS (for subjects ≥6 years of age)
- Achenbach CBCL
- BRIEF-P/BRIEF score
- PedsQL score
- Contact IXRS
- Randomization
- Dispense study medication
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting
- Health care resource use

The subject will take the first dose of study medication in the clinic. The subject will be scheduled to return to the clinic as specified in Table 5-1. On the morning of the next clinic visit, the subject should take concomitant AEDs and study medication at the usual time(s).

8.2 Titration Period: Week 1 to Week 6

Both clinic visits and telephone contacts will be conducted during the Titration Period, beginning with Telephone Contact 2 at the end of Week 1 and continuing through Visit 5 at the end of Week 6. The subject should take concomitant AEDs and study medication at the usual time(s) on the morning of each clinic visit.

At each clinic visit and telephone contact, the investigator, in conjunction with the subject and/or parent(s)/legal representative(s), will decide how to proceed with study medication dosing based on tolerability (including vital signs, body weight, 12-lead ECG, and AE reporting, as applicable to the type of contact). If the withdrawal of study medication is required during the Titration Period, the subject will enter the blinded Taper Period (Section 8.5).

8.2.1 Titration Period: Telephone Contact 2 (Week 1), Telephone Contact 3 (Week 3), and Telephone Contact 4 (Week 5)

During the Titration Period telephone contacts (Telephone Contact 2, Telephone Contact 3, and Telephone Contact 4), the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting

8.2.2 Titration Period: Visit 3 (Week 2), Visit 4 (Week 4), and Visit 5 (Week 6)

During the Titration Period clinic visits (Visit 3, Visit 4, and Visit 5), the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (for subjects with an implanted VNS device)
- Physical examination (brief)
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Neurological examination (brief)
- 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 the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology (Visit 4 and Visit 5 only)
- Urine sample for urinalysis (for subjects ≥5 years of age) (Visit 4 and Visit 5 only)
- Serum pregnancy test (for females of childbearing potential) (Visit 4 and Visit 5 only)
- Urine pregnancy test (for females of childbearing potential) (Visit 3 only)
- Blood sample for determination of concomitant AED plasma concentration (Visit 5 only)

- Blood sample for determination of LCM plasma concentration (Visit 5 only)
- C-SSRS (for subjects ≥6 years of age)
- Achenbach CBCL (same version used at Visit 2) (Visit 5 only)
- Contact IXRS
- Dispense study medication
- Study medication return
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting
- Health care resource use

The subject will be scheduled to return to the clinic as specified in Table 5-1. The morning of the next clinic visit, the subject should take concomitant AEDs and study medication at the usual time(s).

8.3 Maintenance Period: Week 7 to Week 16

Subjects who complete the Titration Period will enter the 10-week Maintenance Period at the study medication dose they received on the final day of the Titration Period. Dose reduction is not allowed during the Maintenance Period; subjects who require dose reduction during the Maintenance Period will be withdrawn from the study. Subjects who are withdrawn will enter the Taper Period (see Section 7.2.4).

Beginning with Visit 6 at the end of Week 8 and continuing up to Visit 8 at the end of Week 16, alternating telephone contacts and clinic visits will be conducted during the Maintenance Period. 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 (Week 8) and Visit 7 (Week 12)

During Visit 6 and Visit 7 (clinic visits) of the Maintenance Period, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessments (for subjects with an implanted VNS device)
- Physical examination (brief)
- Vital signs (BP and pulse rate; including orthostatic assessments)
- Body weight assessment
- Neurological examination (brief)

- 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 the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology (Visit 7 only)
- Urine sample for urinalysis (for subjects ≥5 years of age) (Visit 7 only)
- Serum pregnancy test (for females of childbearing potential) (Visit 7 only)
- Urine pregnancy test (for females of childbearing potential) (Visit 6 only)
- C-SSRS (for subjects ≥6 years of age)
- Contact IXRS
- Dispense study medication
- Study medication return
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting
- Health care resource use

The subject will be scheduled to return to the clinic as specified in Table 5-1. The morning of the next clinic visit, the subject should take concomitant AEDs and study medication at the usual time(s).

8.3.2 Maintenance Period: Telephone Contact 5 (Week 10) and Telephone Contact 6 (Week 14)

During the Maintenance Period telephone contacts (Telephone Contact 5 and Telephone Contact 6); the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting

8.3.3 End of Maintenance Period: Visit 8 (Week 16)

For subjects who complete the Maintenance Period, Visit 8 will be the final Maintenance Period clinic visit.

At the completion of the Maintenance Period, investigators should discuss treatment options with the subject and/or their parent/legal representative to best manage the subject's epilepsy. Subjects who have completed the 10-week Maintenance Period will be given the opportunity to enroll in an open-label extension LCM study (EP0034). The decision made by the subject

or parent(s)/legal representative(s) and investigator regarding participation in the open-label extension study will be recorded in the IXRS and in the CRF. Subjects who plan to enroll in the open-label extension study will enter a 4-week blinded Transition Period.

Subjects who choose not to participate in the open-label extension study (EP0034) will enter a blinded Taper Period (2 to 4 weeks, depending on dose level achieved) (see Section 8.5) after completing Visit 8. Taper of LCM may not be required for some subjects who complete the Maintenance Period depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete Visit 8 and then complete the 30-day Safety Follow-Up Period after Visit 8 (see Section 8.6); the Taper Visit is not required for subjects who complete the Maintenance Period and who do not undergo taper of LCM.

During Visit 8, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (for subjects with an implanted VNS device)
- Physical examination (complete)
- Tanner Stage assessment
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Height assessment
- 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 the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Serum pregnancy test (for females of childbearing potential)
- Blood sample for measurement of concomitant AED plasma concentrations
- Blood sample for measurement of LCM plasma concentration
- C-SSRS (for subjects ≥6 years of age)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change

- Achenbach CBCL (same version used at Visit 2)
- BRIEF-P/BRIEF score (same version used at Visit 2)
- PedsQL score (same version used at Visit 2)
- Contact IXRS
- Dispense study medication for the following 4-week Transition Period or Taper Period (2 to 4 weeks), as applicable
- Study medication return
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting
- Health care resource use

Subjects who plan to enroll in EP0034, will be scheduled to return to the clinic as specified in Table 5-2 and subjects who do not plan to enroll in EP0034 will be scheduled to return to the clinic as specified in Table 5-3. Subjects who do not plan to enter either the Transition Period or the Taper Period due to other treatment choices, should be scheduled to return for a Safety Follow-Up Visit as specified in Table 5-3. The morning of the next clinic visit, the subject should take concomitant AEDs and study medication at the usual time(s).

8.4 Transition Period

Subjects who complete the Maintenance Period and plan to participate in EP0034 will enter a blinded Transition Period of 4 weeks.

8.4.1 Transition Period: Transition Visit 1 (Week 17), Transition Visit 2 (Week 18), and Transition Visit 3 (Week 19)

During Transition Visit 1, Transition Visit 2, and Transition Visit 3 (clinic visits), the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessments (for subjects with an implanted VNS device)
- Physical examination (brief)
- Vital signs (BP and pulse rate; including orthostatic assessments)
- Body weight assessment
- Neurological examination (brief)
- C-SSRS (for subjects ≥6 years of age)
- Contact IXRS
- Dispense study medication

- Study medication return
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting
- Health care resource use

8.4.2 Transition Period: Transition Visit 4 (Week 20)

During Transition Visit 4 (clinic visit), the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (for subjects with an implanted VNS device)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- 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 the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Urine pregnancy test (for females of childbearing potential)
- Blood sample for measurement of concomitant AED plasma concentrations
- Blood sample for measurement of LCM plasma concentration
- C-SSRS (for subjects ≥6 years of age)
- Contact IXRS
- Study medication return
- Subject diary return
- Review withdrawal criteria
- AE reporting
- Health care resource use

8.5 Taper Period

A blinded Taper Period (2 to 4 weeks, depending on dose achieved) will be required for subjects who discontinue study medication prematurely and for subjects who complete the

Maintenance Period but choose not to enter the open-label extension study (EP0034). Taper of LCM may not be required for some subjects who discontinue study medication prematurely depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal representative. The Taper Period is not required for subjects who complete the Maintenance Period and who do not undergo taper of LCM.

8.5.1 Taper Period: Telephone Contact 7 (Week 17)

A telephone contact will be conducted during the first week of the Taper Period. During Telephone Contact 7, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting

If any AEs necessitate a subject's withdrawal from the study, the subject should return for a clinic visit as soon as possible after the occurrence of the AE.

8.5.2 Taper Period: Taper Visit (Week 18, Week 19, or Week 20)

Each subject will have only 1 Taper Visit (clinic visit). The Taper Visit will occur at the end of the Taper Period (Week 18, Week 19, or Week 20, depending on dose level achieved [see Table 7–5]) and include the following assessments:

- Concomitant medications
- Concomitant AEDs
- VNS assessments
- Physical examination (brief)
- Vitals signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Neurological examination (brief)
- 12-lead ECG (2 interpretable recordings to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Serum pregnancy test (for females of childbearing potential)
- C-SSRS (for subjects ≥6 years of age)

- Contact IXRS
- Study medication return
- Subject diary return
- Review withdrawal criteria
- AE reporting
- Health care resource use

The subject will be scheduled to return to the clinic for the next as specified in Table 5-3. The morning of the next clinic visit, the subject should take concomitant AEDs at the usual time(s).

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 Visit

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

- Concomitant medications
- Concomitant AEDs
- VNS assessments (for subjects with an implanted VNS device)
- Physical examination (complete)
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for approximately 5 minutes preceding the recordings and during the recordings) (only for subjects with an abnormal reading at the previous visit)
- Blood sample for clinical chemistry and hematology (only for subjects with an abnormal value at the previous visit)
- Blood sample for endocrinology (only for subjects with an abnormal value at the previous visit)
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Serum pregnancy test (for females of childbearing potential) (only if blood is collected for another assessment)
- Urine pregnancy test (only if blood is not collected for another assessment)

- C-SSRS (for subjects ≥6 years of age)
- AE reporting
- Health care resource use

8.6.2 Safety Follow-Up Telephone Contact

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 may be performed at the investigator's discretion. The following assessments are required:

- Concomitant medications
- Concomitant AEDs
- VNS assessment (for subjects with an implanted VNS device only)
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- C-SSRS for subjects ≥6 years of age (only if visit is related to an AE)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- AE reporting

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

8.8 Early Termination Visit

Subjects who withdraw from the study prematurely for any reason, including AEs, must complete an Early Termination Visit. At the time of withdrawal from the study, investigators should discuss treatment options with the subject and/or their parent/legal guardian to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who discontinue study medication prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. These subjects should complete the Early Termination Visit and then complete the 30-day Safety Follow-Up Period.

The following assessments should be completed at the Early Termination Visit and prior to subjects entering the blinded Taper Period (2 to 4 weeks).

- Concomitant medications
- Concomitant AEDs
- Changes in VNS settings
- Physical examination (complete)
- Tanner Stage assessment
- Vital signs (BP and pulse rate, including orthostatic assessments)
- Body weight assessment
- Height assessment
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings to be performed prior to any blood draws and vital signs assessment and, if possible, with the subject in the supine position for approximately 5 minutes preceding the recordings and during the recordings)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects ≥5 years of age)
- Serum pregnancy test (for females of childbearing potential)
- Blood sample for measurement of concomitant AED plasma concentrations
- Blood sample for measurement of LCM plasma concentration
- C-SSRS (for subjects ≥6 years of age)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Achenbach CBCL (same version used at Visit 2)
- BRIEF-P/BRIEF score (version consistent with that used at Visit 2)
- PedsQL score (version consistent with that used at Visit 2)
- Contact IXRS
- Dispense study medication for the Taper Period (2 to 4 weeks)
- Study medication return
- Reminder to complete subject diary on a daily basis
- AE reporting
- Health care resource use

The subject will be scheduled to return to the clinic for the Taper Visit (see Section 8.5.1). Subjects who do not taper study medication due to other treatment options should be scheduled for a Safety Follow-Up Visit as specified in Table 5-3. The morning of the next clinic visit, the subject should take concomitant AEDs and study medication, as applicable, at the usual time(s).

9 ASSESSMENT OF EFFICACY

9.1 Specification of efficacy parameters

The assessment of efficacy is based on partial-onset seizure frequency.

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period.

The secondary efficacy variables are as follows:

- Proportion of responders, where a responder is a subject experiencing a 50% or greater reduction in partial-onset seizure frequency from Baseline to the Maintenance Period
- Proportion of subjects experiencing a ≥25% to <50%, 50% to 75%, or >75% reduction in partial-onset seizure frequency from Baseline to the end of Maintenance Period
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing a ≥25% to <50%, 50% to 75%, or >75% reduction in partial-onset seizure frequency from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing no change in partial-onset seizure frequency (between <25% reduction and <25% increase) from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Proportion of subjects experiencing an increase in partial-onset seizure frequency of ≥25% from Baseline to the entire treatment (ie, Titration+Maintenance Periods)
- Change in partial-onset seizure frequency per 28 days from Baseline to the entire treatment (ie, Titration+Maintenance Periods) by seizure type
- Proportion of seizure-free days during the Maintenance Period for subjects who entered the Maintenance Period
- Proportion of subjects who achieved "seizure-free" status (yes/no) for subjects who completed the Maintenance Period

Other efficacy variables are as follows:

- 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
- Quality of life assessments (PedsQL)

- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol)

9.2 Methods for assessing efficacy parameters

9.2.1 Primary and secondary efficacy parameters

Primary and secondary efficacy variables will be measured using data obtained from a subject diary. Subjects or parents/caregivers will keep a diary to record the daily seizure activity from the beginning of the Baseline Period until the last visit, recording both seizure type and seizure frequency. The seizure records will be checked by the investigator with regards to correct and thorough daily completion by the subject, and to determine if a dose adjustment is required. At each visit and telephone contact subject and/or legal representative should be reminded to complete the subject diary on a daily basis.

9.2.2 Other efficacy parameters

9.2.2.1 Clinical and Caregiver's Global Impression of Change

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 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.

9.2.2.2 Healthcare resource use

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol.

9.2.2.3 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 2 (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 ≥2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≤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 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.

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC VARIABLE(S)

Blood samples for the determination of LCM and concomitant AED 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 CRF 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 adverse event 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 CRF 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.

11.1.2 Procedures for reporting and recording adverse events

The subject or subject's parent(s)/caregiver(s)/legal representative(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 your 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 CRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event CRF (including judgment of relationship to study drug) are described in the CRF 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 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.

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 Pregnancy

Should a subject become pregnant after the first intake of any IMP, UCB's Drug Safety department should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known, and the following should be completed:

- The subject should return for an Early Termination Visit and Taper Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the Early Termination Visit.
- A Safety Follow-Up Visit should occur 2 weeks ±2 days after the subject has discontinued her IMP.
- A Safety Follow-Up Telephone Contact should occur 30 days (-1/+3 days) after the subject has discontinued IMP.

The investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, UCB will ask the investigator or designee to contact the subject and his partner to request

consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the subject's partner for completion.

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

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

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form.

11.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability or Study Drug Dosing module of the CRF. 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 Drug 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 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. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

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.

Information on SAEs obtained after clinical database lock will be captured through the Drug 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 AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (2nd degree Type I and II and 3rd degree), and marked bradycardia (<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 United States Food and Drug Administration:

  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

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 has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol (Table 11-1).

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
	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; SOC=system organ class; SAE=serious adverse event

11.6 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology and urinalysis testing (for subjects ≥5 years of age) will be collected according to the tabular schedules of study procedures, Section 5.2. Urine assessments will be based on the subject's ability to void and the staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing (for female subjects of childbearing potential) will also be performed (see Section 11.1.6). The procedures for handling and shipping these specimens will be provided to the sites.

The laboratory tests to be performed are presented in Table 11-2.

Table 11-2 Laboratory measurements

Hematology	Clinical chemistry	Endocrinology	Urinalysis[a]
Hematocrit	Calcium	FSH	pH
Hemoglobin	Phosphorus	LH	Ketones
Platelet count	Serum electrolytes (sodium, potassium, chloride, bicarbonate)	Testosterone	Glucose
RBC count	Creatinine	TSH	Albumin
WBC count	BUN	T3 (total and serum-free)	Specific gravity
Differential count	AST	T4 (total and serum-free)	Microscopic exam for blood cells or casts/hpf
	ALT	T3 (total and serum-free)	
	Total bilirubin	T4 (total and serum-free)	
	Alkaline phosphatase		
	GGT		
	Glucose		
	Albumin		
	Total serum protein		
	Uric acid		
	Total cholesterol		
	Triglycerides		

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

[a]Urinalysis will be performed for subjects ≥5 years of age only.

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.

11.8 Pregnancy testing

Females of childbearing potential will have serum and urine pregnancy tests performed during the study according to the tabular schedules of study assessments (Section 5.2).

11.9 Other safety measurements

11.9.1 Physical examination

Physical examinations will be performed according to the tabular schedules 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.

11.9.1.1 Complete physical examination

The complete physical examination will include cardiac and respiratory function via auscultation, temperature, and review of all body systems. Genitourinary and breast examinations will not be performed.

11.9.1.2 Brief physical examination

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

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

11.9.2 Neurological examination

Neurological examinations will be performed according to the tabular schedules 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.

11.9.2.1 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.

11.9.2.2 Brief neurological examination

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

11.9.3 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 schedules of study procedures (Section 5.2). Assessment of orthostatic changes will be as follows: After the 3-minute measurement in supine position, the subject is asked to stand up, and BP and pulse rate are taken approximately 1 minute and approximately 3 minutes after the subject stands 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 schedules of study procedures (Section 5.2).

11.9.4 12-lead ECG

Standard 12-lead ECGs (2 interpretable recordings) will be performed according to the tabular schedules of study assessments (Section 5.2). Care should be taken to ensure proper lead placement and quality ECG recordings. The ECGs will be performed prior to any blood draws and vital signs assessment. The subjects should rest in the supine position for approximately 5 minutes before the ECG recording and during the recording. The recordings should be made 20 to 30 minutes apart.

11.9.5 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 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.

11.9.6 Tanner Stage

The investigator or qualified designee will evaluate the subject's sexual development using the 3-item Tanner scale, according to the tabular schedules of study procedures (Section 5.2). The investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study).

11.9.7 Achenbach CBCL

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. Behavioral problems will be scored by the

parent(s)/legal representative(s). Depending on the subject's age, 2 versions of the CBCL will be used. The CBCL/1½-5 checklist is intended for use in children 18 months to 5 years and 11 months of age. For subjects ≥6 years to <17 years of age at Screening, the CBCL/6-18 version will be used. The Achenbach CBCL will only be administered in countries where a translated version is available.

For each subject, the same version of the scale that is completed at Visit 2 (Baseline) should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Section 5.2) and should be completed by the same parent/legal representative. The completion of the Achenbach CBCL will require approximately 45 minutes.

In both questionnaires, the occurrence of certain problems and behaviors in the past 6 months will be scored on the following scale:

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

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

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

11.9.8 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for Screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedules of study procedures (Section 5.2). All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and use the "Since Last Visit" version at subsequent visits.

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Parents and caregivers should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

11.9.9 BRIEF-P and BRIEF

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each subject, the same version (BRIEF-P or BRIEF) that is used at Visit 2 (Baseline) should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Section 5.2).

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

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

The BRIEF rating form contains items in nonoverlapping clinical scales. These theoretically and statistically derived scales form 2 broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score.

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

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 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 CRFs 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 CRFs, ensure that all protocol requirements, applicable authorities' 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 of CRFs 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 EEG 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 CRF 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 electronic CRFs and in all required reports.

Any change or correction to the electronic Case Report form (eCRF) after saving must be accompanied by a reason for the change.

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

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. This study is performed using RDC; the data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

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 drug 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 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 (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 study 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 follows and will be described in more detail in the Statistical Analysis Plan (SAP).

13.1 Definition of analysis sets

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 a Baseline and at least 1 post-Baseline assessment of seizure frequency data.

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 major protocol deviations.

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 analysis of the safety parameters.

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.

13.2 General statistical considerations

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentages of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n, mean, standard deviation (SD), median, minimum, and maximum. Appropriate inferential statistics will be calculated for the primary and selected secondary efficacy variables. Baseline values for efficacy and safety variables will be based on the last nonmissing data collected prior to the first dose of study medication, unless otherwise noted.

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

Further methods pertaining to the summary and analysis of the efficacy, safety, and PK data are presented in the following sections, and will be described in more detail in the SAP.

13.3 Planned efficacy analyses

13.3.1 Analysis of the primary efficacy variable

The assessment of efficacy is based on seizure frequency.

The primary efficacy variable is the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period.

Seizure frequency per 28 days will be calculated as ([number of seizures over the specified time interval] divided by [number of days in the interval]) multiplied by 28. For subjects who prematurely discontinue the study, last observation carried forward method will be applied to obtain a seizure frequency estimate for the Maintenance Period.

Seizure frequency will be analyzed using analysis of covariance (ANCOVA) with terms for treatment and center (properly pooled), on log-transformed seizure frequency using the transformation of ln(X+1), where X is the seizure frequency. Log transformed baseline seizure frequency will be used as a covariate. The seizure frequency between treatment and placebo will be compared using least squares means (LSMs). The percent reduction over placebo will be estimated as 100 x (1 – exp [LSM LCM– LSM placebo]).

It is planned to properly pool centers by geographic location. The final strategy for pooling will be determined prior to the unblinding of the study.

13.3.2 Analysis of secondary efficacy variables

The secondary efficacy variables for this study are described in Section 4.1.2.

Subjects will be categorized as responders if the reduction in partial-onset seizure frequency from the Baseline Period to the appropriate treatment period meets the level specified in the given analysis. Response to treatment will be summarized for the proportion of subjects experiencing a ≥25% to <50%, 50 to 75%, or >75% reduction in partial-onset seizure frequency from the Baseline Period to the Maintenance Period. Proportion of subjects experiencing no change in partial-onset seizure frequency (ie, between <25% reduction and <25% increase in seizure frequency) and the proportion of subjects experiencing ≥25%

increase in partial-onset seizure frequency from the Baseline Period to the Maintenance Period will be presented. These response categories will also be presented from Baseline to the Treatment Period.

The difference in responder rate for 50% reduction in partial-onset seizure frequency between the LCM treatment group and placebo will be analyzed using a logistic regression model with effects for treatment and pooled center. No other statistical testing will be performed for the other secondary variables related to reduction in partial-onset seizure frequency.

The number and percentage of subjects experiencing a <50%, 50 to 75%, or >75% reduction in seizure frequency from Baseline to each post-Baseline visit will be presented by treatment group. The descriptive statistics for percent change in seizure frequency per 28 days from Baseline to each post-Baseline visit, the Maintenance Period, and entire Treatment and Maintenance Periods will be presented by seizure type and treatment group. No inferential testing will be performed for these summaries.

The change in seizure frequency per 28 days from Baseline to the Treatment Period, defined as the combined Titration and Maintenance Periods, will be summarized by treatment group (LCM or placebo) using descriptive statistics. Statistical testing will be performed using an ANCOVA model with terms for treatment and pooled center and Baseline seizure frequency as a covariate.

The change in seizure frequency by period will also be summarized using descriptive statistics by treatment group and seizure type.

For subjects who enter the Maintenance Period, proportion of seizure-free days during the Maintenance Period will be calculated and summarized by treatment group descriptively.

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 descriptively.

13.3.3 Other efficacy analyses

The number and percentage of subjects with each Clinical Global Impression of Change and Caregiver's Global Impression of Change value will be summarized by treatment group. A descriptive summary of PedsQL will be provided. No statistical testing will be performed for the other efficacy variables.

13.4 Planned safety and other analyses

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

13.4.1 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 which start on or after the date of first study medication administration and within 30 days following the date of last 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, clinical chemistry, urinalysis, and hormone status) and vital signs (including body weight, height and BMI), physical and neurological examination findings, assessments of Tanner stage (if applicable), Achenbach CBCL, and BRIEF-P/BRIEF.

Measurement and change from Baseline in continuous parameters (eg, vital signs and laboratory measurements) will be summarized using descriptive statistics. When analyzing categorical data (eg, overall assessment of 12-lead ECG) 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 post-Baseline status when compared to their Baseline status. Laboratory, ECG, and vital signs data outside of the respective reference ranges will be listed and highlighted.

13.4.2 Pharmacokinetic analyses

13.4.2.1 Descriptive statistics of LCM and AED plasma concentrations

The results of LCM and other AEDs plasma concentrations will be described by the method of descriptive statistics: arithmetic mean, SD, median, range, geometric mean, and geometric coefficient of variation. The evaluations will be done based on separation by LCM dose level and study period.

13.4.3 Population pharmacokinetics

Summarization of PK data relative to time after dose will be performed for the overall group and separated by AED therapy and possibly age groups.

A population PK modeling of the LCM concentration time data will be performed within the NONMEM software. The effects of age, body weight, AED therapy, and other covariates will be evaluated. Simulations will be undertaken for estimating dose adaptations leading to the same exposure as in adults.

The methods will be described in the DAP (Data Analysis Plan) and the results will be reported in a modeling report.

13.4.3.1 Exposure-response

A model-based approach will be used to describe the relationship between LCM and seizure counts data. The PK and PD data will be combined and exploratory analyses will be conducted to determine if a dose-response relationship can be demonstrated. Additional information will be documented separately in a DAP.

13.5 Handling of protocol deviations

After all CRFs have been retrieved and entered, all queries issued and answered to the extent possible, and prior to locking and unblinding the clinical database, a Data Review Meeting will be held. Important protocol deviations (ie, those considered to have an impact on interpretation of safety, efficacy, or study conduct) will be identified and reviewed by appropriate team members.

13.6 Handling of dropouts or missing data

As described in Section 13.3, for subjects who discontinue prior to the Maintenance Period, all available seizure frequency data will be carried forward from the Titration Period for the Maintenance Period analysis. For subjects who prematurely discontinue during the Maintenance Period, all available seizure frequency data in the Maintenance Period will be carried forward for the entire Maintenance Period. Subjects who discontinue prior to any efficacy data collection will not be included in the analyses (ie, data will not be carried forward from Baseline). The imputation for the seizure frequency data will not carry forward into the Transition and Taper Periods.

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.

13.7 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 Drug 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 SP0969 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 13.8) 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; 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 149 subjects per treatment arm and the original estimated overall study dropout rate will not be adjusted above 24%.

13.8 Determination of sample size

Assuming an effect size of 0.342, in which the effect size was calculated using a placebo-subtracted difference of -0.249 and a common SD of 0.73 on the log-transformed data, the difference of -0.249 on the log-transformed data is equivalent to approximately 22%

reduction over placebo after exponentiation. With this effect size, power of 80%, and a 2-sided test at the 5% level of significance, a sample of 135 subjects in each treatment arm will be needed.

Assuming a responder rate of 22% and 40% for the placebo and LCM groups, respectively, a 2-sided continuity corrected Chi-square test at a significance level of 5% will provide approximately 87% power with 135 subjects in the placebo group and 135 subjects in the LCM group.

To account for an anticipated subject dropout rate of approximately 14%, the planned number of subjects to enroll is 154 subjects per treatment arm.

A blinded sample size re-estimation will be performed when 50% of the subjects have been randomized, completed the study, and have data for analysis to check the validity of these assumptions as described in Section 13.7.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

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

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

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

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 United States must include the use of a Health Insurance Portability and Accountability Act (ie, HIPAA) Authorization form.

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

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

Columbia University Medical Center. Columbia-Suicide Severity Rating Scale (2008). http://www.cssrs.columbia.edu/. Accessed 19 Jun 2011.

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.

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

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.

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.

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

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 Protocol amendment 1

Rationale for the amendment

The main purpose of this substantial amendment is to add details to the Statistics section regarding sample size re-estimation and statistical evaluation of secondary and other efficacy variables based on the clarifications made by the [redacted] and aligned to the wording in the SP0967 protocol (a double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in subjects with epilepsy ≥1 month to <4 years of age with partial-onset seizures).

Based on previous recommendations made by the USA FDA, the creatinine clearance has been changed from less than 50mL/min to less than 30mL/min in Exclusion Criterion number 10. In addition, as per request from the [redacted], Exclusion Criterion number 20 has been removed because it is a duplicate of Exclusion Criterion number 23. Exclusion criterion number 22 has been reworded to clarify that the excluded sodium channelopathies are cardiac.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- The creatinine clearance threshold in the exclusion criterion for subjects with impaired renal function (Exclusion Criterion number 10) has been lowered from 50mL/min to 30mL/min.
- Exclusion Criterion number 20 has been removed because it is a duplicate of Exclusion Criterion number 23.
- Exclusion Criterion number 22 has been clarified by adding "cardiac" to the sodium channelopathies.
- In the Statistics section, details related to statistical evaluation of secondary and other efficacy variables have been added, and sample size re-estimation text has been further detailed.
- Administrative changes: the name of the Study Physician, the Clinical Project Manager, and the name of the CRO have been updated, and the Sponsor Declaration has been updated for electronic signature.

Specific changes

Change #1

SPONSOR DECLARATION

Clinical Project Manager

[redacted], BS

Date/Signature

Clinical Trial Biostatistician

[redacted], MPH

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

Sponsor Study Physician

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

Clinical Project Manager

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

Clinical Monitoring Contract Research Organization

Name:	Pharmaceutical Research Associates, Inc.
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted] MD
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]
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Clinical Monitoring Contract Research Organization

Name:	PRA Health Sciences
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Change #3

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 2421 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842 **Japan:** +81 3 6864 7400
Email	**Global:** DS_ICT@ucb.com

Has been changed to:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 2421 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842
Email	**Global:** DSICT@ucb.com

Change #4

Section 4.1.3 Other efficacy variables, last bullet

- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)

Has been changed to:

- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol)

Change #5

Section 5.2 Schedule of study assessments, Table 5-1 footnotes

[a] Visit 1 (V1) may occur over more than 1 day; however, all results of Visit 1 assessments should be available before T1.

[k] The Achenbach CBCL: CBCL/1½ -5 for children 18 months to 5 years and 11 months of age, and CBCL/6-18 for children ≥6 years to <17 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each subject, the same version of the scale that was completed at Visit 2 (CBCL/1½ -5 or CBCL/6-18) should be maintained for the duration of the study and should be completed by the same parent/legal representative. The Achenbach CBCL will be used only in countries where a translated version is available.

Have been changed to:

[a] Visit 1 (V1) may occur over more than 1 day; however, all results of Baseline/Visit 1 assessments should be available before randomization on Visit 2.

[m] The Achenbach CBCL: CBCL/1½ -5 for children 18 months to 5 years and 11 months of age, and CBCL/6-18 for children ≥6 years to <17 years of age at Screening; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each subject, the same version of the scale that was completed at Visit 2 (CBCL/1½ -5 or CBCL/6-18) should be maintained for the duration of the study and should be completed by

the same parent/legal representative. The Achenbach CBCL will be used only in countries where a translated version is available.

And the following footnotes have been added:

[d] Medical history to include demographics (date of birth [where permitted], age group category, age in months and years, race, ethnicity, and gender).

[g] The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

Change #6

Section 5.3 Schematic diagram, Figure 5-1 and Figure 5-2, footnotes

The following footnote has been added:

Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

Change #7

Section 6.2 Exclusion criteria

10. Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level ≥2 times the upper limit of normal (ULN), or creatinine clearance less than 50mL/min.

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

Have been changed to:

10. Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level ≥2 times the upper limit of normal (ULN), or creatinine clearance less than 30mL/min.

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

And the following exclusion criterion has been removed:

20. Subject has epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen Syndrome.

Change #8

Section 7.2 Treatments to be administered, third paragraph

At the end of Visit 2, 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).

Has been changed to:

At the end of Visit 2, subjects should take the first dose of IMP while in the clinic. At each subsequent clinic visit, subjects should take the IMP (and any concomitant AEDs) at the regular time(s). The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

Change #9

Section 7.2.1 Titration Period, Section 7.2.3 Transition Period (for subjects who plan to enter EP0034), and Section 7.2.4 Taper Period (for subjects not entering EP0034); Table 7-1, Table 7-2, Table 7-3, Table 7-4, and Table 7-5, footnotes

The following footnote has been added:

Note: The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

Change #10

Section 8 STUDY PROCEDURES BY VISIT

The following text has been added:

The subject's body weight at Baseline (Visit 2) will be used to determine dose throughout the study.

Change #11

Section 9.1 Specification of efficacy parameters, last bullet

- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)

Has been changed to:

- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol)

Change #12

Section 9.2.2.2 Healthcare resource use

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study.

Has been changed to:

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations including hospitalizations not foreseen by the protocol.

Change #13

Section 11.1.2 Procedures for reporting and recording adverse events, first paragraph

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs.

Has been changed to:

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

Change #14

Section 11.9.7 Achenbach CBCL, first paragraph

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

Has been changed to:

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

Change #15

Section 12.1 Adherence to protocol

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 of the sponsor within 24 hours and follow any local regulatory requirements.

Change #16

Section 13.1 Definition of analysis sets, last paragraph

All subjects from the SS with valid LCM plasma concentration data will be included in the PK Set (PK-PPS).

Has been changed to:

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 13.3.1 Analysis of the primary efficacy variable, last paragraph

It is planned to properly pool centers by geographic location. The final strategy for pooling will be determined at the Data Review Meeting.

Has been changed to:

It is planned to properly pool centers by geographic location. The final strategy for pooling will be determined prior to the unblinding of the study.

Change #18

Section 13.3.2 Analysis of secondary efficacy variables

The secondary efficacy variables for this study are described in Section 4.1.2. Inferential statistics using similar methods as described in Section 13.3.1 will be calculated for the following variables:

- Change in seizure frequency per 28 days from Baseline to the entire Treatment Period
- Proportion of subjects experiencing a 50% or greater reduction in seizure frequency from Baseline to the entire Treatment Period

Additional secondary efficacy variables to be analyzed using inferential statistical methods will be described in the SAP.

The number and percentage of subjects experiencing a <50%, 50 to 75%, or >75% reduction in seizure frequency from Baseline to each post-Baseline visit, the Maintenance Period, and entire Titration and Maintenance Periods will be presented by treatment group. The descriptive statistics for percent change in seizure frequency per 28 days from Baseline to each post-Baseline visit, the Maintenance Period, and entire Treatment and Maintenance Periods will be presented by seizure type and treatment group. For subjects who enter the Maintenance Period, proportion of seizure-free days during the Maintenance Period will be calculated and summarized by treatment group descriptively.

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.

Has been changed to:

The secondary efficacy variables for this study are described in Section 4.1.2.

Subjects will be categorized as responders if the reduction in partial-onset seizure frequency from the Baseline Period to the appropriate treatment period meets the level specified in the given analysis. Response to treatment will be summarized for the proportion of subjects experiencing a ≥25% to <50%, 50 to 75%, or >75% reduction in partial-onset seizure frequency from the Baseline Period to the Maintenance Period. Proportion of subjects experiencing no change in partial-onset seizure frequency (ie, between <25% reduction and <25% increase in seizure frequency) and the proportion of subjects experiencing ≥25% increase in partial-onset seizure frequency from the Baseline Period to the Maintenance Period will be presented. These response categories will also be presented from Baseline to the Treatment Period.

The difference in responder rate for 50% reduction in partial-onset seizure frequency between the LCM treatment group and placebo will be analyzed using a logistic regression model with effects for treatment and pooled center. No other statistical testing will be performed for the other secondary variables related to reduction in partial-onset seizure frequency.

The number and percentage of subjects experiencing a <50%, 50 to 75%, or >75% reduction in seizure frequency from Baseline to each post-Baseline visit will be presented by treatment group. The descriptive statistics for percent change in seizure frequency per 28 days from Baseline to each post-Baseline visit, the Maintenance Period, and entire Treatment and Maintenance Periods will be presented by seizure type and treatment group. No inferential testing will be performed for these summaries.

The change in seizure frequency per 28 days from Baseline to the Treatment Period, defined as the combined Titration and Maintenance Periods, will be summarized by treatment group (LCM or placebo) using descriptive statistics. Statistical testing will be performed using an ANCOVA model with terms for treatment and pooled center and Baseline seizure frequency as a covariate.

The change in seizure frequency by period will also be summarized using descriptive statistics by treatment group and seizure type.

For subjects who enter the Maintenance Period, proportion of seizure-free days during the Maintenance Period will be calculated and summarized by treatment group descriptively.

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 descriptively.

Change #19

Section 13.3.3 Other efficacy analyses

The number and percentage of subjects with each Clinical Global Impression of Change and Caregiver's Global Impression of Change value will be summarized by treatment group. A descriptive summary of PedsQL will be provided.

Has been changed to:

The number and percentage of subjects with each Clinical Global Impression of Change and Caregiver's Global Impression of Change value will be summarized by treatment group. A descriptive summary of PedsQL will be provided. No statistical testing will be performed for the other efficacy variables.

Change #20

Section 13.7 Planned interim analysis and data monitoring

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 Drug 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 SP0969 will be described in an IDMC Charter.

Has been changed to:

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 Drug 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 SP0969 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 13.8) 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; 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 149 subjects per treatment arm and the original estimated overall study dropout rate will not be adjusted above 24%.

Change #21

Section 13.8 Determination of sample size, last paragraph

A blinded sample size re-estimation will be performed to check the validity of these assumptions using interim data from the study. A blinded estimate of variance for the change in partial-onset seizure frequency per 28 days from Baseline to the Maintenance Period will be calculated.

Has been changed to:

A blinded sample size re-estimation will be performed when 50% of the subjects have been randomized, completed the study, and have data for analysis to check the validity of these assumptions as described in Section 13.7.

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.

SP0969 Protocol Amendment 1 - Phase 3, Placebo Control, Double Blind

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	05-Mar-2015 13:44 GMT+01
[redacted]	Clinical Approval	05-Mar-2015 16:19 GMT+01