PROTOCOL SP0966 AMENDMENT 5

A MULTI-CENTER, OPEN-LABEL, EXPLORATORY STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN SUBJECTS ≥1 MONTH TO <18 YEARS WITH EPILEPSY SYNDROMES ASSOCIATED WITH GENERALIZED SEIZURES

PHASE 2

EudraCT Number: 2012-001446-18

IND Number: 73809 (oral solution), 57939 (tablet)

Sponsor:
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Protocol/Amendment number	Date	Type of amendment
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Confidential Material

STUDY CONTACT INFORMATION

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
Bayley-III	Bayley Scales of Infant and Toddler Development®, Third Edition
bid	twice daily
BMI	body mass index
BP	blood pressure
BRIEF®-P/BRIEF®	Behavior Rating Inventory of Executive Function-Preschool Version/ Behavior Rating Inventory of Executive Function
CBCL	Child Behavior Checklist
CDMS	clinical data management system
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
EI-AED	enzyme inducing antiepileptic drugs
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRQoL	Health-related Quality of Life
ICF	informed consent form
ICH	International Conference on Harmonisation
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
LH	luteinizing hormone
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
PedsQL™	Pediatric Quality of Life Inventory
PK	pharmacokinetic
QTc	corrected QT interval
SAE	serious adverse event
SOP	Standard Operating Procedure
SS	Safety Set
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VNS	vagus nerve stimulation

1 SUMMARY

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral lacosamide (LCM, Vimpat®; SPM 927; previously referred to as harkoseride; [R]-2-acetamido-N-benzyl-3-ethoxypropionamide, ADD 234037) as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age. The objectives of this study are to evaluate the safety and tolerability of LCM when added to 1 to 3 concomitant antiepileptic drugs (AEDs) in pediatric subjects with epilepsy syndromes associated with generalized (Type II) seizures, and to obtain preliminary efficacy data of LCM on seizure frequency in pediatric epilepsy syndromes associated with generalized seizures.

The primary variables in this study are changes in the count of generalized spike-wave discharges and change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) from the Baseline Period to the Maintenance Period. The above variables reference partial seizures evolving to secondarily generalized seizures. While these partial seizures will be summarized as a part of the analysis, subjects must have a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1) to possibly be eligible for study participation. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Other variables to be assessed include measures of efficacy, plasma concentrations, and other measures of safety.

Approximately 50 subjects will be enrolled in this study across approximately 50 sites in Europe and North America, and other regions as deemed necessary.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured through daily seizure diaries. At the end of the Baseline Period, subjects will commence a 6-week Titration Period at Visit 2, where subjects will initiate treatment with LCM (LCM dosing flexibility allowed based on tolerability). Subjects weighing <50kg will begin treatment on LCM oral solution 2mg/kg/day, and subjects weighing ≥50kg will begin treatment on LCM tablets 100mg/day (subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead). The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day (oral solution) for subjects weighing <50kg or 600mg/day (tablets/oral solution) for subjects weighing ≥50kg. At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects must titrate to at least 4mg/kg/day for subjects weighing <50kg or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg in order to enter the Maintenance Period. The LCM dose will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study. Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study.

The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in an additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 4mg/kg/day for subjects weighing <50kg or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the additional open-label study or subjects who discontinue LCM due to other reasons will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. 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.

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 new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

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

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

Among the newer AEDs, only 6 (gabapentin, lamotrigine, oxcarbazepine, topiramate, levetiracetam, and perampanel) have successfully demonstrated efficacy as adjunctive therapy in pediatric subjects with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; Glauser et al, 2000; Glauser et al, 2006; Rheims and Ryvlin, 2013). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults. Lacosamide's mode of action is proposed to be mediated by a selective enhancement of slow inactivation of voltage-gated sodium channels which may explain the immediate anticonvulsant effects of LCM (Errington et al, 2008).

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the EU (oral tablets, oral solution, and solution for intravenous [iv] infusion) and as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the USA (oral tablets, oral solution, and solution for iv infusion). The oral solution and the film-coated tablet formulations are suitable for oral administration to pediatric patients.

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 its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution.

In the clinical development program for LCM, safety and tolerability of multiple doses of up to LCM 400mg bid (800mg/day) were evaluated in 868 unique subjects who received oral and/or iv 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 1427 adult subjects with partial-onset seizures, as oral monotherapy in 425 adult subjects with partial-onset seizures, as adjunctive oral therapy in 49 subjects with primary generalized tonic-clonic seizures, and as oral monotherapy in 2435 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

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

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

UCB has completed a Phase 2, open-label safety study (SP0961) of adjunctive LCM treatment for primary generalized tonic-clonic seizures in 49 subjects ≥ 16 years of age with idiopathic generalized epilepsy. The results of SP0961 showed reductions in primary generalized tonic-clonic seizure frequency and myoclonic seizure days, with a small reduction in absence seizure days. A minority of subjects (~10%) showed an increase in absence seizures (reported as TEAEs) that, in this uncontrolled study, cannot be distinguished between the drug versus the natural course of the disease. The AE profile was similar to that of adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

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

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized (Type II) seizures in pediatric subjects ≥1 month to <18 years of age.

3 STUDY OBJECTIVE(S)

- To evaluate the safety and tolerability of LCM when added to 1 to 3 concomitant AEDs in pediatric subjects with epilepsy syndromes associated with generalized seizures
- To obtain preliminary efficacy data of LCM on seizure frequency in pediatric epilepsy syndromes associated with generalized seizures
- An additional objective is to evaluate the PK of LCM in subjects ≥1 month to <18 years of age.

4 STUDY VARIABLES

The variables below reference partial seizures evolving to secondarily generalized seizures. While these partial seizures will be summarized as a part of the analysis, subjects must meet eligibility criteria to be applicable for the study (see inclusion criterion 4 and exclusion criteria 5 and 6 for applicable subjects).

4.1 Safety variables

4.1.1 Primary safety variables

The primary variables assessing safety are:

- Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 to Visit 6
- Change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, partial evolving to secondarily generalized) per 28 days from the Baseline Period to the Maintenance Period

The assessment of seizure days will be based on the seizure diary.

4.1.2 Secondary safety variables

The secondary variables assessing safety are:

- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 6
- AEs as reported spontaneously by the subject and/or caregiver, or observed by the investigator
- Subject withdrawals due to AEs

4.1.3 Other variables assessing safety

The other safety variables are:

- Changes in hematology, clinical chemistry, and urinalysis parameters
- Changes in hormone status (follicle stimulating hormone [FSH], luteinizing hormone [LH], triiodothyronine [T3], thyroxine [T4], thyroid stimulating hormone [TSH], and testosterone, as appropriate)
- Changes in 12-lead electrocardiograms (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 (BMI)
- Changes in Tanner Stage (if applicable)
- Behavioral assessment (Achenbach Child Behavior Checklist [CBCL/1½-5 or CBCL/6-18]) for pediatric subjects ≥18 months of age
- Assessment of cognitive function (Behavior Rating Inventory of Executive Function-Preschool Version for subjects ≥2 years to <5 years of age [BRIEF®-P] or the Behavior Rating Inventory of Executive Function [BRIEF®] for subjects ≥5 years of age)

4.2 Preliminary efficacy variables

Variables used to assess preliminary efficacy will include:

- Change in days with absence seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with myoclonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with tonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with tonic-clonic seizures per 28 days from the Baseline Period to the Maintenance Period

- Change in days with atonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Change in days with partial evolving to secondarily generalized seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, partial evolving to secondarily generalized) per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with absence seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with myoclonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with tonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with tonic-clonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with atonic seizures per 28 days from the Baseline Period to the Maintenance Period
- Percent change in days with partial evolving to secondarily generalized seizures per 28 days from the Baseline Period to the Maintenance Period
- Changes in count of generalized spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 9 or at Early Termination
- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 9 or at Early Termination
- Clinical Global Impression of Change upon completion of the Maintenance Period (Termination) or at Early Termination
- Caregiver's Global Impression of Change upon completion of the Maintenance Period (Termination) or at Early Termination
- Change in quality of life assessment (Pediatric Quality of Life Inventory [PedsQL™]) for subjects ≥1 month to ≤18 years of age
- Health care resource use (concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study)

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

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age.

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.

The study treatment is LCM in either the oral solution formulation or tablet formulation. The formulation of LCM to be administered is based on the weight of the subject. Only subjects weighing ≥50kg who are able and willing to swallow tablets may be dispensed LCM tablets (subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead).

Subjects will not be randomized, but all subjects who sign the informed consent form (ICF) at Visit 1 will be assigned a unique identification number.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured. Subjects/caregivers will maintain a diary to record daily seizure activity from Visit 1 until the end of the study. The subject diary will capture seizure type and seizure frequency information. If all inclusion criteria are met and no exclusion criterion is met, the subject will begin a 6-week Titration Period (LCM dosing flexibility allowed based on tolerability) starting at Visit 2. Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 to begin 24-hour ambulatory EEG recordings. Subjects will initiate treatment with LCM oral solution at 2mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day (oral solution) for subjects weighing <50kg, or 600mg/day (tablets/oral solution) in subjects weighing ≥50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control (see Figure 5-1 and Figure 5-2).

Lacosamide doses will be titrated according to the schedules presented in Table 7-1 and Table 7-2.

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. The LCM dose will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study. Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study.

Subjects must titrate to at least 4mg/kg/day for subjects weighing <50kg, or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg in order to enter the Maintenance Period. Subjects will return to the clinic (on the morning of the day prior to the scheduled visit) at Visit 6 and Visit 9 or Early Termination for 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in the additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 4mg/kg/day for subjects weighing <50kg, and 200mg/day (tablets/oral solution) in subjects weighing ≥50kg. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the open-label study or subjects who discontinue due to other reasons will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. Dosing schedules for the Taper Period are provided in Table 7-4 and 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.

A Data Monitoring Committee (DMC) will oversee the safety of the study.

5.1.1 Study duration per subject

The duration of treatment for an individual subject may be up to approximately 18 weeks excluding the Taper Period.

The study will consist of a 6-week prospective Baseline Period, followed by a 6-week Titration Period and a 12-week Maintenance Period. Subjects may be eligible to enter an additional open-label study (SP848) after completion of the Maintenance Period. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label study will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The total study duration for a subject will be up to a maximum of 32 weeks.

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

5.1.2 Planned number of subjects and site(s)

Approximately 50 subjects will be enrolled. It is planned to enroll approximately 40 subjects between 4 years and <18 years of age and at least 10 subjects between 1 month and <4 years of age.

5.1.3 Anticipated regions and countries

This study will be conducted at approximately 50 sites in Europe and North America, and other regions as deemed necessary.

5.2 Schedule of study assessments

Table 5-1 presents the tabular schedule of study procedures.

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	**V1**	**TC 1**	**V2**	**TC 2**	**V3**	**TC 3**	**V4[c]**	**V5[c]**	**End of Titrat V6**	**TC 4**	**V7**	**TC 5**	**V8**	**TC 6**	**V9/ ET[d]**	**TC 7[e]**	**End of Taper Visit[f]**	**Safety FU Visit[g]**	**Safety FU TC[g]**	**At any time**
Week in study	**-6**	**-3**	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**	**20-22**	**22-24**	**24-26**	
Informed consent	X																			
Inclusion/exclusion criteria	X	X	X																	
Medical history	X																			
Seizure history[h]	X																			
EEG (24h monitoring)[i]			X						X						X					
Concomitant medications	X	X	X	X	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	X	X	X	X
Physical examination (complete)	X		X												X			X		
Physical examination (brief)									X				X				X			

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	**V1**	**TC 1**	**V2**	**TC 2**	**V3**	**TC 3**	**V4[c]**	**V5[c]**	**End of Titrat V6**	**TC 4**	**V7**	**TC 5**	**V8**	**TC 6**	**V9/ ET[d]**	**TC 7[e]**	**End of Taper Visit[f]**	**Safety FU Visit[g]**	**Safety FU TC[g]**	**At any time**
Week in study	**-6**	**-3**	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**	**20-22**	**22-24**	**24-26**	
Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects)	X		X		X		X	X	X		X		X		X		X	X		X
Body weight and height[j]	X		X		X		X	X	X		X		X		X		X	X		X
Head circumference (subjects <4 years)	X														X					
Neurological examination (complete)	X		X												X			X		
Neurological examination (brief)									X				X				X			
ECG (12-lead)[k]	X		X		X		X	X	X		X		X		X		X	X[l]		
Clinical chemistry/ hematology	X		X						X		X		X[l]		X		X	X[l]		
Endocrinology	X														X		X	X[l]		

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC 1	V2	TC 2	V3	TC 3	V4[c]	V5[c]	End of Titrat V6	TC 4	V7	TC 5	V8	TC 6	V9/ ET[d]	TC 7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	
Urinalysis[m]	X		X						X						X		X	X[l]		
Pregnancy test[n]	X		X		X		X	X	X		X		X		X		X	X		
Tanner Stage[o]	X														X					
Concomitant AED plasma concentration[p]			X												X					
LCM plasma concentration[p]			X												X					
C-SSRS[q]	X		X		X		X	X	X		X		X		X		X	X		X[r]
Clinical Global Impression of Change															X					
Caregiver's Global Impression of Change															X					
Achenbach CBCL[s]			X						X						X					
Bayley-III[t]			X																	

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC 1	V2	TC 2	V3	TC 3	V4[c]	V5[c]	End of Titrat V6	TC 4	V7	TC 5	V8	TC 6	V9/ ET[d]	TC 7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	
BRIEF-P/BRIEF[u]			X												X					
PedsQL[v]			X												X					
Contact IXRS	X		X		X		X	X	X		X		X		X		X			
Dispense LCM			X[w]		X		X	X	X		X		X		X[x]					
LCM return					X		X	X	X		X		X		X		X			
Dispense subject diary	X		X		X		X	X	X		X		X		X[x]					
Subject diary return/review[y]		X	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	X	X			X
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of epilepsy surgery	X																			
VNS assessment[z]	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, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)												End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)					Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	**V1**	**TC 1**	**V2**	**TC 2**	**V3**	**TC 3**	**V4[c]**	**V5[c]**	**End of Titrat V6**	**TC 4**	**V7**	**TC 5**	**V8**	**TC 6**	**V9/ ET[d]**	**TC 7[e]**	**End of Taper Visit[f]**	**Safety FU Visit[g]**	**Safety FU TC[g]**	**At any time**
Week in study	**-6**	**-3**	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**	**20-22**	**22-24**	**24-26**	
Health care resource use			X		X		X	X	X		X		X		X		X	X		

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

Note: For all visits outside of the Safety Follow-Up Period, a time window of ±2 days relative to Visit 2 (Titration Period) is applicable. The schedule above displays the maximum possible study duration for a subject.

[a] Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments indicated in the schedule above, the investigator can perform further assessments based on his/her clinical judgment and the medical needs of the subject (eg, assessments of ECG, laboratory tests, physical examination, neurological examination, etc).

[b] The recommended Taper Period duration is up to a maximum of 4 weeks, but a slower or faster taper may be permitted if medically necessary. The End of Taper Visit will occur at the end of the last week of the Taper Period.

[c] Visits 4 and 5 are optional and will only be required if a subject requires further LCM dose adjustment.

[d] At the end of Visit 9 or at ET, all subjects who complete the Maintenance Period and whose daily dose was at least 4mg/kg/day for subjects weighing <50kg, and 200mg/day (tablets/oral solution) for subjects weighing ≥50kg will be offered the opportunity to enroll in an additional open-label extension study, SP848. Visit 9 or the ET Visit of SP0966 will also serve as Visit 1 for SP848. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label extension study will complete the End of Study procedures that include a 2- to 4-week LCM taper followed by a 30-day Safety Follow-Up Period. Taper of LCM may not be

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC 1	V2	TC 2	V3	TC 3	V4[c]	V5[c]	End of Titrat V6	TC 4	V7	TC 5	V8	TC 6	V9/ ET[d]	TC 7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	

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.

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

[f] Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Week 20, Week 21, or Week 22, depending on dose level achieved; see Table 7-4 and Table 7-5). A time window of ±2 days relative to Visit 2 (Titration Period) is applicable. 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.

[g] The Safety Follow-Up Visit will occur 2 weeks (±2 days) after the final dose of LCM. The Safety Follow-Up Telephone Contact will occur 30 days (-1/+3-days) after the final dose of LCM.

[h] Subject or caregiver (including parent/legal representative) will be asked how many seizures the subject has had over the past 4 weeks as a historical baseline.

[i] Ambulatory EEG to begin on the morning prior to the visit eg, the day before Visit 2, Visit 6, and Visit 9.

[j] Height will only be recorded at study visits where a complete physical examination is performed. Height is not required at an Unscheduled Visit.

[k] Two interpretable 12-lead ECG recordings will be performed approximately 20 to 30 minutes apart prior to any blood draws and vital sign assessments. The subject should rest in the supine position for approximately 5 minutes before the recordings and during the recordings, if possible. Recordings should be performed at least 15 minutes after the removal of scalp electrodes used for the 24-hour ambulatory EEG recordings at Visit 2, Visit 6, and Visit 9 or the ET Visit.

[l] 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.

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC 1	V2	TC 2	V3	TC 3	V4[c]	V5[c]	End of Titrat V6	TC 4	V7	TC 5	V8	TC 6	V9/ ET[d]	TC 7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	

[m] For subjects aged 5 to 17 years.

[n] For female subjects of childbearing potential, a serum pregnancy test will be performed at Visit 1, Visit 9 or the ET Visit, and the End of Taper Visit. A serum pregnancy test will also 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. A urine pregnancy test will be performed at all other visits, as scheduled in Table 5-1.

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

[p] Blood samples for analysis of concomitant AED plasma concentrations and LCM plasma concentration will be drawn along with clinical chemistry and hematology samples; predose at Visit 2 and postdose at Visit 9 or the ET Visit.

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

[r] If the Unscheduled Visit is due to an AE, then the C-SSRS is required.

[s] The Achenbach CBCL: CBCL/1½ -5 for pediatric subjects from 18 months to 5 years 11 months and CBCL/6-18 for pediatric subjects aged 6 years and older; 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 same scale should be completed again by the same parent(s)/legal representative(s) later in the open-label study, SP848 (if applicable). The Achenbach CBCL will be used only in countries where a translated version is available.

[t] Bayley Scales of Infant and Toddler Development®, Third Edition for pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.

[u] 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.

[v] 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

Table 5–1: Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)												End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)					Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC 1	V2	TC 2	V3	TC 3	V4[c]	V5[c]	End of Titrat V6	TC 4	V7	TC 5	V8	TC 6	V9/ ET[d]	TC 7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	

the study. The PedsQL will be used only in countries where a translated version is available.

[w] At the end of Visit 2, subjects should take the first dose of LCM in the clinic.

[x] For subjects entering Taper Period and not entering SP848.

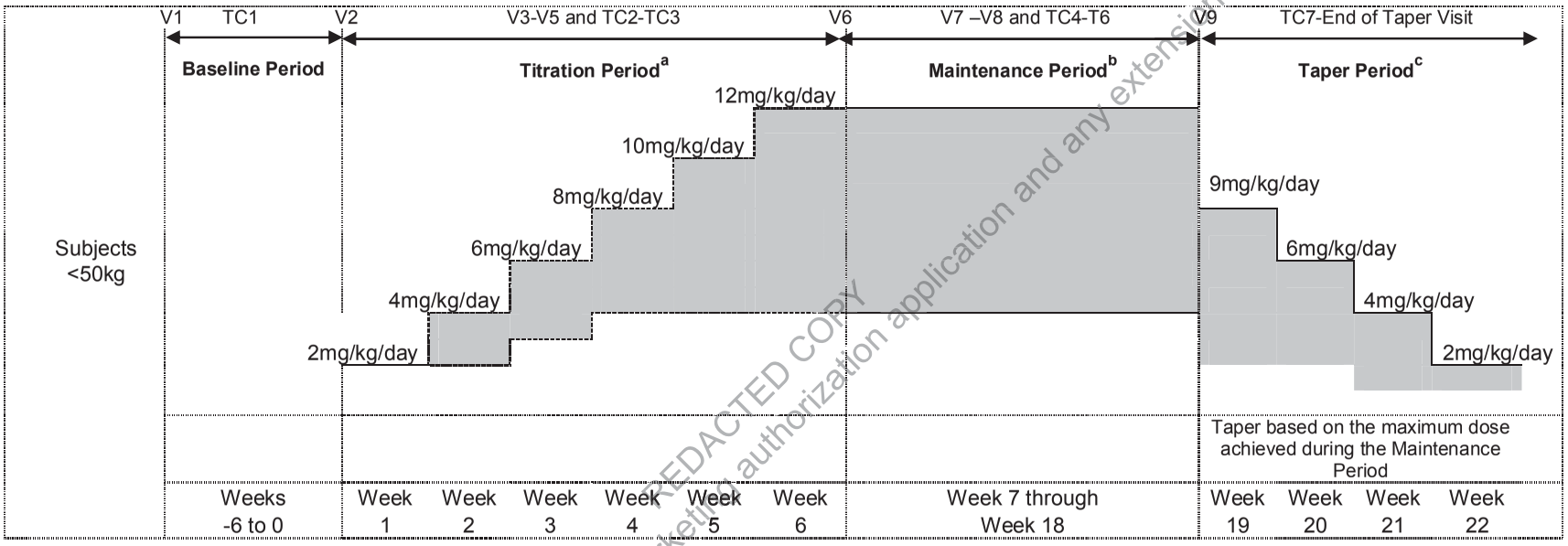
[y] The subject diary will be dispensed at Visit 1. At all subsequent visits, the subject and/or legal representative(s) will be reminded to complete the diary on a daily basis.

[z] As applicable, VNS assessment will only be performed for subjects with an implanted VNS device at Visit 1.

5.3 Schematic diagram

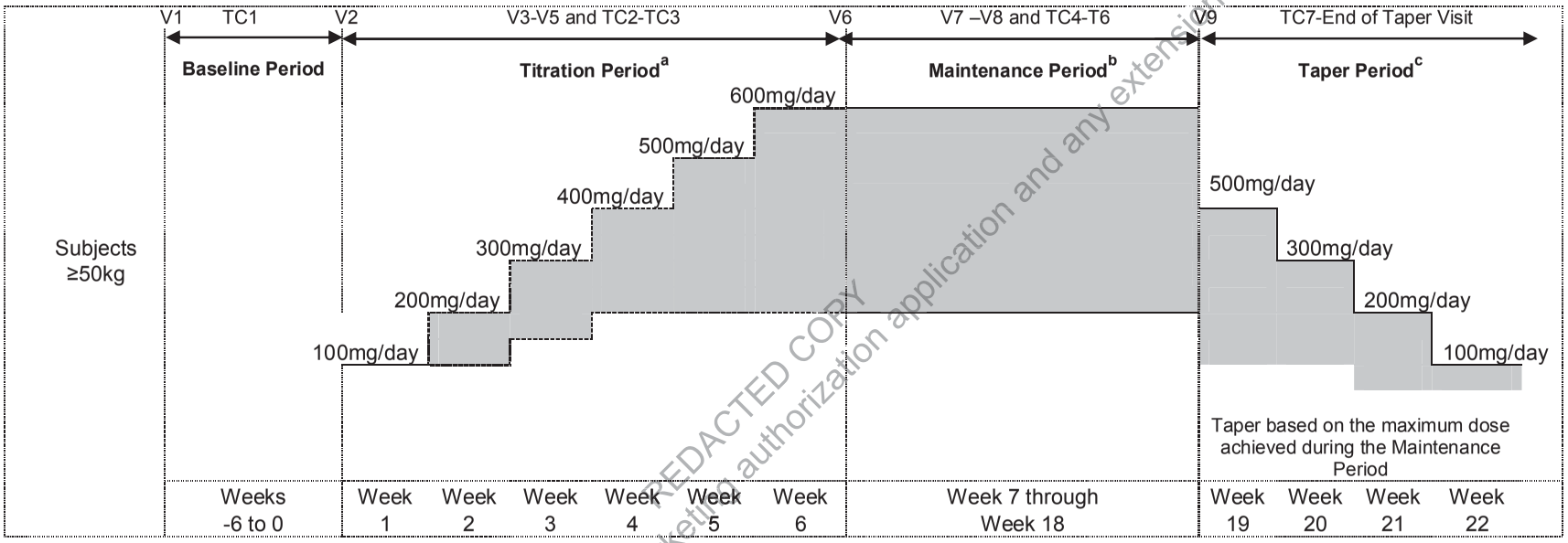
Figure 5-1 presents a schematic diagram of the LCM dosing and taper schedule for subjects <50kg receiving the oral solution formulation, and Figure 5-2 presents a schematic diagram of the LCM dosing and taper schedule for subjects ≥50kg receiving the oral solution or tablet formulation.

Figure 5–1: Schematic diagram - LCM dosing and taper schedule for subjects <50kg receiving oral solution formulation



TC=Telephone Contact; V=Visit
Note: LCM dosing is designated as "mg/kg/day"
[a] During Titration Period dosage may be adjusted up or down based on investigator's clinical judgment.
[b] Dose reached at the end of Titration Period will be taken throughout Maintenance Period. Subjects may be eligible for participation in the additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 4mg/kg/day. Subjects will begin SP848 on the LCM dose they achieved in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.
[c] Subjects with doses <3mg/kg/day do not need to taper. See Table 7-5 for exact taper schedule. Taper is not required for subjects participating in the additional open-label study (SP848). A slower or faster taper is permitted if medically necessary. 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 followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Figure 5–2: Schematic diagram - LCM dosing and taper schedule for subjects ≥50kg receiving oral solution or tablet formulation



TC=Telephone Contact; V=Visit
Note: LCM dosing is designated as "mg/day"
[a] During Titration Period dosage may be adjusted up or down based on investigator's clinical judgment.
[b] Dose reached at the end of Titration Period will be taken throughout Maintenance Period. Subjects may be eligible for participation in the additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 200mg/day (tablets/oral solution). Subjects will begin SP848 on the LCM dose they achieved in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open label study after consultation with the medical monitor.
[c] Subjects with doses <150mg/day do not need to taper. See Table 7-5 for exact taper schedule. Taper is not required for subjects participating in the additional open-label study (SP848). A slower or faster taper is permitted if medically necessary. 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 followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

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 adult subjects with partial-onset seizures, and the experience with other AEDs in pediatric subjects, it is expected that LCM will also exhibit an acceptable benefit/risk profile in the pediatric population with uncontrolled generalized seizures.

In this study, the safety and tolerability of LCM will be studied when added to 1 to 3 concomitant AEDs in pediatric subjects with epilepsy syndromes associated with generalized seizures. The study will also obtain preliminary efficacy data of LCM on seizure frequency in pediatric epilepsy syndromes associated with generalized seizures.

This study is an exploratory study to investigate on which syndromes LCM has a beneficial effect in order to plan confirmatory study(ies) and exclude syndromes for which LCM has no clear benefit or possibly induces exacerbations.

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 SP0966 are as follows:

- Lacosamide dosing should aim to achieve LCM plasma concentrations equivalent to the average steady-state LCM plasma concentration reached after a LCM 200 to 600mg/day dose administration in adult studies.
- A weight-based flexible dosing scheme is recommended:
  - Subjects <50kg: LCM 4-12mg/kg/day (oral solution)
  - Subjects ≥50kg: LCM 200 to 600mg/day (tablets/oral solution)

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. A signed informed consent has been obtained from the parent/legal representative and assent has been obtained from the subject (when possible or as required according to local Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).
2. Subject and/or caregiver (which may be a parent, a legal representative, or other caregiver) are willing and able to comply with all study requirements including maintaining a daily seizure diary.
3. Subject is male or female, ≥1 month to <18 years of age. For preterm infants <1 year old, the corrected gestational age should be used when determining eligibility. The generally accepted definition of corrected gestational age, which is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age, will be used for this study.

4. Subject has a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1). The underlying epilepsy syndrome should be documented. Diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. Documentation of the EEG finding of generalized spike waves (EEG recording or a report) is required. The EEG should have been performed no more than 18 months prior to Visit 1 (with no change to diagnosis or seizure types during this time).
5. Subject must have experienced 2 or more events (typical generalized seizures associated with diagnosed epilepsy syndrome) within the 6-week prospective Baseline Period.
6. Subject is on a stable dosage regimen of 1 to 3 AEDs. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of at least 4 weeks prior to the Baseline Period.
7. Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. The VNS device must be implanted for at least 6 months before Visit 1 and the device settings must be stable for at least 4 weeks before Visit 1 and be kept stable during the Baseline Period and the Treatment Period. Use of the VNS device magnet is allowed.
8. Body weight at Visit 1 is at least 4kg for infants.
9. Females of childbearing potential must have a negative pregnancy test at Visit 1.
10. Subjects with West Syndrome are eligible if Baseline EEG demonstrates hypsarrhythmia despite treatment with at least 2 AEDs appropriate for the treatment of this syndrome.

6.2 Exclusion criteria

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

1. Subject has previously participated in this study, subject has been assigned to LCM in a previous LCM study, or subject has ever received LCM.
2. Subject is currently participating or has participated within the last 2 months in any study of an investigational drug or experimental device.
3. Subject has a history of convulsive status epilepticus within 1 month prior to Visit 1.
4. Subject has a current or previous diagnosis of pseudoseizures, conversion disorders, or other nonepileptic ictal events that could be confused with seizures.
5. Subject has exclusively typical absence (Type IIA1) or atypical absence (Type IIA2) seizures (no other generalized seizure types are reported), or has only partial-onset seizures (Type I).
6. Subject has primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy.
7. Subject has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize the subject's health or would compromise the subject's ability to participate in this study.

8. 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.
9. Subject has a known hypersensitivity to any components of the investigational medicinal product (IMP).
10. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
11. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
12. Subject has any history of alcohol or drug abuse within the previous 2 years.
13. 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).
14. Subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥2x the upper limit of normal (ULN) or has alkaline phosphatase levels ≥3x ULN.
15. Subject has impaired renal function (ie, creatinine clearance is lower than 30mL/min) at Visit 1.
16. Subject has sick sinus syndrome without a pacemaker, or second- or third-degree atrioventricular (AV) block.
17. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second- or third-degree heart block or a corrected QT interval [QTc] greater than 450ms).
18. Subject has hemodynamically significant heart disease (eg, heart failure).
19. Subject has an arrhythmic heart condition requiring medical therapy.
20. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.
21. 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 World Health Organization 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.

22. 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.
23. 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 less than 12 months are excluded. Note: any subject who has been treated with felbamate for at least 12 months and has not experienced serious toxicity issues is eligible.
24. Subject is taking monoamine oxidase (MAO) inhibitors or narcotic analgesics.
25. Subject is on a ketogenic or other specialized diet. If he/she was on a specialized diet in the past, he/she must be off the diet for at least 2 months prior to the Screening Visit (Visit 1).

6.3 Withdrawal criteria

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

All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

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

1. Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. Female subject achieves menarche and does not practice contraception as provided in Exclusion Criterion 21, unless sexually abstinent.
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. Subject has QTc interval of ≥500ms that is confirmed by a cardiologist overread on any ECG.
6. Subject develops second- or third-degree AV block.
7. 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.
8. Investigator decides that withdrawal from further participation would be in the subject's best interest.
9. Subject has a prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the investigator as serious enough to warrant discontinuation from the study.

10. Subject uses rescue medication in excess of that permitted by the protocol.
11. Subject needs any alteration in AED daily dose or VNS settings.
12. 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, LCM 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.
13. For subjects ≥6 years of age, subject has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

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

1. 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 (see Section 7.8).
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Transaminases (AST, ALT, or both) ≥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 LCM.

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 an effort (at least 1 phone call and 1 written message to the subject), 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 electronic Case Report form (eCRF) 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 TREATMENT(S)

7.1 Description of IMP(s)

The oral solution formulation contains 10mg/mL of drug substance and is colorless to pale yellow in appearance. Oral solution doses will be measured and administered via a dosing syringe. The tablet formulation will be supplied in doses of 50mg and 100mg. The 50mg tablets are light pink, oval, film-coated tablets debossed with "SP" on one side and "50" on the other. The 100mg tablets are dark yellow, oval, film-coated tablets debossed with "SP" on one side and "100" on the other.

7.2 Treatment(s) to be administered

Lacosamide will be administered orally bid (at approximately 12-hour intervals in the morning and in the evening). Administration of oral solution by feeding tube is permitted for subjects who are unable to swallow the oral solution. At the end of the Baseline Period and completion of Visit 2, subjects who meet the eligibility criteria will commence a 6-week Titration Period (LCM dosing flexibility allowed based on tolerability).

As described in Section 5.1, subjects will initiate treatment with LCM oral solution at 2mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day (oral solution) for subjects weighing <50kg, or 600mg/day (tablets/oral solution) in subjects weighing ≥50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control (see Figure 5-1 and Figure 5-2). During the Titration Period only, back-titration is permitted.

The planned doses for each week of the Titration Period for subjects taking the LCM oral solution and tablet formulations are displayed in Table 7-1.

Table 7–1: Lacosamide dose titration during the Titration Period

Body weight category (formulation)	Flexible doses for the Titration Period by study week					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
<50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/ day	12mg/kg/ day
≥50kg (tablets/oral solution)	100mg/day	200mg/day	300mg/day	400mg/day	500mg/day	600mg/day

LCM=lacosamide
Note: Subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead.

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. The flexible LCM dosing over the remainder of the Titration Period is outlined in Table 7-2.

Table 7–2: Flexible LCM dosing during the Titration Period

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

LCM=lacosamide; Max=maximum; Min=minimum
[a] Titration step to achieve a dose not previously administered
[b] Titration step subsequent to a back-titration
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)

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 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 LCM 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 LCM 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 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 dose for at least the final 3 days of Week 6

Body weight category (formulation)	LCM for at least the final 3 days of Week 6	
	Minimum	Maximum
<50kg (oral solution)	4mg/kg/day	12mg/kg/day
≥50kg (tablets/oral solution)	200mg/day	600mg/day

LCM=lacosamide

Eligible subjects (those who reach and maintain at least the minimum LCM dose for at least the final 3 days of the Titration Period) will enter a 12-week Maintenance Period at the dose they achieved at the last day of Week 6. The LCM dose will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period

will be withdrawn from the study. Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study. Subjects may be eligible for participation in the additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 4mg/kg/day for subjects weighing <50kg, and 200mg/day (tablets/oral solution) for subjects weighing ≥50kg. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.

Subjects who choose not to participate in the open-label study or subjects who discontinue due to other reasons will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The doses to be used during the Taper Period and the duration of the Taper Period will depend on the dose maintained during the Maintenance Period.

Table 7-4 and Table 7-5 display the recommended LCM dose reductions during the Taper Period for subjects <50kg and ≥50kg, respectively. A slower 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 exit 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 7–4: Recommended LCM dose taper for subjects <50kg receiving oral solution formulation

Maximum LCM dose achieved	Taper schedule			
	Week 19	Week 20	Week 21	Week 22
11-12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9-10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7-8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day
5-6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day	NA
3-4mg/kg/day	2mg/kg/day	2mg/kg/day	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: Subjects with doses <3mg/kg/day do not need to taper. End of Taper Visit will be at the end of Week 22 for subjects undergoing 4 weeks of taper, at the end of Week 21 for subjects undergoing 3 weeks of taper, and at the end of Week 20 for subjects undergoing 2 weeks of taper.
Note: Subjects not requiring taper will enter directly into the Safety Follow-Up Period and not attend any Taper Period visits.
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.

Table 7–5: Recommended LCM dose taper for subjects ≥50kg receiving oral solution or tablet formulation

Maximum LCM dose maintained	Taper schedule			
	Week 19	Week 20	Week 21	Week 22
550-600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
450-500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
350-400mg/day	300mg/day	200mg/day	100mg/day	100mg/day
250-300mg/day	200mg/day	100mg/day	100mg/day	NA
150-200mg/day	100mg/day	100mg/day	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: Subjects with doses <150mg/day do not need to taper. End of Taper Visit will be at the end of Week 22 for subjects undergoing 4 weeks of taper, at the end of Week 21 for subjects undergoing 3 weeks of taper, and at the end of Week 20 for subjects undergoing 2 weeks of taper.
Note: Subjects not requiring taper will enter directly into the Safety Follow-Up Period and not attend any Taper Period visits.
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 is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. It is suitably packaged in such a way as to protect the product from deterioration during transport and storage.

Lacosamide tablets will be packaged in high-density polyethylene bottles with a child-proof polypropylene screw cap. The oral solution will be packaged in amber polyethylene terephthalate bottles with a white, child-proof, polypropylene screw cap.

7.4 Labeling

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

7.5 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access.

Lacosamide is to be stored according to the instructions on the label. Lacosamide is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be refrigerated or frozen.

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. Data should

be available to support the temperature conditions maintained at the clinical site (eg manual temperature logs or automated chart recordings).

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, 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 period 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. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

At each visit after IMP is dispensed, subjects must return all used, unused, 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 <75% or >125% compliant with the dosage schedule), the sponsor, in conjunction with the investigator, will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant medication(s)/treatment(s)

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 at least 4 weeks prior to Visit 1 (ie, prior to entry into the Baseline Period); the dose regimen of the AEDs must be kept stable through the end of the Maintenance Period.

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

stable for at least 4 weeks before Visit 1 and be kept stable during the Baseline Period and through the end of the Maintenance Period.

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

- Neuroleptics
- MAO 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 less than 12 months are also excluded. Any subject who has been treated with felbamate for at least 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 are allowed 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 week (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 1 day per week (with up to 3 doses within 24 hours) during study participation; more frequent use precludes subjects from study participation.

7.9 Blinding

SP0966 is an open-label study; thus, there will be no blinding.

7.10 Randomization and numbering of subjects

Subjects will not be randomized in this study. A unique 5-digit identification number will be assigned by an Interactive Voice/Web Response System (IXRS) to all subjects who sign the ICF at Visit 1. This subject number will be used to identify the subject throughout the study and to maintain subject confidentiality. At subsequent visits, the IXRS will assign the applicable LCM bottle number. Further instructions will be provided in the IXRS manual.

8 STUDY PROCEDURES BY VISIT

All visits occur at the end of the respective week in the study; a window of ±2 days relative to Visit 2 is applicable for all visits and telephone contacts.

A detailed tabular schedule of study procedures is provided in Section 5.2.

8.1 Baseline Period

8.1.1 Visit 1 (Week -6) Screening Visit

At Visit 1, subjects will be evaluated for their suitability for enrollment. The Screening Visit assessments will be conducted 6 weeks prior to the first administration of LCM. It is acceptable for the Screening assessments to be conducted over >1 day. 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 (when possible or as required according to local IRBs/IECs) and the subject's parent/legal representative by the investigator (or designee). The subject's parent/legal representative will be requested to sign and date the IRB/IEC-approved ICF. When possible, or as required by the local IRB/IEC, the subject will be requested to give assent to participate in the study.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature on an ICF 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 and Section 11 of this protocol):

- Contact IXRS to obtain unique subject identification number.
- Review seizure history. The subject or caregiver (including parent/legal representative) will be asked how many seizures the subject has had over the past 4 weeks as a historical Baseline.
- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Medical history assessment.
- Complete physical examination.
- Complete neurological examination.

- 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).
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight and height assessment.
- Head circumference in subjects <4 years of age.
- Epilepsy surgery assessment.
- C-SSRS (if applicable). The C-SSRS will be completed for all subjects ≥6 years of age.
- Blood sample for clinical chemistry, hematology, and endocrinology.
- Serum pregnancy test (if applicable).
- Urine sample for urinalysis (if applicable). Will be performed for subjects aged 5 to 17 years.
- Tanner Stage (if applicable). 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.
- Dispense subject diary and remind subject to complete subject diary on a daily basis.
- AE reporting.

Eligible subjects will be scheduled to return to the clinic (Visit 2, Day 1) approximately 6 weeks ±2 days after the Screening Visit.

8.1.2 Telephone contact (Week -3)

Three weeks before Visit 2 (±2 days), the investigator or designee should contact the subject's caregiver (including parent/legal representative) by telephone. The investigator (or designee) should remind the subject's caregiver (including parent/legal representative) to ensure the diary is completed. The following should be performed via telephone:

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

8.2 Titration Period

8.2.1 Visit 2 (Day 1)

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 (end of Week 0) to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately

24 hours later (for Visit 2, Day 1) for removal of the scalp electrodes and return of the recording device. At Visit 2, the investigator should determine whether the subject is still eligible and willing to continue in the study.

The following will be performed prior to the first dose of LCM:

- Review inclusion/exclusion criteria.
- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.
- 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. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight and height assessment.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Blood sample for LCM and concomitant AED plasma concentrations (before dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.
- Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III Scales) (if applicable). For pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (version consistent with age at the visit).
- PedsQL for subjects ≥1 month to ≤18 years of age (version consistent with age at the visit).
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).
- Subject diary return/review.
- AE reporting.

- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.
- Reminder to complete subject diary on a daily basis.
- Health care resource use.
- Dispense LCM. Subjects should take the first dose of LCM (based on body weight) in the clinic. The starting dose for subjects taking the oral solution formulation will be 2mg/kg/day, and the starting dose for subjects taking the tablet formulation will be 100mg/day.

8.2.2 Telephone contacts (Weeks 1 and 3)

At the end of Weeks 1 and 3 (±2 days), the investigator or designee should contact the subject's caregiver (including parent/legal representative) by telephone. The assessments for these telephone contacts are the same as those performed during the telephone contact at Week -3 in Section 8.1.2 with the exception that inclusion/exclusion criteria do not need to be checked at Weeks 1 and 3.

8.2.3 Visit 3 (Week 2)

At Visit 3 (end of Week 2 ±2 days), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight assessment.
- Urine pregnancy test (if applicable)
- C-SSRS (if applicable).
- 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).
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.

- Reminder to complete subject diary on a daily basis.
- Health care resource use.
- Dispense LCM.

8.2.4 Visit 4 (Week 4)

Assessments for Visit 4 (end of Week 4 ±2 days) are the same as those described for Visit 3 (end of Week 2) in Section 8.2.3. This visit is optional and will only be required if a subject requires further LCM dose adjustment.

8.2.5 Visit 5 (Week 5)

Assessments for Visit 5 (end of Week 5 ±2 days) are the same as those described for Visit 3 (end of Week 2) in Section 8.2.3. This visit is optional and will only be required if a subject requires further LCM dose adjustment.

8.2.6 Visit 6 (Week 6, End of Titration)

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 6 (end of Week 6 ±2 days) to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 6) for removal of the scalp electrodes and return of the recording device.

At Visit 6 (end of Week 6), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- 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. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight assessment.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).

- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age (same version that was used at Visit 2).
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.
- Reminder to complete subject diary on a daily basis.
- Health care resource use.
- Dispense LCM for the first 4 weeks of the Maintenance Period.

8.3 Maintenance Period

8.3.1 Telephone contacts (Weeks 8, 12, and 16)

At the end of Weeks 8, 12, and 16 (±2 days), the investigator or designee should contact the subject's caregiver (including parent/legal representative) by telephone. The assessments for these telephone contacts are the same as those performed during the telephone contact at Week -3 in Section 8.1.2 with the exception that inclusion/exclusion criteria do not need to be checked at Weeks 8, 12, and 16.

Subjects must titrate to at least 4mg/kg/day for subjects weighing <50kg, or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg in order to enter the Maintenance Period.

8.3.2 Visit 7 (Week 10)

At Visit 7 (end of Week 10 ±2 days), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight assessment.
- 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).
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.

- Urine pregnancy test (if applicable).
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.
- Reminder to complete subject diary on a daily basis.
- Health care resource use.
- Dispense LCM.

8.3.3 Visit 8 (Week 14)

Assessments for Visit 8 (end of Week 14 ±2 days) are the same as those described for Visit 7 (end of Week 10) in Section 8.3.2 with the addition of:

- Brief physical examination.
- Brief neurological examination.

For the assessment of clinical chemistry and hematology, if no abnormality is observed in the laboratory blood samples from the previous visit, the assessment does not have to be performed.

8.3.4 Visit 9 (Week 18)/Early Termination Visit

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 9 (end of Week 18 ±2 days)/Early Termination to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 9/Early Termination Visit) for removal of the scalp electrodes and return of the recording device.

At Visit 9 (end of Week 18) or the Early Termination Visit (if applicable), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.

- 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. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight and height assessment.
- Head circumference in subjects <4 years of age.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry, hematology, and endocrinology.
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Urine sample for urinalysis (if applicable).
- Serum pregnancy test (if applicable).
- Clinical Global Impression of Change assessment.
- Caregiver's Global Impression of Change assessment.
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age (same version that was used at Visit 2).
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (same version that was used at Visit 2).
- PedsQL for subjects ≥1 month to ≤18 years of age (same version that was used at Visit 2).
- Tanner Stage (if applicable). The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary (for subjects entering Taper Period and not SP848).
- Reminder to complete subject diary on a daily basis (if applicable).
- Health care resource use.
- Dispense LCM (for subjects entering Taper Period and not SP848).

Subjects may be eligible for participation in the open-label study (SP848) if they have been maintained on a dose of at least 4mg/kg/day (oral solution) for subjects weighing <50kg, or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg in the Maintenance Period. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966.

Subjects who choose not to participate in the open-label study or subjects who discontinue due to other reasons will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Investigators should discuss treatment options with the subject and/or his/her parent/legal representative 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 representative. These subjects should complete Visit 9/Early Termination Visit and then complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The End of Taper Visit is not required for subjects who complete or withdraw from the study and who do not undergo taper of LCM.

8.4 End of Study Period

For subjects who enter the open-label study (SP848), the end of the study will be the date of the subject's last assessment in SP0966 (end of Maintenance Period or Early Termination Visit). Subjects who do not enroll in SP848 will enter a Taper Period followed by a Safety Follow-Up Period as described below, and the end of the study will be the date of the last Safety Follow-Up Telephone Contact.

8.4.1 Taper Period

For subjects who do not enroll in the open-label study (SP848), a 2- to 4 week (depending on dose achieved) Taper Period will be scheduled. For subjects completing the full duration of the Maintenance Period, the Taper Period will begin at Week 19 (±2 days). For subjects who do not complete the full duration of the Maintenance Period, the Taper Period will begin earlier, at the time that they end the Maintenance Period. Please refer to Section 7.2 for details of the taper schedule. 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. These subjects should complete Visit 9/Early Termination Visit and then complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

8.4.1.1 Telephone Contact (Week 19)

At the end of Week 19 (±2 days) during the first week of the Taper Period, the investigator or designee should contact the subject's caregiver (including parent/legal representative) by telephone. The following assessments will be performed:

- Concomitant AED(s) assessment

- Concomitant medication(s) assessment
- Reminder to complete subject diary on a daily basis
- AE reporting
- Review withdrawal criteria

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.

8.4.1.2 End of Taper Visit (Weeks 20 to 22)

The End of Taper Visit is not required for subjects who complete or withdraw from the study and who do not undergo taper of LCM. Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Week 20, Week 21, or Week 22, depending on dose level achieved; see Table 7-4 and Table 7-5). A time window of ±2 days relative to Visit 2 (Titration Period) is applicable.

The following will be performed at the End of Taper Visit at the end of the last week of the Taper Period:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight assessment.
- 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).
- C-SSRS (if applicable).
- Blood sample for clinical chemistry, hematology and endocrinology.
- Urine sample for urinalysis (if applicable).
- Serum pregnancy test (if applicable).
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.

- Health care resource use.

8.4.2 Safety Follow-up

Safety Follow-up is required only for subjects who do not enroll in the open-label study (SP848).

8.4.2.1 Safety Follow-Up Visit (Weeks 22 to 24)

The Safety Follow-Up Visit will occur 2 weeks (±2 days) after the final dose of LCM.

The following assessments will be performed:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight and height assessment.
- 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) (only for subjects with an abnormal reading at the previous visit).
- C-SSRS (if applicable).
- Blood sample for clinical chemistry, hematology and endocrinology (only for subjects with an abnormal value at the previous visit).
- Urine sample for urinalysis (if applicable) (only for subjects with an abnormal value at the previous visit).
- Urine pregnancy test (if applicable) (only if blood is not collected for another assessment).
- AE reporting.
- Health care resource use.

8.4.2.2 Safety Follow-Up Telephone Contact (Weeks 24 to 26)

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

- Concomitant AED(s) assessment
- Concomitant medication(s) assessment
- AE reporting

8.5 Unscheduled Visit

Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. During an Unscheduled Visit, the following assessments are required:

- Concomitant AED(s) assessment.
- VNS assessment (for subjects with an implanted VNS device).
- Concomitant medication(s) assessment.
- Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).
- Body weight assessment (height is not required).
- Subject diary return/review.
- Reminder to complete subject diary on a daily basis.
- AE reporting.
- Review withdrawal criteria.

If the Unscheduled Visit is due to an AE, then the C-SSRS is required.

In addition to the required assessments listed above, the investigator can perform further assessments based on his/her clinical judgment and the medical needs of the subject (eg, assessments of ECG, laboratory tests, physical examination, neurological examination, etc).

9 ASSESSMENT OF EFFICACY

9.1 Seizure frequency

At the Screening Visit (Visit 1), seizure history will be based on the subject or caregiver (including parent/legal representative) being asked how many seizures the subject has had over the past 4 weeks.

During the study, subjects will keep a diary to record daily seizure activity from the Screening Visit until the end of the study. At each visit and telephone contact the subject and/or legal representative should be reminded to complete the subject diary on a daily basis and to bring the diary with them to each clinic visit (including Unscheduled Visits). The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

The investigator should discuss the possibility of the emergence of other seizure types with parents and caregivers, and advise that all seizures should be recorded in the diary.

9.2 Global Impression of Change

9.2.1 Clinical Global Impression of Change

The Clinical Global Impression of Change should be completed by an investigator or subinvestigator. It will be used to assess the change in the subject's clinical status that resulted from LCM, including an evaluation of seizure frequency and intensity, the

occurrence of AEs, and the subject's overall functional status. The Clinical Global Impression of Change will be completed according to the tabular schedule of study procedures, Section 5.2.

9.2.2 Caregiver's Global Impression of Change

For the assessment of the Caregiver Global Impression of Change, the caregiver (including parent/legal representative) should provide his/her assessment of the subject's clinical status that resulted from LCM, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's overall functional status. The Caregiver Global Impression of Change will be completed according to the tabular schedule of study procedures, Section 5.2.

9.3 Pediatric Quality of Life Inventory

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001; Varni et al, 2011). The PedsQL will be administered at Visit 2 and at Visit 9/Early Termination. For the Visit 9/Early Termination assessment, subjects will complete the version consistent with their age at Visit 2.

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects ≥1 month to ≤12 months; ≥13 months to ≤24 months; >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≥1 month to ≤18 years of age.

The multidimensional PedsQL 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 of the individual items, with higher scores indicating higher HRQoL.

9.4 Health care resource use

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study. Health care resource use parameters will be collected according to the tabular schedule of study procedures, Section 5.2.

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC VARIABLES

Blood samples for the determination of LCM and concomitant AED plasma concentrations will be collected at Visits 2 and 9 (at any time after dosing with the exception of the sample at Visit 2, which should be predose) along with clinical chemistry and hematology samples (according to the tabular schedule of study procedures in Section 5.2). In each case, the time

the subject took the most recent dose of LCM and concomitant AEDs and the time of blood sampling must be recorded. Actual sampling times will be recorded in the eCRF to the minute.

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

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definition of AE

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

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

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

11.1.2 Procedures for reporting and recording AEs

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. 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 AEs

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

Details for completion of the AE eCRF (including judgment of relationship to LCM) are described in the eCRF Completion Guidelines.

11.1.4 Follow up of AEs

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

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

11.1.5 Rule for repetition of an AE

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, the UCB 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 the Early Termination 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 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 IMP

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 eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be an AE.

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.

A DMC will oversee the safety of the study. See Section 13.7 for further details.

11.2 Serious adverse events

11.2.1 Definition of SAE

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.)

  Hospitalization for the 24-hour ambulatory EEG assessments planned in this protocol will not be considered SAEs.

11.2.2 Procedures for reporting SAEs

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 SAE 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 SAEs

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 LCM AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second-degree, Type I and II, and third-degree), and marked bradycardia for subject's age
- 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 USA Food and Drug Administration (FDA):

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

    Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:

    ◦ Eosinophils % ≥10%

    ◦ Eosinophils absolute ≥0.5G/L

    ◦ Neutrophils absolute <1.5G/L

    ◦ Platelets ≤100G/L

- ALT ≥2x ULN
- AST ≥2x ULN

Adverse events of special interest must be reported in the same way as SAEs (see Section 11.2.2).

11.4 Immediate reporting of AEs

The following AEs must be reported immediately by the investigator to the sponsor:

- 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 SAEs

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the epilepsy population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 11.2.2.

Table 11–1 Anticipated SAEs for the pediatric epilepsy population

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

MedDRA=Medical Dictionary for Regulatory Activities

11.6 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, and urinalysis testing will be collected according to the tabular schedule of study procedures, Section 5.2. Urinalysis will be performed for subjects aged 5 to 17 years only. A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 11.6.3). 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	Chemistry	Urinalysis
RBC count WBC count Differential count Platelet count Hematocrit Hemoglobin	Calcium Serum electrolytes (sodium, potassium, chloride, bicarbonate) Total serum protein Albumin Phosphorus Glucose Uric acid Alkaline phosphatase BUN Creatinine AST ALT GGT Total bilirubin Cholesterol Triglycerides	Albumin Specific gravity Ketones Glucose pH Microscopic exam for blood cells or casts/high power field

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

11.6.1 Additional laboratory tests

In order to assess changes in thyroid and sex hormone concentrations, laboratory tests for FSH, LH, T3, T4, TSH, and testosterone, as appropriate, will be performed. The assessments will be performed according to the tabular schedule of study procedures (Section 5.2). The use of any oral contraceptives should be recorded.

11.6.2 Liver function tests

Refer to Section 6.3 for LFT withdrawal criteria.

Transaminases (AST, ALT, or both) ≥3xULN but <5xULN, in the presence of total bilirubin ≥2xULN, or transaminases (AST, ALT, or both) ≥5xULN will result in immediate

discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case >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.

11.6.3 Pregnancy testing

Females of childbearing potential will have serum and urine pregnancy tests performed during the study according to the tabular schedule of study procedures; see Section 5.2.

11.7 Other safety measurements

11.7.1 Seizure frequency

See Section 9.1.

11.7.2 24-hour ambulatory EEG

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2, Visit 6, and Visit 9/Early Termination to begin 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges.

11.7.3 12-lead ECG

Standard 12-lead ECGs will be performed according to the tabular schedule of study procedures in Section 5.2. Two interpretable recordings approximately 20 to 30 minutes apart are required. At Visit 2, Visit 6, and Visit 9/Early Termination, the 12-lead ECG recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording and prior to blood sample collection. At all other visits, 2 recordings will be performed prior to blood sample collection and measurement of vital signs.

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in the supine position for approximately 5 minutes before the ECG recordings and during the recordings, if possible.

11.7.3.1 Overall ECG interpretation

An immediate initial review of the ECGs will be conducted locally by the investigator, subinvestigator, or qualified designated reader. If this reading identifies abnormal ECG findings that are assessed by the investigator or subinvestigator to be clinically significant, then the ECG should be repeated in 1 hour, unless circumstances require a more rapid assessment. If the clinically significant abnormality is confirmed by the repeat ECG or if the

investigator feels it is medically necessary, then the subject must be withdrawn from the study (see Section 6.3). The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

11.7.4 Vital signs, body weight and height

Noninvasive BP (systolic and diastolic) and pulse rate will be measured at clinic visits after at least 3 minutes at rest in a supine position, according to the tabular schedule of study procedures (Section 5.2). Assessment of orthostatic changes (only in ambulatory subjects) 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 at approximately 1 minute and 3 minutes after standing up, as feasible. Body weight will be determined without shoes and wearing light clothing, and height will be measured without shoes. Body weight and height will be assessed according to the tabular schedule of study procedures in Section 5.2.

11.7.5 Physical examination

The physical examination should be performed by a medically qualified clinician licensed to perform the examination, according to the tabular schedule of study procedures in Section 5.2. If possible, the same clinician should conduct all physical examinations for the same subject during the study. Subsequent to Visit 1, clinically significant physical examination findings should be reported as AEs.

11.7.5.1 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.

11.7.5.2 Brief physical examination

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

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

11.7.6 Neurological examination

Neurological examinations will be performed by a medically qualified clinician with documented training in the conduct of neurological examinations, according to the tabular schedule of study procedures in Section 5.2. 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 generalized seizures.

11.7.6.1 Complete neurological examination

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

11.7.6.2 Brief neurological examination

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

11.7.7 Tanner Stage

At Visit 1 and Visit 9 (or the Early Termination Visit) for applicable subjects, the investigator or qualified designee will evaluate the subject's sexual development using the 3-item scale. The investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 1 or those subjects who become pubescent during the course of the study).

11.7.8 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) or legal representative(s). Depending on the subject's age, 1 of 2 versions of the CBCL will be used. The CBCL/1½-5 checklist is intended for use in pediatric subjects aged between 18 months and 5 years and 11 months. For subjects between 6 and <18 years, the CBCL/6-18 version will be used. The Achenbach CBCL will not be applied to pediatric subjects <18 months of age.

The same scale will be completed at Visit 2, Visit 6, and Visit 9 (or the Early Termination Visit) and again by the same parent(s) or legal representative(s) in the open-label study, SP848 (if applicable). 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.

11.7.9 Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley-III scales are recognized internationally as one of the most comprehensive developmental assessment instruments (Sattler and Hoge, 2006) used to examine the major facets of a young child's development (Bayley, 2006). The Bayley-III scales are a standardized, individually administered adaptive assessment that measures the developmental functioning of infants and young pediatric subjects from 1 month to 42 months of age (Bayley, 2006). The Bayley-III scales measure cognitive, language, motor, social-emotional, and adaptive development and are a revision of the predecessor, the Bayley Scales of Infant Development, Second Edition (Bayley, 1993). The Bayley-III scales are a technically sound instrument, with strong internal consistency, as well as test-retest stability. The Bayley-III scales are validated only in English.

This scale is validated as a tool for assessment of neurological development in young pediatric subjects and is therefore considered appropriate for SP0966.

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

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

The same scale will be completed at Visit 2 and again in the open-label study, SP848 (if applicable).

11.7.10 Behavior Rating Inventory of Executive Function

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P/BRIEF will be administered at Visit 2 and at Visit 9/Early Termination. For the Visit 9/Early Termination assessment, subjects will complete the version consistent with their age at Visit 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.

11.7.11 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures in Section 5.2.

The "Since Last Visit" version of the C-SSRS will be used, with the following exceptions:

- The "Baseline/Screening" version of the C-SSRS should be completed at Visit 1.
- If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.

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.

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 eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable 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).

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. If the monitor is given access to the electronic data, the computer-generated documents do not need to be printed.

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 eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 Case Report form completion

The study will be performed using remote data capture; the investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

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. 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 LCM and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition

records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's 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.

13.1 Definition of analysis sets

The primary analysis set will be the Safety Set (SS) and will include all enrolled subjects who take at least 1 dose of LCM.

The analysis set for the preliminary efficacy variables will be the Full Analysis Set and will include all subjects in the SS having had a Baseline and at least 1 post-Baseline efficacy related assessment.

13.2 General statistical considerations

In general, descriptive statistics will be used to provide an overview of the primary, secondary, and other variable results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include number of subjects, mean, standard deviation, median, minimum, and maximum.

Unless otherwise specified, Baseline will be based on the last nonmissing data collected prior to the first dose of LCM, ie, assessments on Visit 1 or Visit 2. Baseline of seizure data will be defined as the data collected in the seizure diary during the Baseline Period, ie, from Visit 1 up to 1 day prior to Visit 2.

13.3 Planned safety analyses

13.3.1 Analysis of the primary safety variables

The actual change in the count of generalized spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 6 will be calculated and summarized descriptively.

The change in the number of days with any generalized seizure from the Baseline Period to the Maintenance Period (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) will be calculated and summarized descriptively. For these analyses the number of days with seizures will be normalized to days per 28 days. The assessment of seizure days will be based on the seizure diary.

13.3.2 Secondary safety variables

The actual change in the count of 3Hz spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 6 will be calculated and summarized descriptively.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Summary tables for number and percentage of subjects reporting at least 1 TEAE tabulated by System Organ Class and preferred term will be presented. Furthermore, TEAEs that lead to early discontinuation from the study and serious TEAEs will be tabulated. Treatment-emergent AEs will be defined as those events which start on or after the date of first LCM administration and within 30 days following the date of last LCM administration, or whose severity worsens within this time frame.

Subject withdrawal due to AEs will be analyzed by presenting number and percentage of subjects with "AE(s)" given as primary reason of premature study discontinuation.

13.3.3 Other safety analyses

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. 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.

The analysis of the Bayley-III scales data will be performed in the follow-up study, SP848.

13.4 Planned preliminary efficacy and other analyses

13.4.1 Preliminary efficacy analyses

Percent change in seizure days is calculated as the respective seizure days per 28 days during the Maintenance Period minus respective seizure days during Baseline per 28 days divided by Baseline days and then multiplied by 100. The respective seizure days per 28 days will be calculated as ([number of seizure days over the specified time interval] divided by [number of days in the interval]) multiplied by 28. Seizure days for all generalized seizure types will be based on the seizure diary.

Descriptive statistics to summarize the absolute and percent change in seizure days per 28 days from Baseline Period to the Maintenance Period will be presented for any generalized seizures reported and for each generalized seizure type.

The actual change in the count of generalized and 3Hz spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 9 or Early Termination will be calculated and summarized descriptively.

Descriptive summaries will also be presented for the Clinical and Caregiver's Global Impression of Change, health care resource use, and the PedsQL.

13.4.2 Pharmacokinetic analyses

A listing of LCM and AED plasma concentrations will be presented. A statistical analysis of the effect of LCM on AED concentrations will be performed.

13.5 Handling of protocol deviations

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

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

13.6 Handling of dropouts or missing data

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

To assess the change and percent change in seizure days for generalized seizure types (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) and any generalized seizures from the Baseline Period to the Maintenance Period for subjects who prematurely discontinue the study, a last observation carried forward convention will be applied in the following manner to obtain an estimate for the Maintenance Period:

- Subjects discontinued prematurely during the Titration Period: estimates will be calculated using all available data in the Titration Period and carried forward for the Maintenance Period.
- Subjects discontinued prematurely during the Maintenance Period: estimates will be calculated using all available data in the Maintenance Period and carried forward for the entire Maintenance Period.
- Subjects completing the Maintenance Period: estimates will be calculated using all data from the Maintenance Period.

The imputation for data will not be carried forward into the End-of-Study Period.

No further substitution of missing data will be conducted.

13.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC. The DMC will oversee the safety of the study by convening to review safety data after 15 subjects have completed Visit 6 or withdrawn from the study, then again after 30 subjects have completed Visit 6 or withdrawn from the study. The DMC will consist of a UCB neurologist, a neurologist from the European region, a drug safety physician, a biostatistician, and an independent medical expert. Study enrollment will not be halted during planned DMC review of the safety data. The sponsor can convene an ad hoc DMC meeting to review the data and make recommendations on the continuation or modification of the study. The objectives and procedures for the DMC will be detailed in the DMC Charter.

13.8 Determination of sample size

A total of 50 evaluable subjects are planned for enrollment for this study across 2 age groups. The first age group will consist of approximately 40 subjects between 4 years and <18 years of age. The second age group will consist of at least 10 subjects between 1 month and <4 years of age. Since the primary objective of this open-label exploratory study is to assess the safety and preliminary efficacy of LCM in subjects with generalized seizures and other epilepsy syndromes, a sample size of 50 evaluable subjects is deemed adequate for meeting the objectives of the study. No formal sample size calculations were performed.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Informed consent must be obtained from the subject's parent/legal representative and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki. When

possible or as required according to local IRB/IEC, assent also has to be obtained from the subject.

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

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

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

All studies conducted at centers in the USA must include the use of a Health Insurance Portability and Accountability Act 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 and/or the subject's parent/legal representative has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained the subject's parent/legal representative's written consent and the subject's assent 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 IECs

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, ICF, 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.

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.

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17 APPENDICES

17.1 International Classification of Epileptic Seizures (1981)

Adapted from the International Classification of Epileptic Seizures (1981)

I. Partial seizures (focal, local)

A. Simple partial seizures (consciousness not impaired)

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

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

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

II. Generalized seizures (convulsive or non-convulsive)

A. Absence seizures

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

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures - (Astatic)

Unclassified epileptic seizures

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

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

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

17.2 Protocol Amendment 1

Rationale for the amendment

The present Amendment has been issued following a Special Protocol Assessment performed by the USA FDA on SP0969, a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM as adjunctive therapy in epilepsy subjects ≥4 years to <17 years of age with uncontrolled partial-onset seizures. Where applicable, the recommendations made by the FDA for SP0969 have been incorporated into the current protocol. In addition, updates were made to improve the clarity of the protocol, particularly with regard to inclusion/exclusion criteria, additional assessments for safety and efficacy were added, and the number of sites was increased. The following major changes were made:

- Dosing was changed to match SP0969 (based on subject weight).
- Inclusion criteria for concomitant AEDs and VNS were modified to match with SP0969.
- Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy were excluded. The effect of LCM in this population is planned to be investigated in a confirmatory study; therefore, this population will not be included in this exploratory study.
- Exclusion criteria for felbamate and vigabatrin were modified.
- The Behavior Rating Inventory of Executive Function was added as an additional safety assessment.
- The Pediatric Quality of Life Inventory was added as an additional efficacy assessment.
- Health care resource use was added as an efficacy variable.
- The requirement to measure height was restricted to visits where a complete physical examination is required.
- A new withdrawal criteria based on the use of rescue medication was added.
- An additional assessment at end of titration was added for the Achenbach Child Behavior Checklist.
- Orthostatic blood pressure and pulse assessments were added.
- Concomitant and prohibited medications, and rescue medication were modified to match SP0969.
- The terminology “syrup” was replaced with oral solution in the protocol.
- Assessment time points for scales and questionnaires were modified.
- Additional assessments for VNS assessments and urinalysis were added.
- The number of sites was increased to 40.
- Additional text was added clarifying which version of the C-SSRS should be used at study entry and for subjects turning 6 years of age.

- Administrative changes were made; the CPM and safety reporting contact details were updated.
- Typographical changes were made to improve clarity of wording.

Modifications and changes

Global changes

The following key changes were made throughout the protocol:

- Dosing was changed, so that following titration the maximum doses by body weight were:

Subjects weighing ≤30kg LCM 12mg/kg/day (oral solution)	Subjects weighing >30kg to ≤50kg LCM 8mg/kg/day (oral solution)	Subjects weighing >50kg LCM 400mg/day (tablet)

Specific changes

Change #1

SPONSOR DECLARATION

Clinical Project Manager

[redacted]

Has been changed to:

Clinical Project Manager

[redacted]**, RN, MSN**

Change #2

STUDY CONTACT INFORMATION

Clinical Project Manager

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

Has been changed to:

Clinical Project Manager

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

Change #3

Serious Adverse Event Reporting

Serious adverse event reporting (24h) and safety related issues	
Fax	**Europe and Rest of the World (except Japan):** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842
Email	**Europe and Rest of the World (except Japan):** GCSP@ucb.com **USA and Canada:** GCSP@ucb.com

Has been changed to:

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

Change #4

LIST OF ABBREVIATIONS

The following abbreviations have been added:

BRIEF®-P/BRIEF®	Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function
FDA	Food and Drug Administration
HRQoL	Health-related Quality of Life
PedsQL™	Pediatric Quality of Life Inventory

Change #5

Section 1 SUMMARY

The primary variables in this study are changes in the count of generalized spike-wave discharges and change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) from the Baseline Period to the Maintenance Period. Other variables to be assessed include efficacy, plasma concentrations, and other measures of safety.

Approximately 50 subjects will be enrolled in this study across approximately 30 sites in Europe, USA, and other regions as deemed necessary.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured through daily seizure diaries. At the end of the Baseline Period (completion of Visit 2), subjects will commence a 4-week Titration Period. Subjects will initiate treatment with LCM at 3mg/kg/day (oral solution) or 100mg/day (tablets) per week and the dose can be titrated to a level to optimize tolerability and seizure control, not to exceed a 12mg/kg/day or 400mg/day dose, whichever is lower, based on body weight. At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in an additional open-label study (SP848) upon completion of the Maintenance Period and a minimum dose of 6mg/kg/day or 200mg/day. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the additional open-label study, subjects who are not able to tolerate the lowest LCM dose (100mg/day for the tablet formulation or 3mg/kg/day for the syrup formulation), or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Has been changed to:

The primary variables in this study are changes in the count of generalized spike-wave discharges and change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) from the Baseline

Period to the Maintenance Period. **The above variables reference partial seizures evolving to secondarily generalized seizures. While these partial seizures will be summarized as a part of the analysis, subjects must have a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1) to possibly be eligible for study participation. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are also not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.** Other variables to be assessed include **measures of** efficacy, plasma concentrations, and other measures of safety.

Approximately 50 subjects will be enrolled in this study across approximately **40** sites in Europe, USA, and other regions as deemed necessary.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured through daily seizure diaries. At the end of the Baseline Period (completion of Visit 2), subjects will commence a 4-week Titration Period, **where subjects will initiate treatment with LCM. Subjects weighing ≤30kg will begin treatment on LCM oral solution (syrup) 3mg/kg/day, subjects weighing >30kg to ≤50kg will begin treatment on LCM oral solution 2mg/kg/day, and subjects weighing >50kg will begin treatment on LCM tablets 100mg/day (subjects weighing >50kg who are unable or unwilling to swallow tablets can also be dispensed LCM oral solution). The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day for subjects weighing ≤30kg, or 8mg/kg/day for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg.** At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. **Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period.**

The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in an additional open-label study (SP848) if they have completed the Maintenance Period and a minimum dose of **6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg.** Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the additional open-label study, subjects who are **only** able to tolerate the lowest LCM dose (100mg/day for the tablet formulation, **3mg/kg/day or 2mg/kg/day for the oral solution formulation)**, or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Change #6

Section 2 INTRODUCTION

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the EU (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) and as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the USA (oral tablets, oral solution, and solution for iv infusion). The oral solution (syrup) and the film-coated tablet formulations are suitable for oral administration to pediatric patients.

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

UCB has completed a Phase 2, open-label safety study (SP0961) of adjunctive LCM treatment for primary generalized tonic-clonic seizures in adult subjects with idiopathic generalized epilepsy. The results of SP0961 showed reductions in primary generalized tonic-clonic seizure frequency and myoclonic seizure days, with a small reduction in absence seizure days. A minority of subjects (~10%) showed an increase in absence seizures (reported as TEAEs) that, in this uncontrolled study, cannot be distinguished between the drug versus the natural course of the disease. The AE profile was similar to that of adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

Has been changed to:

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the EU (oral tablets, **oral solution**, and solution for intravenous [iv] infusion) and as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the USA (oral tablets, oral solution, and solution for iv infusion). The **oral solution** and the film-coated tablet formulations are suitable for oral administration to pediatric patients.

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 its major metabolite, SPM 12809 (O-desmethyl-LCM), in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as **oral solution**.

UCB has completed a Phase 2, open-label safety study (SP0961) of adjunctive LCM treatment for primary generalized tonic-clonic seizures **in subjects ≥ 16 years of age** with idiopathic generalized epilepsy. The results of SP0961 showed reductions in primary generalized tonic-clonic seizure frequency and myoclonic seizure days, with a small reduction in absence seizure days. A minority of subjects (~10%) showed an increase in absence seizures (reported as TEAEs) that, in this uncontrolled study, cannot be distinguished

between the drug versus the natural course of the disease. The AE profile was similar to that of adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

Change #7

Section 4 STUDY VARIABLES

The following text has been added:

The variables below reference partial seizures evolving to secondarily generalized seizures. While these partial seizures will be summarized as a part of the analysis, subjects must meet eligibility criteria to be applicable for the study (see inclusion criterion 4 and exclusion criteria 5 and 6 for applicable subjects).

Change #8

Section 4.1.3 Other variables assessing safety

Behavioral and cognition assessment (Achenbach Child Behavior Checklist [CBCL/1½-5 or CBCL/6-18]) for pediatric subjects ≥18 months of age

Has been changed to:

Behavioral assessment (Achenbach Child Behavior Checklist [CBCL/1½-5 or CBCL/6-18]) for pediatric subjects ≥18 months of age

Assessment of cognitive function (Behavior Rating Inventory of Executive Function-Preschool Version for subjects ≥2 years to <5 years of age [BRIEF®-P] or the Behavior Rating Inventory of Executive Function [BRIEF®] for subjects ≥5 years of age)

Change #9

Section 4.2 Preliminary efficacy variables

The following assessments have been added:

Change in quality of life assessment (Pediatric Quality of Life Inventory [PedsQL™]) for subjects ≥1 month to ≤18 years of age

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

Change #10

Section 5.1 Study description

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥4 years of age will be included in this study. Once the LCM dose range has been defined in subjects <4 years of age, enrollment of subjects in the younger cohort will begin.

Subjects should have a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. Subjects with exclusively typical absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges.

The study treatment is LCM in either the oral syrup formulation or tablet formulation. The formulation of LCM to be administered will be decided by the investigator and the subject.

Subjects will not be randomized, but all subjects who sign the informed consent form (ICF) at Visit 1 will be assigned a unique identification number.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured. Subjects/caregivers will maintain a diary to record daily seizure activity from Visit 1 until the end of the study. The subject diary will capture seizure type and seizure frequency information. If all inclusion criteria are met and no exclusion criteria are met, the subject will begin a 4-week Titration Period starting at Visit 2. Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 to begin 24-hour ambulatory EEG recordings. Subjects will initiate treatment with LCM at 3mg/kg/day (oral solution) or 100mg/day (tablets) per week and the dose can be titrated to a level to optimize tolerability and seizure control, not to exceed a 12mg/kg/day or 400mg/day dose, whichever is lower, based on body weight.

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects will return to the clinic (on the morning of the day prior to the scheduled visit) at Visit 6 and Visit 9 or Early Termination for 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in the additional open-label study (SP848) upon completion of the Maintenance Period and a minimum dose of 6mg/kg/day or 200mg/day. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the open-label study, subjects who are not able to tolerate the lowest LCM dose (100mg/day for the tablet formulation or 3mg/kg/day for the syrup formulation), or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Has been changed to:

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥4 years of age will be included in this study. Once the LCM dose range has been defined in subjects <4 years of age, enrollment of subjects in the younger cohort will begin.

Subjects should have a **current** diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. **The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are also not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.**

The study treatment is LCM in either the oral **solution** formulation or tablet formulation. **The formulation of LCM to be administered is based on the weight of the subject. Only subjects weighing >50kg who are able and willing to swallow tablets may be dispensed LCM tablets.**

Subjects will not be randomized, but all subjects who sign the informed consent form (ICF) at Visit 1 will be assigned a unique identification number.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured. Subjects/caregivers will maintain a diary to record daily seizure activity from Visit 1 until the end of the study. The subject diary will capture seizure type and seizure frequency information. If all inclusion criteria are met and no exclusion criteria are met, the subject will begin a 4-week Titration Period starting at Visit 2. Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 to begin 24-hour ambulatory EEG recordings. **Subjects will initiate treatment with LCM oral solution at 2mg/kg/day or 3mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day for subjects weighing ≤30kg, or 8mg/kg/day for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control. During the Titration period only, one back-titration step is permitted; once the dose of LCM has been back-titrated, the dose cannot be increased for the duration of the study (see Figure 5-1 and Figure 5-2).**

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or 400mg/kg/day), then the highest optimized dose will be maintained until the end of the Titration Period. The Titration Period will last 4 weeks, regardless

of the doses administered. Subjects who are not able to tolerate the minimum required dose (at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day [tablets/oral solution] for subjects weighing >50kg) of LCM (even after back-titration) will be withdrawn from the study. Study medication doses will be titrated according to the schedules presented in Table 7-1.

The maximum LCM dose is not to exceed 12mg/kg/day (oral solution) for subjects weighing ≤30kg, 8mg/kg/day (oral solution) for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg.

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. **Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period.** Subjects will return to the clinic (on the morning of the day prior to the scheduled visit) at Visit 6 and Visit 9 or Early Termination for 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in the additional open-label study (SP848) upon completion of the Maintenance Period and a minimum **dose of 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg.** Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the open-label study, subjects who are **only** able to tolerate the lowest LCM dose **(100mg/day for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation),** or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. **Dosing schedules for the Taper Period are provided in Table 7-2, Table 7-3, and Table 7-4.**

Change #11

Section 5.1.1 Study duration per subject

The study will consist of a 6-week prospective Baseline Period, followed by a 4-week Titration Period, and a 12-week Maintenance Period. Subjects may be eligible to enter an additional open-label study (SP848) after completion of the Maintenance Period, or, if they do not continue in the open-label study, subjects will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. The total study duration for a subject will be up to a maximum of 21 weeks.

Has been changed to:

The study will consist of a 6-week prospective Baseline Period, followed by a 4-week Titration Period, and a 12-week Maintenance Period. Subjects may be eligible to enter an additional open-label study (SP848) after completion of the Maintenance Period. **Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to**

enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label study will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. The total study duration for a subject will be up to a maximum of **27** weeks.

Change #12

Section 5.1.3 Anticipated regions and countries

This study will be conducted at approximately 30 sites in Europe, USA, and other regions as deemed necessary.

Has been changed to:

This study will be conducted at approximately **40** sites in Europe, USA, and other regions as deemed necessary.

Change #13

Section 5.2 Schedule of study assessments

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

The following assessments have been modified/added:

- **Vital signs: orthostatic assessments were added**
- **Urinalysis was added at Visit 9/ET**
- **The Behavior Rating Inventory of Executive Function (BRIEF-P/BRIEF) was added at Visit 2 and Visit 9/ET**
- **The Pediatric Quality of Life Inventory (PedsQL) was added at Visit 2 and Visit 9/ET**
- **The Achenbach Child Behavior Checklist was added at Visit 6**
- **The Bayley-III and Achenbach Child Behavior Checklist were moved from Visit 1 to Visit 2**
- **Assessment of VNS changes was added at all clinic visits**
- **Health care resource use was added at all clinic visits**

The following abbreviations have been added:

- **BRIEF-P/BRIEF=Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function**
- **PedsQL=Pediatric Quality of Life Inventory**

The following footnotes have been modified/added:

[a] Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments indicated in the schedule above, further assessments can be completed as needed and may include ECG, laboratory tests, physical examination, **neurological examination**, etc.

[b] The recommended Taper Period duration for subjects taking the tablet formulation is 2 weeks, but a slower taper over 4 weeks may be permitted if medically necessary. The duration of the Taper Period for the **oral solution** formulation is 4 weeks. The End of Taper Visit will occur at the end of the last week of the Taper Period.

[c] At the end of Visit 9 or at ET, all subjects who complete the Maintenance Period and whose daily dose was at least **6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg** will be offered the opportunity to enroll in an additional open-label extension study, SP848. Visit 9 or the ET Visit of SP0966 will also serve as Visit 1 for SP848. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label extension study will complete the End of Study procedures that include up to a 4-week LCM taper followed by a 1-week Safety Follow-up Period and Final Safety telephone contact.

[f] **Height will only be recorded at study visits where a complete physical examination is performed. Height is not required at an Unscheduled Visit.**

[o] **If the Unscheduled Visit is due to an AE, then the C-SSRS is required.**

[s] **For subjects entering Taper Period and not SP848.**

Change #14

Section 5.3 Schematic diagram

Figure 5-2 presents a schematic diagram of the LCM syrup dosing and taper schedule.

Has been changed to:

Figure 5-2 presents a schematic diagram of the LCM **oral solution** dosing and taper schedule.

Figure 5-1 Schematic diagram - LCM tablet dosing and taper schedule

The following modifications have been made to the Maintenance Period:

- **Solid lines were added to indicate that the 200, 300 and 400mg/day dose can be carried through to the Maintenance Period; with no further dose modifications. The label "400mg/day" was removed from the Maintenance Period.**

Figure 5-2 Schematic diagram - LCM syrup dosing and taper schedule

The Figure title has been changed to:

- **Figure 5-2 Schematic diagram - LCM oral solution dosing and taper schedule**

The following titration steps have been added:

- **3mg/kg/day or 2mg/kg/day**
- **6mg/kg/day or 4mg/kg/day**
- **9mg/kg/day or 6mg/kg/day**
- **12mg/kg/day or 8mg/kg/day**

The following modifications have been made to the Maintenance Period:

- **Solid lines were added to indicate that the 6mg/kg/day or 4mg/kg/day, 9mg/kg/day or 6mg/kg/day and 12mg/kg/day or 8mg/kg/day dose can be carried through to the Maintenance Period; with no further dose modifications. The label "12mg/kg/day" was removed from the Maintenance Period.**

The following taper steps have been added:

- **9mg/kg/day or 6mg/kg/day**
- **6mg/kg/day or 4mg/kg/day**
- **3mg/kg/day or 2mg/kg/day**

Change #15

Section 5.4 Rationale for study design and selection of dose

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 SP0966 are that a maximum dose of 12mg/kg/day in SP0966 should aim to achieve LCM plasma concentrations equivalent to the average steady-state LCM plasma concentration reached after a LCM 400mg/day dose administration in adult studies, which is approximately 8µg/mL.

Has been changed to:

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 SP0966 **are as follows:**

- **LCM dosing should aim to achieve LCM plasma concentrations equivalent to the average steady-state LCM plasma concentration reached after a LCM 400mg/day dose administration in adult studies, which is approximately 8µg/mL.**
- **A weight-based dosing scheme is recommended:**
  - **Subjects ≤30kg: LCM 12mg/kg/day (oral solution)**

- **Subjects >30kg to ≤50kg: LCM 8mg/kg/day (oral solution, up to a maximum of LCM 400mg/day)**
- **Subjects weighing >50kg: 400mg/day (tablets/oral solution)**

Change #16

Section 6.1 Inclusion criteria

4. Subject has a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1). The underlying epilepsy syndrome should be documented. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. Documentation of the EEG finding of generalized spike waves (EEG recording or a report) is required. The EEG should have been performed no more than 18 months prior to Visit 1 (with no change to diagnosis or seizures during this time).
6. Subject has been maintained on a stable dose regimen of 1 to 3 marketed AEDs for at least 28 days prior to Visit 1 and with or without additional concurrent stable VNS. Vagus nerve stimulation must have been in place for at least 6 months prior to study entry with constant settings for at least 1 week prior to Visit 1.

Has been changed to:

4. Subject has a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1). The underlying epilepsy syndrome **should be documented. Diagnosis should have** been established by clinical history and an EEG with generalized spike-wave discharges. Documentation of the EEG finding of generalized spike waves (EEG recording or a report) is required. The EEG should have been performed no more than 18 months prior to Visit 1 (with no change to diagnosis or **seizure types** during this time).
6. **Subject is on a stable dosage regimen of 1 to 3 AEDs. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of at least 4 weeks prior to the Baseline Period.**
7. **Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. Vagal nerve stimulation (implanted for at least 6 months and stable for at least 4 weeks before Visit 1) must be kept stable during the Baseline Period and the Maintenance Period.**

Change #17

Section 6.2 Exclusion criteria

The following exclusion criterion has been added:

6. Subject has primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy.

The following exclusion criteria have been modified:

8. Subject has a known hypersensitivity to any components of the investigational medicinal product (IMP). Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.

20. Subject has been treated with vigabatrin or felbamate for at least 12 months prior to entering the study and has experienced any toxicity issues with these treatments. Note: any subject who is currently treated with vigabatrin or felbamate, and has received vigabatrin or felbamate for a period of less than 12 months, is excluded from the study. Subjects who have received vigabatrin in the past must have completed vigabatrin therapy at least 6 months prior to study entry. Subjects must have documentation of an assessment for visual field defects prior to study entry or documentation of why visual field testing cannot be performed.

Have been changed to:

9. Subject has a known hypersensitivity to any components of the investigational medicinal product (IMP).

10. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.

22. 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.

23. 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 less than 12 months are excluded. Note: any subject who has been treated with felbamate for at least 12 months and has not experienced serious toxicity issues is eligible.

Change #18

Section 6.3 Withdrawal criteria

All subjects discontinuing treatment with LCM for any reason should taper off LCM. It is recommended that the dosage be tapered off in weekly decrements of 3mg/kg/day (oral solution) or 200mg/day (tablet) (see Section 7.2). A slow taper 100mg/day (tablet) 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 exit criteria have been met.

Has been changed to:

All subjects discontinuing treatment with LCM for any reason should taper off LCM. It is recommended that the dosage be tapered off in weekly decrements of **2 mg/kg/day or** 3mg/kg/day (oral solution) or 200mg/day (tablet) (see Section 7.2). **A slower 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 exit criteria have been met.

The following withdrawal criterion has been added:

10. Subject requires the use of rescue medication in excess of that permitted by the protocol.

Change #19

Section 7.2 Treatment(s) to be administered

At the end of the Baseline Period (completion of Visit 2), subjects who meet the eligibility criteria will commence a 4-week Titration Period. Subjects will initiate treatment with LCM at 3mg/kg/day (oral solution) or 100mg/day (tablets) per week, and the dose can be titrated to a level to optimize tolerability and seizure control, not to exceed a 12mg/kg/day or 400mg/day dose, whichever is lower, based on body weight.

The planned doses for each week of the Titration Period for subjects taking the LCM syrup and tablet formulations are displayed in Table 7-1.

Table 7-1 Lacosamide dose titration during the Titration Period

	Dose			
Formulation	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Syrup	3mg/kg/day	6mg/kg/day	9mg/kg/day	12mg/kg/day
Tablet	100mg/day	200mg/day	300mg/day	400mg/day

Based on tolerability, a 1-step back-titration of LCM 3mg/kg/day or 100mg/day, depending on the formulation is allowed during the Titration Period. Only 1 back-titration is permitted and once the dose of LCM has been back-titrated, the dose cannot be increased later. If a subject does not achieve the maximum dose level (12mg/kg/day or 400mg/kg/day), then the highest dose achieved will be maintained until the end of the Titration Period. The Titration Period will last 4 weeks, regardless of the doses administered. Subjects who are not able to tolerate LCM (even after back-titration) will be withdrawn from the study.

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects will enter the Maintenance Period at the LCM dose achieved at the end of the Titration Period; up to a maximum of 12mg/kg/day for the syrup formulation or 400mg/day

for the tablet formulation. No dose modification is permitted during the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study.

Subjects may be eligible for participation in the additional open-label study (SP848) upon completion of the Maintenance Period and a minimum dose of 6mg/kg/day or 200mg/day. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.

Subjects who choose not to participate in the open-label study, subjects who are not able to tolerate the lowest LCM dose (100mg/day for the tablet formulation or 3mg/kg/day for the syrup formulation), or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. The doses to be used during the Taper Period and the duration of the Taper Period will depend on the dose maintained during the Maintenance Period. For subjects taking the LCM syrup, weekly decrements of 3mg/kg/day are recommended during the Taper Period. For subjects taking the LCM tablets, a weekly decrement of 200mg/day per week during the Taper Period is recommended.

Table 7-2 and Table 7-3 display the recommended LCM dose reductions during the Taper Period for the LCM syrup and tablet formulations, respectively.

Table 7-2 Recommended LCM dose taper for oral solution (syrup) formulation

Maximum LCM dose maintained	Taper schedule			
	Week 17	Week 18	Week 19	Week 20
12mg/kg/day	9mg/kg/day	6mg/kg/day	3mg/kg/day	0
9mg/kg/day	6mg/kg/day	3mg/kg/day	0	-
6mg/kg/day	3mg/kg/day	0	-	-
3mg/kg/day	0	-	-	-

LCM=lacosamide

Table 7-3 Recommended LCM dose taper for tablet formulation

Maximum LCM dose maintained	Taper schedule	
	Week 17	Week 18
400mg/day	200mg/day	0
300mg/day	100mg/day	0
200mg/day	0	-
100mg/day	0	-

LCM=lacosamide

All subjects discontinuing treatment with LCM for any reason should taper off LCM. It is recommended that the dosage be tapered off in weekly decrements of 3mg/kg/day (oral solution) or 200mg/day (tablet). A slow taper 100mg/day over 4 weeks (tablet) 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 exit criteria have been met. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

If subjects discontinue prematurely from the study, an Early Termination Visit will occur where subjects will be instructed to taper their LCM dose as appropriate. These subjects will not be eligible to participate in the open-label study (SP848), unless the medical monitor has approved their transition to SP848.

Has been changed to:

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

At the end of the Baseline Period (completion of Visit 2), subjects who meet the eligibility criteria will commence a 4-week Titration Period.

As described in Section 5.1, subjects will initiate treatment with LCM oral solution at 2mg/kg/day or 3mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day for subjects weighing ≤30kg, or 8mg/kg/day for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control. During the Titration period only, one back-titration step is permitted; once the dose of LCM has been back-titrated, the dose cannot be increased for the duration of the study (see Figure 5-1 and Figure 5-2).

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or 400mg/kg/day), then the highest optimized dose will be maintained until the end of the Titration Period. The Titration Period will last 4 weeks, regardless of the doses administered. Subjects who are not able to tolerate the minimum required dose (at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day [tablets/oral solution] for subjects weighing >50kg) of LCM (even after back-titration) will be withdrawn from the study. Study medication doses will be titrated according to the schedules presented in Table 7-1.

The maximum LCM dose is not to exceed 12mg/kg/day (oral solution) for subjects weighing ≤30kg, 8mg/kg/day (oral solution) for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg.

The planned doses for each week of the Titration Period for subjects taking the LCM oral solution and tablet formulations are displayed in Table 7-1.

Table 7-1 Lacosamide dose titration during the Titration Period

Week	Study Medication Dose		
	Subjects weighing ≤30kg LCM 12mg/kg/day (oral solution)	Subjects weighing >30kg to ≤50kg LCM 8mg/kg/day (oral solution)	Subjects weighing >50kg LCM 400mg/day (tablet)
1	3mg/kg/day	2mg/kg/day	100mg/day
2	6mg/kg/day	4mg/kg/day	200mg/day
3	9mg/kg/day	6mg/kg/day	300mg/day
4	12mg/kg/day	8mg/kg/day	400mg/day

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. **Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period.** Subjects will enter the Maintenance Period at the LCM dose achieved at the end of the Titration Period. No dose modification is permitted during the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study. **Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study.**

Subjects may be eligible for participation in the additional open-label study (SP848) upon completion of the Maintenance Period **and a minimum dose of 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg.** Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.

Subjects who choose not to participate in the open-label study, subjects who are **only** able to tolerate the lowest LCM dose **(100mg/day for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation),** or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. The doses to be used during the Taper Period and the duration of the Taper Period will depend on the dose maintained during the Maintenance Period. For subjects taking the LCM **oral solution,** weekly decrements of **either 2mg/kg/day or** 3mg/kg/day **(based on body weight)** are recommended during the Taper Period. For subjects taking the LCM tablets, a weekly decrement of 200mg/day per week during the Taper Period is recommended.

Table 7-2, Table 7-3 and Table 7-4 display the recommended LCM dose reductions during the Taper Period for the LCM **oral solution** and tablet formulations, respectively.

Table 7-2 Recommended LCM dose taper for oral solution formulation for subjects weighing ≤30kg

Maximum LCM dose maintained	Taper schedule			
	Week 17	Week 18	Week 19	Week 20
12mg/kg/day	9mg/kg/day	6mg/kg/day	3mg/kg/day	0
9mg/kg/day	6mg/kg/day	3mg/kg/day	0	-
6mg/kg/day	3mg/kg/day	0	-	-
3mg/kg/day	0	-	-	-

LCM=lacosamide

Table 7-3 Recommended LCM dose taper for oral solution formulation for subjects weighing >30kg to ≤50kg

Maximum LCM dose maintained	Taper schedule			
	Week 17	Week 18	Week 19	Week 20
8mg/kg/day	**6mg/kg/day**	**4mg/kg/day**	**2mg/kg/day**	**0**
6mg/kg/day	**4mg/kg/day**	**2mg/kg/day**	**0**	**-**
4mg/kg/day	**2mg/kg/day**	**0**	**-**	**-**
2mg/kg/day	**0**	**-**	**-**	**-**

LCM=lacosamide

Table 7-4 Recommended LCM dose taper for tablet formulation for subjects weighing >50kg

Maximum LCM dose maintained	Taper schedule	
	Week 17	Week 18
400mg/day	**200mg/day**	**0**
300mg/day	**100mg/day**	**0**
200mg/day	**0**	**-**
100mg/day	**0**	**-**

LCM=lacosamide

All subjects discontinuing treatment with LCM for any reason should taper off LCM. It is recommended that the dosage be tapered off in weekly decrements of **either 2mg/kg/day or**

3mg/kg/day (based on body weight; oral solution) or 200mg/day (tablet). A **slower** 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 exit criteria have been met. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

If subjects discontinue prematurely from the study, an Early Termination Visit will occur where subjects will be instructed to taper their LCM dose as appropriate. **Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.**

Change #20

Section 7.3 packaging

Lacosamide tablets will be packaged in high-density polyethylene bottles with a child-proof polypropylene screw cap. The oral solution (syrup) will be packaged in amber polyethylene terephthalate bottles with a white, child-proof, polypropylene screw cap.

Has been changed to:

Lacosamide tablets will be packaged in high-density polyethylene bottles with a child-proof polypropylene screw cap. **The oral solution will** be packaged in amber polyethylene terephthalate bottles with a white, child-proof, polypropylene screw cap.

Change #21

Section 7.8.1 Permitted concomitant treatments (medication and therapies)

Benzodiazepines are allowed as 1 of 3 stable concomitant AEDs for treatment of epilepsy. See Section 7.8.3 for use of benzodiazepines as rescue medication.

Section 7.8.2 (Prohibited concomitant treatments (medication and therapies)

The following concomitant medications are prohibited during the study:

- MAO inhibitors
- Narcotic analgesics

All concomitant medications and treatments must be recorded in the appropriate study documents (eCRF and source document) and doses should remain stable during the study.

The use of MAO inhibitors and narcotic analgesics is prohibited throughout the study. Only stable use of amphetamines and sedative antihistamines is allowed during the study. Also, only stable, low doses of anxiolytics or hypnotics (ie, diazepam 5mg/day) are allowed for nonepilepsy indications.

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

Section 7.8.3 Rescue medication

The use of rescue medication (including benzodiazepines as rescue therapy for epilepsy) is allowed if taken at a maximum frequency of 1 day per month, where 1 month is defined as 28 days. Intermittent use of benzodiazepines for any other indication is prohibited during the study. If rescue medication use or the most recent seizure is within 24 hours of assessments, the seizure/rescue medication date relative to assessments should be documented.

Have been changed to:

Section 7.8.1 Permitted and prohibited concomitant treatments (medications and therapies)

Subject must have been maintained on a stable dose regimen of up to 3 marketed AEDs for at least 4 weeks prior to Visit 1 (ie, prior to entry into the Baseline Period).

Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. Vagal nerve stimulation (implanted for at least 6 months and stable for at least 4 weeks before Visit 1) must be kept stable during the Baseline Period and the Maintenance Period.

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

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

Only stable use of amphetamines and sedative antihistamines is allowed during the study. Only stable, low doses of anxiolytics or once-daily hypnotics are allowed for non epilepsy indications.

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 less than 12 months are also excluded. Any subject who has been treated with felbamate for at least 12 months and has not experienced serious toxicity issues is eligible for the study.

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 at least 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).

Oral contraceptive use is allowed if ethinylestradiol dosage is at least 30µg per intake (50µg if associated with carbamazepine or other strong enzyme inducers [eg, phenobarbital, primidone, oxcarbazepine]).

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.

Section 7.8.2 Rescue medication

The 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) during study participation; more frequent use precludes subjects from study participation.

Change #22

Section 8.1.1 Visit 1 (Week -6) Screening Visit

The following assessments have been modified/added:

- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**
- **Epilepsy surgery assessment.**
- **Health care resource use.**

The following assessments have been deleted:

- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.
- Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III Scales) (if applicable). For pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.

Change #23

Section 8.1.3 Visit 2 (Week 0)

The following assessments have been modified/added:

- **Review inclusion/exclusion criteria.**
- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**
- **Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.**

- **Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III Scales) (if applicable). For pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.**
- **BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (version consistent with age at the visit).**
- **PedsQL for subjects ≥1 month to ≤18 years of age (version consistent with age at the visit).**
- **Health care resource use.**
- Dispense LCM. Subjects should take the first dose of LCM **based on body weight** in the clinic. The starting dose for subjects taking the **oral solution formulation** will be **either 2mg/kg/day or** 3mg/kg/day, and the starting dose for subjects taking the tablet formulation will be 100mg/day.

Change #24

Section 8.2.1 Visit 3 (Week 1)

The following assessments have been modified/added:

- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**
- **Body weight assessment.**
- **Health care resource use.**
- Dispense LCM. The subject's **LCM** dose can be titrated **based on body weight to either 4mg/kg/day or** 6mg/kg/day **(oral solution)** or 200mg/day (tablets), if clinically appropriate.

Change #25

Section 8.2.2 Visit 4 (Week 2)

The subject's dose can be titrated to LCM 9mg/kg/day (syrup) or 300mg/day (tablets), if clinically appropriate.

Has been changed to:

The subject's **LCM** dose can be titrated **based on body weight to either 6mg/kg/day or** 9mg/kg/day **(oral solution)** or 300mg/day (tablets), if clinically appropriate.

Change #26

Section 8.2.3 Visit 5 (Week 3)

The subject's dose can be titrated to LCM 12mg/kg/day (syrup) or 400mg/day (tablets), if clinically appropriate.

Has been changed to:

The subject's **LCM** dose can be titrated **based on body weight to either 8mg/kg/day or** 12mg/kg/day **(oral solution)** or 400mg/day (tablets), if clinically appropriate.

Change #27

Section 8.2.4 Visit 6 (Week 4)

The following assessments have been modified/added:

- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**
- **Body weight assessment.**
- **Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.**
- **Health care resource use.**

Change #28

Section 8.3.1 Telephone contacts (Weeks 6, 10 and 14)

The following text has been added:

Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period.

Change #29

Section 8.3.2 Visit 7 (Week 8)

The following assessments have been modified/added:

- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**

- **Body weight assessment.**
- **Health care resource use.**

Change #30

Section 8.3.4 Visit 9 (Week 16)/Early Termination Visit

The following assessments have been modified/added:

- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**
- **Urine sample for urinalysis (if applicable).**
- **BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (version consistent with age at Visit 2).**
- **PedsQL for subjects ≥1 month to ≤18 years of age (version consistent with age at Visit 2).**
- Dispense subject diary **(for subjects entering Taper Period and not SP848).**
- **Health care resource use.**
- Dispense LCM **(for subjects entering Taper Period and not SP848).**

Subjects may be eligible for participation in the open-label study (SP848) if they have been maintained on a dose of at least 6mg/kg/day (syrup) or 200mg/day (tablets) LCM in the Maintenance Period. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966.

Subjects who choose not to participate in the open-label study, subjects who are not able to tolerate the lowest LCM dose (100mg/day for the tablet formulation or 3mg/kg/day for the syrup formulation), or subjects discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Has been changed to:

Subjects may be eligible for participation in the open-label study (SP848) if they have been maintained on a dose of at least 6mg/kg/day **(oral solution) for subjects weighing ≤30kg, 4mg/kg/day (oral solution) for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg** in the Maintenance Period. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966.

Subjects who choose not to participate in the open-label study, subjects who are **only** able to tolerate the lowest LCM dose (100mg/day **for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation),** or subjects discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Change #31

Section 8.4.1 Taper Period (Weeks 17 to 20)/End of Taper Visit

The following assessments have been modified/added:

- **Changes in VNS settings.**
- Vital signs (BP and pulse**, including orthostatic assessments).**
- **Body weight assessment.**
- **Health care resource use.**

Change #32

Section 8.5 Unscheduled Visit

The following assessments have been modified/added:

- **Changes in VNS settings**
- Vital signs (BP and pulse**, including orthostatic assessments)**
- **Health care resource use**

The following text has been added:

In addition to the required assessments listed above, further assessments can be completed as needed and may include ECG, laboratory tests, physical examination, **neurological examination,** etc.

Change #33

Section 9 ASSESSMENT OF EFFICACY

The following sections have been added:

Section 9.3 Pediatric Quality of Life Inventory

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001; Varni et al, 2011). The PedsQL will be administered at Visit 2 and at Visit 9/Early Termination. For the Visit 9/Early Termination assessment, subjects will complete the version consistent with their age at Visit 2.

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects ≥1 month to ≤12 months; ≥13 months to ≤24 months; >2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to ≤18 years of age. Self-report is measured for pediatric subjects ≥5 years to ≤18 years of age, and parent

proxy report of child health-related quality of life (HRQoL) is measured for pediatric subjects ≥1 month to ≤18 years of age.

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

Section 9.4 Health care resource use

For health care resource use parameters, the following will be evaluated: concomitant AEDs, medical procedures, health care provider consultations not related to study, hospitalizations not related to study. Health care resource use parameters will be collected according to the tabular schedule of study procedures, Section 5.2.

Change #34

Section 11.3 Adverse events of special interest

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

Has been changed to:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree, Type I and II, and third degree), and marked bradycardia **for subject's age**

Change #35

Section 11.7.4 Vital signs, body weight and height

Noninvasive BP (systolic and diastolic) and pulse will be measured at clinic visits in a sitting position after at least 3 minutes at rest, according to the tabular schedule of study procedures in Section 5.2. Body weight will be determined without shoes and wearing light clothing, and height will be measured without shoes. Body weight and height will be assessed according to the tabular schedule of study procedures in Section 5.2.

Has been changed to:

Noninvasive BP (systolic and diastolic) **and pulse rate** will be measured at clinic visits **after at least 3 minutes at rest in a supine position,** according to the tabular schedule of study procedures **(Section 5.2). Assessment of orthostatic changes (only in ambulatory subjects) 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 at approximately 1 minute**

and 3 minutes after standing up, as feasible. Body weight will be determined without shoes and wearing light clothing, and height will be measured without shoes. Body weight and height will be assessed according to the tabular schedule of study procedures in Section 5.2.

Change #36

Section 11.7.8 Achenbach CBCL

The same scale will be completed at Visit 1, Visit 9 (or the Early Termination Visit) and again by the same parent(s) or legal representative(s) in the open-label study, SP848 (if applicable). The completion of the Achenbach CBCL will require approximately 45 minutes.

Has been changed to:

The same scale will be completed at Visit **2, Visit 6, and** Visit 9 (or the Early Termination Visit) and again by the same parent(s) or legal representative(s) in the open-label study, SP848 (if applicable). The completion of the Achenbach CBCL will require approximately 45 minutes.

Change #37

Section 11.7.9 Bayley Scales of Infant and Toddler Development, Third Edition

The same scale will be completed at Visit 1 and again in the open-label study, SP848 (if applicable).

Has been changed to:

The same scale will be completed at Visit **2** and again in the open-label study, SP848 (if applicable).

Change #38

The following section has been added:

Section 11.7.10 Behavior Rating Inventory of Executive Function

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P/BRIEF will be administered at Visit 2 and at Visit 9/Early Termination. For the Visit 9/Early Termination assessment, subjects will complete the version consistent with their age at Visit 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.

Change #39

Section 11.7.11 Assessment of suicidality

The following text has been added:

The "Since Last Visit" version of the C-SSRS will be used, with the following exceptions:

- **The "Baseline/Screening" version of the C-SSRS should be completed at Visit 1.**
- **If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.**

Change #40

Section 13.3.3 Other safety analyses

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, and assessments of Tanner stage (if applicable), and Achenbach CBCL.

Has been changed to:

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.**

Change #41

Section 13.4.1 Preliminary efficacy analyses

Descriptive statistics to summarize the percent change in seizure days per 28 days from Baseline Period to the Maintenance Period will be presented for any generalized seizures reported and for each generalized seizure type.

Descriptive summaries will also be presented for the Clinical and Caregiver's Global Impression of Change.

Has been changed to:

Descriptive statistics to summarize the **absolute and** percent change in seizure days per 28 days from Baseline Period to the Maintenance Period will be presented for any generalized seizures reported and for each generalized seizure type.

Descriptive summaries will also be presented for the Clinical and Caregiver's Global Impression of Change, **health care resource use, and the PedsQL.**

Change #42

Section 13.6 Handling of drop outs or missing data

- Subjects discontinued prematurely during the Titration Period: estimates will be calculated using all available data in the Titration Period and carried forward for the Maintenance

Has been changed to:

- Subjects discontinued prematurely during the Titration Period: estimates will be calculated using all available data in the Titration Period and carried forward for the Maintenance **Period.**

Change #43

Section 16 References

The following references have been added:

Varni JW, Limbers CA, Neighbors K, Schulz K, Lieu JE, Heffer RW, et al. The PedsQL™ Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Qual Life Res. 2011;20:45-55.

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

17.3 Protocol Amendment 2

Rationale for the amendment

This nonsubstantial Amendment has been issued in order to correct a typographical error in the protocol. An LCM dose of 400mg/kg/day was stated in the protocol, but the correct dose is 400mg/day.

In addition, a requirement to practice 2 combined methods of contraception was added to the protocol (for consistency with SP0969), and wording pertaining to suicide attempts and suicidal ideation captured by the C-SSRS was updated, in order to ensure the protocol is consistent with this global change for all UCB protocols. Furthermore, more detail was added as guidance to the investigator regarding the proper storage of the IMP (LCM) at the site.

Modifications and changes

Specific changes

Change #1

Section 5.1 Study description

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or 400mg/kg/day), then the highest optimized dose will be maintained until the end of the Titration Period.

Has been changed to:

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or **400mg/day**), then the highest optimized dose will be maintained until the end of the Titration Period.

Change #2

Section 6.2 Exclusion criteria

Exclusion criterion number 8

Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening.

Has been changed to:

Exclusion criterion number 8

Subject 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.

Exclusion criterion number 21

Subject is a female of childbearing potential or the subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study.

- Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone, oxcarbazepine]) which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.
- The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit (Visit 1).

Has been changed to:

Exclusion criterion number 21

Subject is a female **who is pregnant or nursing, and/or a female of childbearing potential (or who achieves menarche during the study) who does not practice 2 combined methods of contraception, unless sexually abstinent, for the duration of the study. Male subject who does not agree to practice 2 combined methods of contraception (eg, condom, spermicide), unless sexually abstinent, for the duration of the study.**

- Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone, oxcarbazepine]), which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.
- The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit (Visit 1).

Change #3

Section 6.3 Withdrawal criteria

Withdrawal criterion number 12

Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Has been changed to:

Withdrawal criterion number 12

Subject has **actual** suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Change #4

Section 7.2 Treatments(s) to be administered

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or 400mg/kg/day), then the highest optimized dose will be maintained until the end of the Titration Period.

Has been changed to:

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or **400mg/day**), then the highest optimized dose will be maintained until the end of the Titration Period.

Change #5

Section 7.5 Handling and storage requirements

Lacosamide is to be stored according to the instructions on the label.

Has been changed to:

Lacosamide is to be stored according to the instructions on the label. **Lacosamide is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be frozen.**

17.4 Protocol Amendment 3

Rationale for the amendment

The present amendment has been issued following additional feedback from the USA FDA on both SP0969 and SP0966. Where applicable, the recommendations made by the FDA have been incorporated into the current protocol. In addition, updates were made for consistency with other LCM protocols. The following major changes were made:

- The titration and taper schedules were changed to include different weight categories, a 600mg/day LCM dose, and an extended (slower) titration schedule.
- The schedule of assessments was modified to include the changes to the titration schedule, additional visits, and changes to the assessments at each visit.
- The schematic diagrams were updated to reflect the additional changes to the titration and taper schedules.
- Inclusion criteria were modified to allow inclusion of subjects with West syndrome.
- Measurements of head circumference were included.
- The language regarding unscheduled visits was updated to make it clear that investigators can perform additional procedures based on their judgment and medical need.
- The age allowed for initial enrollment was reduced from 4 to 2 years.
- The duration of the safety follow-up was made consistent with other LCM studies (SP0969).
- The definition of end of study for the subjects has been clarified to account for subjects who enter and do not enter the open-label study.
- Additional language was added describing the procedures if the study is completed and the taper is not required at the end of the study.
- The language regarding study medication storage has been updated according to the clinical label.
- The language regarding some of the scales used in this study has been updated for clarification.
- The number of sites and countries in the study were increased.
- Administrative changes were made; the Clinical Project Manager details were updated-.
- Typographical changes were made to improve clarity of wording and to reflect the contents of other LCM studies (SP0969).

Modifications and changes

Global changes

The following key changes were made throughout the protocol:

- Dosing was changed: SP0966 will explore doses of LCM at 4 to 12mg/kg/day in children <50kg and LCM 200 to 600mg/day for subjects weighing ≥50kg.
- Flexible titration was introduced to allow back-titration if subjects can not tolerate higher doses of LCM.
- The taper schedule was modified.
- Numbers for Visit and Week were updated as needed.
- Text was changed throughout the protocol to match other LCM studies (SP0969) and to reflect changes to the schedule of assessments and visits.

Specific changes

Change #1

SPONSOR DECLARATION

Clinical Project Manager

[redacted], RN, MSN

Has been changed to:

Clinical Project Manager

[redacted], **MD**

Change #2

STUDY CONTACT INFORMATION

Clinical Project Manager

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

Has been changed to:

Clinical Project Manager

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

Change #3

LIST OF ABBREVIATIONS

The following abbreviations were added to the protocol:

EI-AED	**enzyme inducing antiepileptic drugs**
QTc	**corrected QT interval**

The following abbreviation was deleted from the protocol:

CPM	**Clinical Project Manager**

Change #4

Section 1 SUMMARY, paragraphs 3, 4 and 5

Approximately 50 subjects will be enrolled in this study across approximately 40 sites in Europe, USA, and other regions as deemed necessary.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured through daily seizure diaries. At the end of the Baseline Period (completion of Visit 2), subjects will commence a 4-week Titration Period, where subjects will initiate treatment with LCM. Subjects weighing ≤30kg will begin treatment on LCM oral solution (syrup) 3mg/kg/day, subjects weighing >30kg to ≤50kg will begin treatment on LCM oral solution 2mg/kg/day, and subjects weighing >50kg will begin treatment on LCM tablets 100mg/day (subjects weighing >50kg who are unable or unwilling to swallow tablets can also be dispensed LCM oral solution). The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day for subjects weighing ≤30kg, or 8mg/kg/day for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg. At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects must titrate to

at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period.

The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in an additional open-label study (SP848) upon completion of the Maintenance Period and a minimum dose of 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the additional open-label study, subjects who are only able to tolerate the lowest LCM dose (100mg/day for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation), or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Have been changed to:

Approximately 50 subjects will be enrolled in this study across approximately **50 sites in Europe, Russia, and North America**, and other regions as deemed necessary.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured through daily seizure diaries. At the end of the Baseline Period, subjects will commence a **6-week** Titration Period **at Visit 2**, where subjects will initiate treatment with LCM **(LCM dosing flexibility allowed based on tolerability). Subjects weighing <50kg will begin treatment on LCM oral solution 2mg/kg/day, and subjects weighing ≥50kg will begin treatment on LCM tablets 100mg/day** (subjects weighing **≥50kg** who are unable or unwilling to swallow tablets can be dispensed LCM oral solution **instead**). The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed **12mg/kg/day (oral solution) for subjects weighing <50kg or 600mg/day (tablets/oral solution) for subjects weighing ≥50kg.** At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects must titrate to **at least 4mg/kg/day for subjects weighing <50kg or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg** in order to enter the Maintenance Period. **The LCM dose will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study. Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study.**

The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in an additional open-label study (SP848) **if they have completed** the Maintenance Period and **are taking** a minimum dose of **4mg/kg/day for subjects weighing <50kg or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg**. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the additional open-label study or subjects who discontinue LCM due to other reasons will enter

a **2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. 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.**

Change #5

Section 2 INTRODUCTION, paragraphs 1, 4, 5, 8, 11, and 13

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in pediatric subjects 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, >25% of pediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults. Lacosamide's mode of action is proposed to be mediated by a selective enhancement of slow inactivation of voltage-gated sodium channels which may explain the immediate analgesic and anticonvulsant effects of LCM (Errington et al, 2008).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to 400mg bid (800mg/day) were evaluated in approximately 856 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2200 adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

UCB has completed a Phase 2, open-label safety study (SP0961) of adjunctive LCM treatment for primary generalized tonic-clonic seizures in subjects ≥ 16 years of age with idiopathic generalized epilepsy. The results of SP0961 showed reductions in primary generalized tonic-clonic seizure frequency and myoclonic seizure days, with a small

reduction in absence seizure days. A minority of subjects (~10%) showed an increase in absence seizures (reported as TEAEs) that, in this uncontrolled study, cannot be distinguished between the drug versus the natural course of the disease. The AE profile was similar to that of adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized (Type II) seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥4 years of age will be included in this study. Once the LCM dose range has been defined in subjects <4 years of age, enrollment of subjects in the younger cohort will begin.

Have been changed to:

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 new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

Among the newer AEDs, only **6** (gabapentin, lamotrigine, oxcarbazepine, topiramate, levetiracetam, **and perampanel**) have successfully demonstrated efficacy as adjunctive therapy in pediatric subjects with difficult to treat partial-onset seizures (Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999; **Glauser et al, 2000; Glauser et al, 2006; Rheims and Ryvlin, 2013**). Despite the availability of new AEDs, **more than** 25% of pediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a twice daily (bid) dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults. Lacosamide's mode of action is proposed to be mediated by a selective enhancement of slow inactivation of voltage-gated sodium channels which may explain the immediate anticonvulsant effects of LCM (Errington et al, 2008).

In the clinical development program for LCM, safety and tolerability of multiple doses of up to **LCM** 400mg bid (800mg/day) were evaluated in **868** unique **subjects** who received **oral and/or iv** 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 **1427** adult subjects with partial-onset seizures**, as oral monotherapy in 425 adult subjects with partial-onset seizures, as**

adjunctive oral therapy in 49 subjects with primary generalized tonic-clonic seizures, and as oral monotherapy in **2435** adult subjects in other indications (eg, neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (199 patients) who were receiving adjunctive LCM tablets.

UCB has completed a Phase 2, open-label safety study (SP0961) of adjunctive LCM treatment for primary generalized tonic-clonic seizures in **49** subjects ≥ 16 years of age with idiopathic generalized epilepsy. The results of SP0961 showed reductions in primary generalized tonic-clonic seizure frequency and myoclonic seizure days, with a small reduction in absence seizure days. A minority of subjects (~10%) showed an increase in absence seizures (reported as TEAEs) that, in this uncontrolled study, cannot be distinguished between the drug versus the natural course of the disease. The AE profile was similar to that of adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized (Type II) seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥**2** years of age will be included in this study. Once the LCM dose range has been defined **for** subjects <**2** years of age **based on SP847**, enrollment of subjects in **this age group** will begin **in SP0966**.

Change #6

Section 3 STUDY OBJECTIVES

The following objective has been added:

- **An additional objective is to evaluate the PK of LCM in subjects ≥1 month to <18 years of age.**

Change #7

Section 4.1.1 Primary safety variables

- Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 (Baseline Period) to Visit 6 (start of Maintenance Period)

Has been changed to:

- Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 to Visit 6

Change #8

Section 4.1.2 Secondary safety variables

- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 (Baseline Period) to Visit 6 (start of Maintenance Period)

Has been changed to:

- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 6

Change #9

Section 4.2 Preliminary efficacy variables

- Changes in count of generalized spike-wave discharges on 24-hour ambulatory EEG from Visit 2 (Baseline Period) to Visit 9 (end of Maintenance Period) or at Early Termination
- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 (Baseline Period) to Visit 9 (end of Maintenance Period) or at Early Termination

Has been changed to:

- Changes in count of generalized spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 9 or at Early Termination
- Changes in count of 3Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 9 or at Early Termination

Change #10

Section 4.3 Pharmacokinetic variables

- Plasma concentrations of LCM and concomitant AEDs

Has been changed to:

Section 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**

Change #11

Section 5.1 Study description

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥4 years of age will be included in this study. Once the LCM dose range has been defined in subjects <4 years of age, enrollment of subjects in the younger cohort will begin.

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are also not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.

The study treatment is LCM in either the oral solution formulation or tablet formulation. The formulation of LCM to be administered is based on the weight of the subject. Only subjects weighing >50kg who are able and willing to swallow tablets may be dispensed LCM tablets.

Subjects will not be randomized, but all subjects who sign the informed consent form (ICF) at Visit 1 will be assigned a unique identification number.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured. Subjects/caregivers will maintain a diary to record daily seizure activity from Visit 1 until the end of the study. The subject diary will capture seizure type and seizure frequency information. If all inclusion criteria are met and no exclusion criteria are met, the subject will begin a 4-week Titration Period starting at Visit 2. Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 to begin 24-hour ambulatory EEG recordings. Subjects will initiate treatment with LCM oral solution at 2mg/kg/day or 3mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day for subjects weighing ≤30kg, or 8mg/kg/day for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control. During the Titration period only, one back-titration step is permitted; once the dose of LCM has been back-titrated, the dose cannot be increased for the duration of the study (see Figure 5-1 and Figure 5-2).

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or 400mg/day), then the highest optimized dose will be maintained until the end of the Titration Period. The Titration Period will last 4 weeks, regardless of the doses administered.

Subjects who are not able to tolerate the minimum required dose (at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day [tablets/oral solution] for subjects weighting >50kg) of LCM (even after back-titration) will be withdrawn from the study. Study medication doses will be titrated according to the schedules presented in Table 7-1.

The maximum LCM dose is not to exceed 12mg/kg/day (oral solution) for subjects weighing ≤30kg, 8mg/kg/day (oral solution) for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg.

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period. Subjects will return to the clinic (on the morning of the day prior to the scheduled visit) at Visit 6 and Visit 9 or Early Termination for 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in the additional open-label study (SP848) upon completion of the Maintenance Period and a minimum dose of 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the open-label study, subjects who are only able to tolerate the lowest LCM dose (100mg/day for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation), or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. Dosing schedules for the Taper Period are provided in Table 7-2, Table 7-3, and Table 7-4.

A Data Monitoring Committee (DMC) will oversee the safety of the study.

Has been changed to:

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥**2** years of age will be included in this study. Once the LCM dose range has been defined **for** subjects <**2** years of age **based on confirmation of supportive PK, safety, and tolerability dosing data from SP847**, enrollment of subjects in **this age group** will begin **in SP0966**.

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of

idiopathic generalized epilepsy are also not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.

The study treatment is LCM in either the oral solution formulation or tablet formulation. The formulation of LCM to be administered is based on the weight of the subject. Only subjects weighing ≥50kg who are able and willing to swallow tablets may be dispensed LCM tablets **(subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead).**

Subjects will not be randomized, but all subjects who sign the informed consent form (ICF) at Visit 1 will be assigned a unique identification number.

The study will begin with subject screening at Visit 1 and will consist of a 6-week prospective Baseline Period where seizure frequency will be captured. Subjects/caregivers will maintain a diary to record daily seizure activity from Visit 1 until the end of the study. The subject diary will capture seizure type and seizure frequency information. If all inclusion criteria are met and no exclusion **criterion is met**, the subject will begin a **6-week** Titration Period **(LCM dosing flexibility allowed based on tolerability)** starting at Visit 2. Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 to begin 24-hour ambulatory EEG recordings. Subjects will initiate treatment with LCM oral solution at **2mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day (oral solution) for subjects weighing <50kg, or 600mg/day (tablets/oral solution) in subjects weighing ≥50kg.** Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control **(see Figure 5-1 and Figure 5-2).**

Lacosamide doses will be titrated according to the schedules presented **in Table 7-1 and Table 7-2.**

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. **The LCM dose will remain stable throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study. Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study.**

Subjects must titrate to at least **4mg/kg/day for subjects weighing <50kg, or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg** in order to enter the Maintenance Period. Subjects will return to the clinic (on the morning of the day prior to the scheduled visit) at Visit 6 and Visit 9 or Early Termination for 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. The end of the Maintenance Period will be Visit 9, or, if subjects withdraw early, the Early Termination Visit. Subjects may be eligible for participation in the additional open-label study (SP848) **if they have completed** the Maintenance Period and **are** taking a minimum dose of **4mg/kg/day for subjects weighing <50kg, and 200mg/day (tablets/oral solution) in subjects weighing ≥50kg**. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who choose not to participate in the open-label study or subjects who **discontinue** due to other reasons will enter **a 2- to 4-week Taper Period followed by a Safety**

Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. Dosing schedules for the Taper Period are provided in **Table 7-4 and 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.**

A Data Monitoring Committee (DMC) will oversee the safety of the study.

Change #12

Section 5.1.1 Study duration per subject

The duration of treatment for an individual subject may be up to approximately 16 weeks excluding the Taper Period (due to the maximum allowed visit windows).

The study will consist of a 6-week prospective Baseline Period, followed by a 4-week Titration Period and a 12-week Maintenance Period. Subjects may be eligible to enter an additional open-label study (SP848) after completion of the Maintenance Period. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label study will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. The total study duration for a subject will be up to a maximum of 27 weeks.

Has been changed to:

The duration of treatment for an individual subject may be up to approximately **18** weeks excluding the Taper Period.

The study will consist of a 6-week prospective Baseline Period, followed by a **6-week** Titration Period and a 12-week Maintenance Period. Subjects may be eligible to enter an additional open-label study (SP848) after completion of the Maintenance Period. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label study will enter **a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.** The total study duration for a subject will be up to a maximum of **32** weeks.

Change #13

Section 5.1.2 Planned number of subjects and site(s)

It is planned to enroll approximately 50 subjects across 2 age cohorts. The first cohort will consist of approximately 40 subjects between 4 years and <18 years of age. The second cohort will consist of at least 10 subjects between 1 month and <4 years of age.

Has been changed to:

Approximately 50 subjects **will be enrolled. It is planned to enroll** approximately 40 subjects between 4 years and <18 years of age **and** at least 10 subjects between 1 month and <4 years of age.

Change #14

Section 5.1.3 Anticipated regions and countries

This study will be conducted at approximately 40 sites in Europe, USA, and other regions as deemed necessary.

Has been changed to:

This study will be conducted at approximately **50** sites in Europe**, Russia, and North America**, and other regions as deemed necessary.

of study assessments

e of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study nd Unscheduled Visit)

			Treatment (16 weeks)										End of Study Period		Unsched Visit[a]
aseline Period (6 weeks)			Titration Period (4 weeks)				Maintenance Period (12 weeks)						Taper Period[b]	Safety Follow -up	
1	TC1	V2	V3	V4	V5	V6	TC2	V7	TC3	V8	TC4	V9/ET[c]	End of Taper Visit	TC5	At any time
5	-3	0	1	2	3	4	6	8	10	12	14	16	17-20	21	
	X	X													
		X				X						X			
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		X										X			
			X	X	X	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, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)			Treatment (16 weeks)										End of Study Period		Unsched Visit[a]
				Titration Period (4 weeks)				Maintenance Period (12 weeks)						Taper Period[b]	Safety Follow -up	
Visit	**V1**	**TC1**	**V2**	**V3**	**V4**	**V5**	**V6**	**TC2**	**V7**	**TC3**	**V8**	**TC4**	**V9/ET[c]**	**End of Taper Visit**	**TC5**	**At any time**
Week in study	**-6**	**-3**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17-20**	**21**	
Body weight and height[f]	X		X	X	X	X	X		X		X		X	X		X
Neurological examination (complete)	X		X										X			
Neurological examination (brief)				X	X	X	X		X		X			X		
ECG (12-lead)[g]	X		X	X	X	X	X		X		X		X	X		
Clinical chemistry/hematology	X		X		X		X		X		X		X	X[h]		
Endocrinology blood sample	X												X	X[h]		
Urinalysis[i]	X		X		X		X		X				X	X[j]		
Pregnancy test[k]	X		X				X		X		X		X	X		
Tanner Stage[l]	X												X			
Concomitant AED plasma concentration[m]			X				X						X			
LCM plasma concentration[m]			X				X						X			

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)			Treatment (16 weeks)										End of Study Period		Unsched Visit[a]
				Titration Period (4 weeks)				Maintenance Period (12 weeks)						Taper Period[b]	Safety Follow -up	
Visit	**V1**	**TC1**	**V2**	**V3**	**V4**	**V5**	**V6**	**TC2**	**V7**	**TC3**	**V8**	**TC4**	**V9/ET[c]**	**End of Taper Visit**	**TC5**	**At any time**
Week in study	**-6**	**-3**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**17-20**	**21**	
C-SSRS[n]	X		X	X	X	X	X		X		X		X	X		X[o]
Clinical Global Impression of Change													X			
Caregiver's Global Impression of Change													X			
Achenbach CBCL[p]			X				X						X			
Bayley-III[q]			X													
BRIEF-P/BRIEF			X										X			
PedsQL			X										X			
Contact IXRS	X		X	X	X	X	X		X		X		X			X
Dispense study medication			X[r]	X	X	X	X		X		X		X[s]			
Study medication return				X	X	X	X		X		X		X	X		
Dispense subject diary	X		X	X	X	X	X		X		X		X[s]			
Subject diary return/review		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

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)			Treatment (16 weeks)										End of Study Period		Unsched Visit[a]
				Titration Period (4 weeks)				Maintenance Period (12 weeks)						Taper Period[b]	Safety Follow -up	
Visit	V1	TC1	V2	V3	V4	V5	V6	TC2	V7	TC3	V8	TC4	V9/ET[c]	End of Taper Visit	TC5	At any time
Week in study	-6	-3	0	1	2	3	4	6	8	10	12	14	16	17-20	21	
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of epilepsy surgery	X															
Changes in VNS settings	X		X	X	X	X	X		X		X		X	X		X
Health care resource use	X		X	X	X	X	X		X		X		X	X		X

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

Note: For all visits a time window of ±2 days relative to Visit 2 (Baseline Period) is applicable. The schedule above displays the maximum possible study duration for a subject.

[a] Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments indicated in the schedule above, further assessments can be completed as needed and may include ECG, laboratory tests, physical examination, neurological examination, etc.

[b] The recommended Taper Period duration for subjects taking the tablet formulation is 2 weeks, but a slower taper over 4 weeks may be permitted if medically necessary. The duration of the Taper Period for the oral solution formulation is 4 weeks. The End of Taper Visit will occur at the end of the last week of the Taper Period.

[c] At the end of Visit 9 or at ET, all subjects who complete the Maintenance Period and whose daily dose was at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg will be offered the opportunity to enroll in an additional open-label extension study, SP848. Visit 9 or the ET Visit of SP0966 will also serve as Visit 1 for SP848. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label extension study will complete the End of Study procedures that include up to a 4-week

Table 5-1 Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)			Treatment (16 weeks)										End of Study Period		Unsched Visit[a]
				Titration Period (4 weeks)				Maintenance Period (12 weeks)						Taper Period[b]	Safety Follow -up	
Visit	V1	TC1	V2	V3	V4	V5	V6	TC2	V7	TC3	V8	TC4	V9/ET[c]	End of Taper Visit	TC5	At any time
Week in study	-6	-3	0	1	2	3	4	6	8	10	12	14	16	17-20	21	

LCM taper followed by a 1-week Safety Follow-up Period and Final Safety telephone contact.

[d] Subject or caregiver (including parent/legal guardian) will be asked how many seizures the subject has had over the past 4 weeks as a historical baseline.

[e] Ambulatory EEG to begin on the morning prior to the visit eg, the day before Visit 2.

[f] Height will only be recorded at study visits where a complete physical examination is performed. Height is not required at an Unscheduled Visit.

[g] Two interpretable 12-lead ECG recordings will be performed approximately 20 to 30 minutes apart prior to any blood draws and vital sign assessments and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings. Recordings should be performed at least 15 minutes after the removal of scalp electrodes used for the 24-hour ambulatory EEG recordings at Visit 2, Visit 6, and Visit 9 or the ET Visit.

[h] If no abnormality is observed in the laboratory blood samples from the previous visit, this End of Taper assessment does not have to be performed.

[i] For subjects aged 5 to 17 years.

[j] If no abnormality is observed in the 2 previous urinalysis tests, this End of Taper assessment will not need to be performed.

[k] For female subjects of childbearing potential, a serum pregnancy test will be performed at Visit 1, Visit 9 or the ET Visit, and the End of Taper Visit. A urine dipstick pregnancy test will be performed at Visit 2, Visit 6, Visit 7, and Visit 8.

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

[m] Blood samples for analysis of concomitant AED plasma concentrations and LCM will be drawn along with clinical chemistry and hematology samples; predose at Visit 2 and postdose at Visit 6 and Visit 9 or the ET Visit.

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

[o] If the Unscheduled Visit is due to an AE, then the C-SSRS is required.

[p] The Achenbach CBCL: CBCL/1½ -5 for pediatric subjects from 18 months to 5 years 11 months and CBCL/6-18 for pediatric subjects 6 years and older; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). The same scale will be completed again by the same parent(s)/legal representative(s) later in the open-label study, SP848 (if applicable).

[q] Bayley Scales of Infant and Toddler Development®, Third Edition for pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.

[r] At the end of Visit 2, subjects should take the first dose of study medication in the clinic.

[s] For subjects entering Taper Period and not SP848.

Has been changed to:

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC1	V2	TC2	V3	TC3	V4[c]	V5[c]	End of Titrat V6	TC4	V7	TC5	V8	TC6	V9/ ET[d]	TC7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	
Informed consent	X																			
Inclusion/exclusion criteria	X	X	X																	
Medical history	X																			
Seizure history[h]	X																			
EEG (24h monitoring)[i]			X						X						X					
Concomitant medications	X	X	X	**X**	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	X	**X**	X	X
Physical examination (complete)	X		X												X			**X**		
Physical examination (brief)									X				X				X			

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	**V1**	**TC1**	**V2**	**TC2**	**V3**	**TC3**	**V4[c]**	**V5[c]**	**End of Titrat V6**	**TC4**	**V7**	**TC5**	**V8**	**TC6**	**V9/ ET[d]**	**TC7[e]**	**End of Taper Visit[f]**	**Safety FU Visit[g]**	**Safety FU TC[g]**	**At any time**
Week in study	**-6**	**-3**	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**	**20-22**	**22-24**	**24-26**	
Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**)	X		X		X		X	X	X		X		X		X		X	**X**		X
Body weight and height[j]	X		X		X		X	X	X		X		X		X		X	**X**		X
Head circumference	**X**														**X**					
Neurological examination (complete)	X		X												X			**X**		
Neurological examination (brief)									X				X				X			
ECG (12-lead)[k]	X		X		X		X	X	X		X		X		X		X	**X[l]**		
Clinical chemistry/ hematology	X		X						X		X		X[l]		X		X	**X[l]**		
Endocrinology	X														X		X	**X[l]**		
Urinalysis[m]	X		X						X						X		X	**X[l]**		

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC1	V2	TC2	V3	TC3	V4[c]	V5[c]	End of Titrat V6	TC4	V7	TC5	V8	TC6	V9/ ET[d]	TC7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	
Pregnancy test[n]	X		X		X		X	X	X		X		X		X		X	**X**		
Tanner Stage[o]	X														X					
Concomitant AED plasma concentration[p]			X												X					
LCM plasma concentration[p]			X												X					
C-SSRS[q]	X		X		X		X	X	X		X		X		X		X	**X**		X[r]
Clinical Global Impression of Change															X					
Caregiver's Global Impression of Change															X					
Achenbach CBCL[s]			X						X						X					
Bayley-III[t]			X																	
BRIEF-P/BRIEF[u]			X												X					
PedsQL[v]			X												X					
Contact IXRS	X		X		X		X	X	X		X		X		X		X			

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	**V1**	**TC1**	**V2**	**TC2**	**V3**	**TC3**	**V4[c]**	**V5[c]**	**End of Titrat V6**	**TC4**	**V7**	**TC5**	**V8**	**TC6**	**V9/ ET[d]**	**TC7[e]**	**End of Taper Visit[f]**	**Safety FU Visit[g]**	**Safety FU TC[g]**	**At any time**
Week in study	**-6**	**-3**	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**	**20-22**	**22-24**	**24-26**	
Dispense **LCM**			X[w]		X		X	X	X		X		X		X[x]					
LCM return					X		X	X	X		X		X		X		X			
Dispense subject diary	X		X		X		X	X	X		X		X		X[x]					
Subject diary return/review[y]		X	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	X	X			X
AE reporting	X	X	X	**X**	X	**X**	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X
Assessment of epilepsy surgery	X																			
VNS **assessment**[z]	X		X		X		X	X	X		X		X		X		X	**X**		X
Health care resource use			X		X		X	X	X		X		X		X		X	**X**		

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF-P/BRIEF=Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EEG=electroencephalogram; ET=Early Termination; **FU=Follow-Up;** IXRS= interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; TC=telephone contact; **Titrat=Titration**; V=Visit; VNS=vagus nerve stimulation

Note: For all visits **outside of the Safety Follow-Up Period,** a time window of ±2 days relative to Visit 2 (Titration Period) is applicable. The schedule above displays the maximum possible study duration for a subject.

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC1	V2	TC2	V3	TC3	V4[c]	V5[c]	End of Titrat V6	TC4	V7	TC5	V8	TC6	V9/ ET[d]	TC7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	

[a] Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments indicated in the schedule above, **the investigator can perform further assessments based on his/her clinical judgment and the medical needs of the subject (eg, assessments of** ECG, laboratory tests, physical examination, neurological examination, etc).

[b] The recommended Taper Period duration is **up to a maximum of 4 weeks**, but a slower or faster taper may be permitted if medically necessary. The End of Taper Visit will occur at the end of the last week of the Taper Period.

[c] **Visits 4 and 5 are optional and will only be required if a subject requires further LCM dose adjustment.**

[d] At the end of Visit 9 or at ET, all subjects who complete the Maintenance Period and whose daily dose was at least 4mg/kg/day for subjects weighing <50kg, and 200mg/day (tablets/oral solution) **for** subjects weighing ≥50kg will be offered the opportunity to enroll in an additional open-label extension study, SP848. Visit 9 or the ET Visit of SP0966 will also serve as Visit 1 for SP848. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor. Subjects who do not continue in the open-label extension study will complete the End of Study procedures that include a **2- to 4-week** LCM taper followed by a **30-day Safety Follow-Up 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**.

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

[f] **Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Week 20, Week 21, or Week 22, depending on dose level achieved; see Table 7-4 and Table 7-5). A time window of ±2 days relative to Visit 2 (Titration Period) is applicable. 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**.

[g] **The Safety Follow-Up Visit will occur 2 weeks (±2 days) after the final dose of LCM. The Safety Follow-Up Telephone Contact will occur 30 days (-1/+3 days) after the final dose of LCM**.

[h] Subject or caregiver (including parent/legal **representative**) will be asked how many seizures the subject has had over the past 4 weeks as a historical baseline.

[i] Ambulatory EEG to begin on the morning prior to the visit eg, the day before Visit 2**, Visit 6, and Visit 9**.

[j] Height will only be recorded at study visits where a complete physical examination is performed. Height is not required at an Unscheduled Visit.

[k] Two interpretable 12-lead ECG recordings will be performed approximately 20 to 30 minutes apart prior to any blood draws and vital sign assessments. **The subject should rest in the supine position for approximately 5 minutes before the recordings and during the recordings, if possible.** Recordings should

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC1	V2	TC2	V3	TC3	V4[c]	V5[c]	End of Titrat V6	TC4	V7	TC5	V8	TC6	V9/ ET[d]	TC7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	

be performed at least 15 minutes after the removal of scalp electrodes used for the 24-hour ambulatory EEG recordings at Visit 2, Visit 6, and Visit 9 or the ET Visit.

[l] **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.**

[m] For subjects aged 5 to 17 years.

[n] For female subjects of childbearing potential, a serum pregnancy test will be performed at Visit 1, Visit 9 or the ET Visit, **and the End of Taper Visit. A serum pregnancy test will also 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.** A urine pregnancy test will be performed **at all other visits, as scheduled in Table 5-1**.

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

[p] Blood samples for analysis of concomitant AED plasma concentrations and LCM plasma concentration will be drawn along with clinical chemistry and hematology samples; predose at Visit 2 and postdose at Visit 9 or the ET Visit.

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

[r] If the Unscheduled Visit is due to an AE, then the C-SSRS is required.

[s] The Achenbach CBCL: CBCL/1½-5 for pediatric subjects from 18 months to 5 years 11 months and CBCL/6-18 for pediatric subjects aged 6 years and older; 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 same scale should be completed again by the same parent(s)/legal representative(s) later in the open-label study, SP848 (if applicable). The Achenbach CBCL will be used only in countries where a translated version is available.

[t] Bayley Scales of Infant and Toddler Development®, Third Edition for pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.

[u] **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.**

[v] **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.**

Table 5–1:Schedule of study assessments (Baseline Period, Titration Period, Maintenance Period, End of Study Period and Unscheduled Visit)

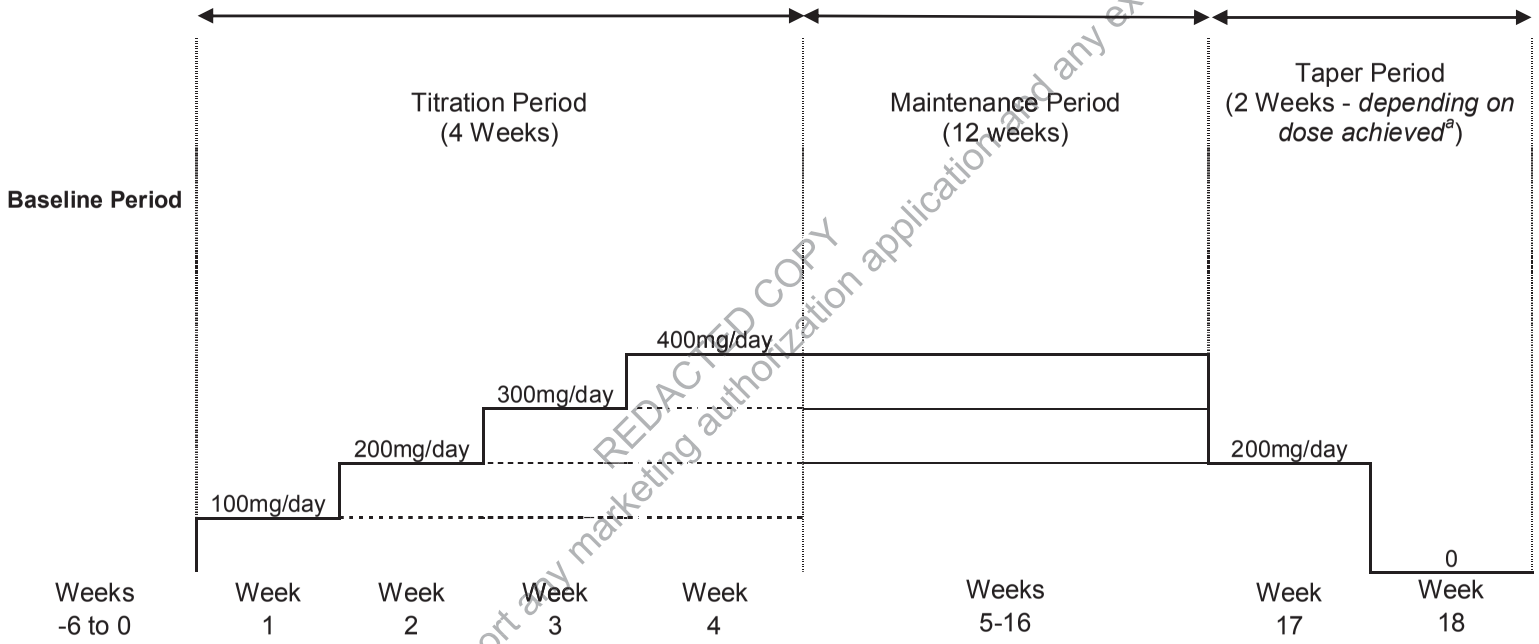
Assessments	Baseline Period (6 weeks)		Treatment (18 weeks)													End of Study Period				Unsched Visit[a]
			Titration Period (6 weeks)							Maintenance Period (12 weeks)						Taper Period (2-4 weeks)[b]		Safety Follow-Up (30 days)		
Visit	V1	TC1	V2	TC2	V3	TC3	V4[c]	V5[c]	End of Titrat V6	TC4	V7	TC5	V8	TC6	V9/ ET[d]	TC7[e]	End of Taper Visit[f]	Safety FU Visit[g]	Safety FU TC[g]	At any time
Week in study	-6	-3	Day 1	1	2	3	4	5	6	8	10	12	14	16	18	19	20-22	22-24	24-26	

[w] At the end of Visit 2, subjects should take the first dose of **LCM** in the clinic.
[x] For subjects entering Taper Period and not entering SP848.
[y] **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.**
[z] **As applicable, VNS assessment will only be performed for subjects with an implanted VNS device at Visit 1.**

Change #16

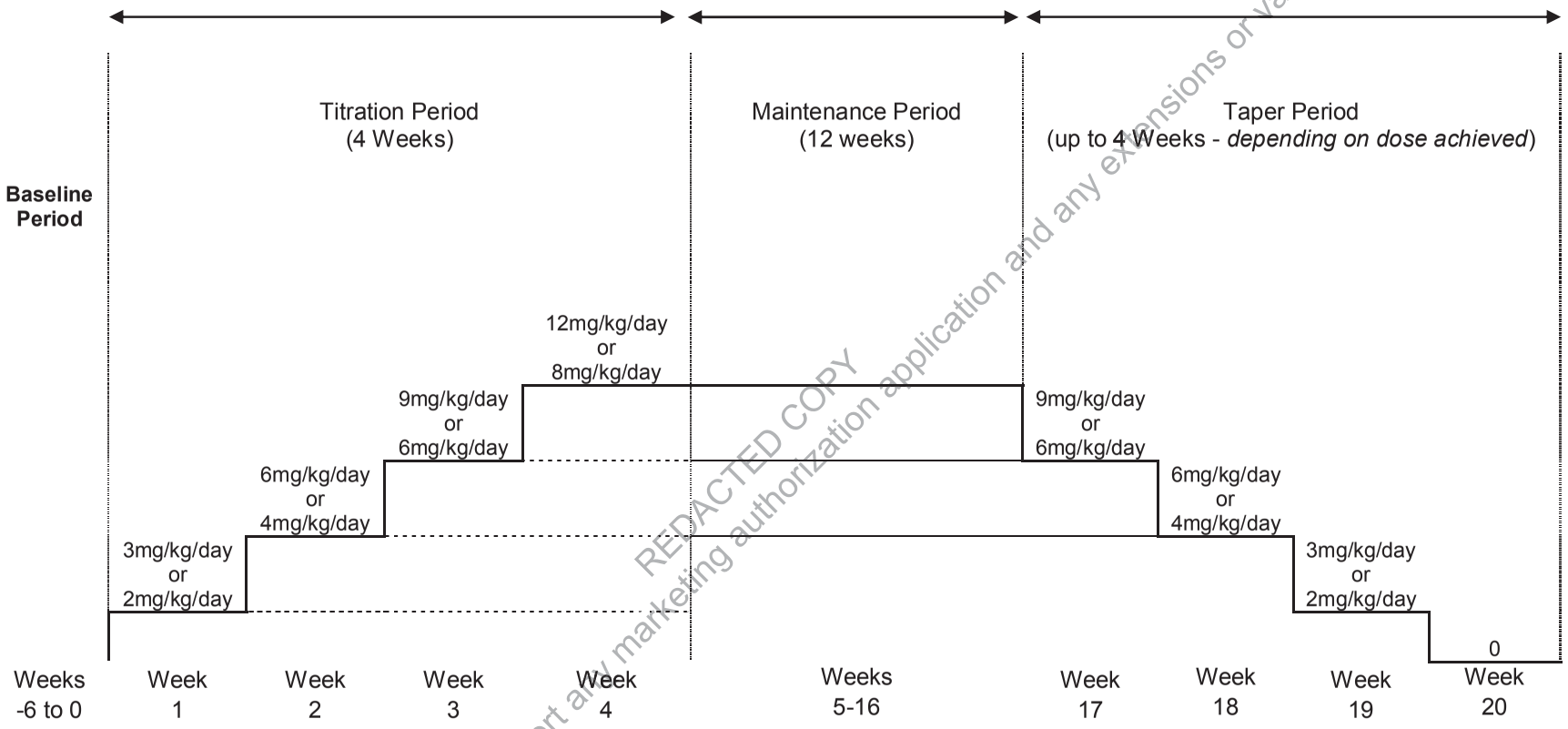
Section 5.3 Schematic diagram

Figure 5-1 Schematic diagram - LCM tablet dosing and taper schedule



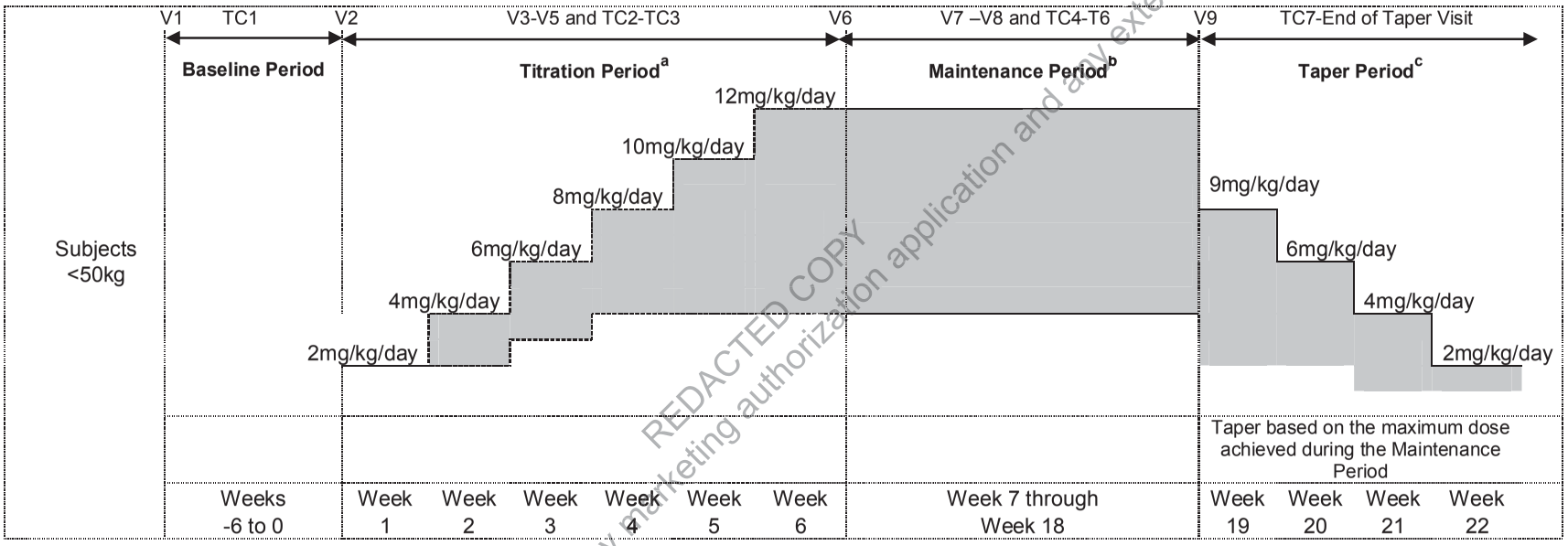
[a] Schematic shows standard 2-week Taper Period. If medically necessary, a slow taper over 4 weeks, with decrements of LCM 100mg/day per week may be permitted.

Figure 5-2 Schematic diagram - LCM oral solution dosing and taper schedule



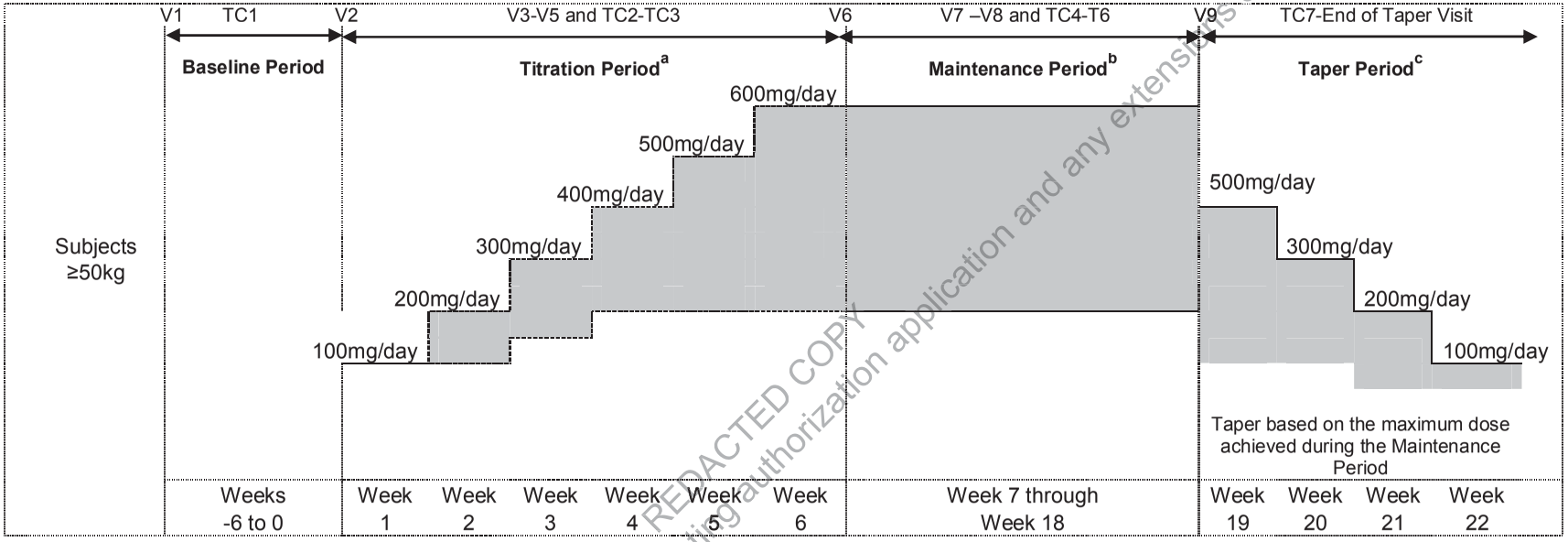
Has been changed to:

Figure 5-1: Schematic diagram - LCM dosing and taper schedule for subjects <50kg receiving oral solution formulation



TC=Telephone Contact; V=Visit
Note: LCM dosing is designated as "mg/kg/day"
[a] During Titration Period dosage may be adjusted up or down based on investigator's clinical judgment.
[b] Dose reached at the end of Titration Period will be taken throughout Maintenance Period. Subjects may be eligible for participation in the additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 4mg/kg/day. Subjects will begin SP848 on the LCM dose they achieved in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.
[c] Subjects with doses <3mg/kg/day do not need to taper. See Table 7-5 for exact taper schedule. Taper is not required for subjects participating in the additional open-label study (SP848). A slower or faster taper is permitted if medically necessary. 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 followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Figure 5-2: Schematic diagram - LCM dosing and taper schedule for subjects ≥50kg receiving oral solution or tablet formulation



TC=Telephone Contact; V=Visit
Note: LCM dosing is designated as "mg/day"
[a] During Titration Period dosage may be adjusted up or down based on investigator's clinical judgment.
[b] Dose reached at the end of Titration Period will be taken throughout Maintenance Period. Subjects may be eligible for participation in the additional open-label study (SP848) if they have completed the Maintenance Period and are taking a minimum dose of 200mg/day (tablets/oral solution). Subjects will begin SP848 on the LCM dose they achieved in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open label study after consultation with the medical monitor.
[c] Subjects with doses <150mg/day do not need to taper. See Table 7-5 for exact taper schedule. Taper is not required for subjects participating in the additional open-label study (SP848). A slower or faster taper is permitted if medically necessary. 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 followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Change #17

Section 5.4 Rationale for study design and selection of dose

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 SP0966 are as follows:

- LCM dosing should aim to achieve LCM plasma concentrations equivalent to the average steady-state LCM plasma concentration reached after a LCM 400mg/day dose administration in adult studies, which is approximately 8µg/mL.
- A weight-based dosing scheme is recommended:
  - Subjects ≤30kg: LCM 12mg/kg/day (oral solution)
  - Subjects >30kg to ≤50kg: LCM 8mg/kg/day (oral solution, up to a maximum of LCM 400mg/day)
  - Subjects weighing >50kg: 400mg/day (tablets/oral solution)

Has been changed to:

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 SP0966 are as follows:

- **Lacosamide** dosing should aim to achieve LCM plasma concentrations equivalent to the average steady-state LCM plasma concentration reached after a LCM **200 to 6**00mg/day dose administration in adult studies.
- A weight-based **flexible** dosing scheme is recommended:
  - **Subjects <50kg: LCM 4-12mg/kg/day (oral solution)**
  - **Subjects ≥50kg: LCM 200 to 600mg/day (tablets/oral solution)**

Change #18

Section 6.1 Inclusion criteria

1. A signed informed consent has been obtained from the parent/guardian and assent has been obtained from the subject (when possible or as required according to local Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).
2. Subject and caregiver (which may be a parent, a legal guardian, or other caregiver) are willing and able to comply with all study requirements including maintaining a daily seizure diary.
3. Subject is male or female, ≥1 month to <18 years of age. (Note, until the LCM dose range has been defined in subjects <4 years of age, only subjects ≥4 years of age will be enrolled.) For preterm infants <1 year old, the corrected gestational age should be used when determining eligibility. The generally accepted definition of corrected gestational

age, which is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age, will be used for this study.

7. Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. Vagal nerve stimulation (implanted for at least 6 months and stable for at least 4 weeks before Visit 1) must be kept stable during the Baseline Period and the Maintenance Period.
8. Body weight at Visit 1 is at least 5kg for infants.
9. Females with childbearing potential must have a negative pregnancy test at Visit 1.

Has been changed to:

1. A signed informed consent has been obtained from the parent/**legal representative** and assent has been obtained from the subject (when possible or as required according to local Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).
2. Subject and caregiver (which may be a parent, a legal **representative**, or other caregiver) are willing and able to comply with all study requirements including maintaining a daily seizure diary.
3. Subject is male or female, ≥1 month to <18 years of age. (Note, until the LCM dose range has been defined in subjects <**2 years** of age **based on SP847**, only subjects ≥**2 years** of age will be enrolled.) For preterm infants <1 year old, the corrected gestational age should be used when determining eligibility. The generally accepted definition of corrected gestational age, which is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age, will be used for this study.
7. Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. **The VNS device must be implanted for at least 6 months before Visit 1, and the device settings must be stable for at least 4 weeks before Visit 1 and be kept stable during the Baseline Period and the Treatment Period. Use of the VNS device magnet is allowed.**
8. Body weight at Visit 1 is at least **4**kg for infants.
9. Females **of** childbearing potential must have a negative pregnancy test at Visit 1.

Change #19

Section 6.1 Inclusion criteria

The following criterion has been added:

10. Subjects with West Syndrome are eligible if Baseline EEG demonstrates hypsarrhythmia despite treatment with at least 2 AEDs appropriate for the treatment of this syndrome.

Change #20

Section 6.2 Exclusion criteria

1. Subject has previously participated in this study or subject has previously been assigned to any treatment in a LCM study.

5. Subject has exclusively typical absence (Type IIA1) or atypical absence (Type IIA2) seizures (no other generalized seizure types are reported).

8. Subject 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.

17. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a QT prolongation greater than 450ms).

21. Subject is a female who is pregnant or nursing, and/or a female of childbearing potential (or who achieves menarche during the study) who does not practice 2 combined methods of contraception, unless sexually abstinent, for the duration of the study. Male subject who does not agree to practice 2 combined methods of contraception (eg, condom, spermicide), unless sexually abstinent, for the duration of the study.

    - Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone, oxcarbazepine]), which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.
    - The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit (Visit 1).

Has been changed to:

1. Subject has previously participated in this study**,** subject **has been assigned to LCM in a previous LCM study, or subject has ever received LCM.**

5. Subject has exclusively typical absence (Type IIA1) or atypical absence (Type IIA2) seizures (no other generalized seizure types are reported**), or has only partial-onset seizures (Type I**).

8. **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.

17. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a **corrected QT interval [QTc]** greater than 450ms).

21. **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 World Health Organization 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.**

Change #21

Section 6.3 Withdrawal criteria

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

All subjects discontinuing treatment with LCM for any reason should taper off LCM. It is recommended that the dosage be tapered off in weekly decrements of 2 mg/kg/day or 3mg/kg/day (oral solution) or 200mg/day (tablet) (see Section 7.2). A slower 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 exit criteria have been met.

All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

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

1. Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject achieves menarche during the study and does not practice an acceptable method of contraception for the duration of the study (unless sexually abstinent).
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. A QTc interval of ≥500ms is confirmed by a cardiologist overread on any ECG.
6. Subject develops a second degree AV block while awake or develops a third degree AV block.
7. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in the study.
8. Investigator decides that withdrawal from further participation would be in the subject's best interest.
9. Subject has a prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the investigator as serious enough to warrant discontinuation from the study.
10. Subject requires the use of rescue medication in excess of that permitted by the protocol.
11. 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.
12. Subject has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

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

1. Any clinically relevant change in medical or psychiatric condition (if in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol (see Section 7.8).
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Subject needs any alteration in AED daily dose or dosing frequency or VNS settings.

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.

Has been changed to:

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

All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable.

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

1. Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. **Female subject achieves menarche and does not practice contraception as provided in Exclusion Criterion 21, unless sexually abstinent.**
4. Subject becomes pregnant, as evidenced by a positive pregnancy test.
5. **Subject has** QTc interval of ≥500ms **that** is confirmed by a cardiologist overread on any ECG.
6. Subject develops a second degree AV block while awake or develops a third degree AV block.
7. 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.
8. Investigator decides that withdrawal from further participation would be in the subject's best interest.
9. Subject has a prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the investigator as serious enough to warrant discontinuation from the study.
10. Subject **uses** rescue medication in excess of that permitted by the protocol.
11. **Subject needs any alteration in AED daily dose or VNS settings.**
12. 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, **LCM** 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.
13. **For subjects ≥6 years of age, subject** has actual suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

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

1. 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 (see Section 7.8).
3. Subject and/or delegated caregiver is unable to manage the completion of the diary or is noncompliant with study procedures or medication, in the opinion of the investigator.
4. Transaminases (AST, ALT, or both) ≥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 **LCM**.

Change #22

Section 7.2 Treatment(s) to be administered

At the end of the Baseline Period (completion of Visit 2), subjects who meet the eligibility criteria will commence a 4-week Titration Period.

As described in Section 5.1, subjects will initiate treatment with LCM oral solution at 2mg/kg/day or 3mg/kg/day, or LCM tablets at 100mg/day based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed 12mg/kg/day for subjects weighing ≤30kg, or 8mg/kg/day for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control. During the Titration period only, one back-titration step is permitted; once the dose of LCM has been back-titrated, the dose cannot be increased for the duration of the study (see Figure 5-1 and Figure 5-2).

If a subject does not achieve or require the maximum dose level (8mg/kg/day, 12mg/kg/day, or 400mg/day), then the highest optimized dose will be maintained until the end of the Titration Period. The Titration Period will last 4 weeks, regardless of the doses administered. Subjects who are not able to tolerate the minimum required dose (at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day [tablets/oral solution] for subjects weighting >50kg) of LCM (even after back-titration) will be withdrawn from the study. Study medication doses will be titrated according to the schedules presented in Table 7-1.

The maximum LCM dose is not to exceed 12mg/kg/day (oral solution) for subjects weighing ≤30kg, 8mg/kg/day (oral solution) for subjects weighing >30kg to ≤50kg, and 400mg/day (tablets/oral solution) in subjects weighing >50kg.

The planned doses for each week of the Titration Period for subjects taking the LCM oral solution and tablet formulations are displayed in Table 7-1.

Table 7-1 Lacosamide dose titration during the Titration Period

Week	Study Medication Dose		
	Subjects weighing ≤30kg LCM 12mg/kg/day (oral solution)	**Subjects weighing >30kg to ≤50kg LCM 8mg/kg/day (oral solution)**	**Subjects weighing >50kg LCM 400mg/day (tablet)**
1	3mg/kg/day	2mg/kg/day	100mg/day
2	6mg/kg/day	4mg/kg/day	200mg/day
3	9mg/kg/day	6mg/kg/day	300mg/day
4	12mg/kg/day	8mg/kg/day	400mg/day

At the end of the Titration Period (Visit 6), a 12-week Maintenance Period will begin. Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period. Subjects will enter the Maintenance Period at the LCM dose achieved at the end of the Titration Period. No dose modification is permitted during the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study.

Subjects may be eligible for participation in the additional open-label study (SP848) upon completion of the Maintenance Period and a minimum dose of 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.

Subjects who choose not to participate in the open-label study, subjects who are only able to tolerate the lowest LCM dose (100mg/day for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation), or subjects who are discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact. The doses to be used during the Taper Period and the duration of the Taper Period will depend on the dose maintained during the Maintenance Period. For subjects taking the LCM oral solution, weekly decrements of either 2mg/kg/day or 3mg/kg/day (based on body weight) are recommended during the Taper Period. For subjects taking the LCM tablets, a weekly decrement of 200mg/day per week during the Taper Period is recommended.

Table 7-2, Table 7-3 and Table 7-4 display the recommended LCM dose reductions during the Taper Period for the LCM oral solution and tablet formulations, respectively.

Table 7-2 Recommended LCM dose taper for oral solution formulation for subjects weighing ≤30kg

Maximum LCM dose maintained	Taper schedule			
	Week 17	Week 18	Week 19	Week 20
12mg/kg/day	9mg/kg/day	6mg/kg/day	3mg/kg/day	0
9mg/kg/day	6mg/kg/day	3mg/kg/day	0	-
6mg/kg/day	3mg/kg/day	0	-	-
3mg/kg/day	0	-	-	-

LCM=lacosamide

Table 7-3 Recommended LCM dose taper for oral solution formulation for subjects weighing >30kg to ≤50kg

Maximum LCM dose maintained	Taper schedule			
	Week 17	Week 18	Week 19	Week 20
8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	0
6mg/kg/day	4mg/kg/day	2mg/kg/day	0	-
4mg/kg/day	2mg/kg/day	0	-	-
2mg/kg/day	0	-	-	-

LCM=lacosamide

Table 7-4 Recommended LCM dose taper for tablet formulation for subjects weighing >50kg

Maximum LCM dose maintained	Taper schedule	
	Week 17	Week 18
400mg/day	200mg/day	0
300mg/day	100mg/day	0
200mg/day	0	-
100mg/day	0	-

LCM=lacosamide

All subjects discontinuing treatment with LCM for any reason should taper off LCM. It is recommended that the dosage be tapered off in weekly decrements of either 2mg/kg/day or 3mg/kg/day (based on body weight; oral solution) or 200mg/day (tablet). A slower 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 exit criteria have been met. In case of an emergency, a faster taper is permitted after discussion with the medical monitor, whenever possible.

If subjects discontinue prematurely from the study, an Early Termination Visit will occur where subjects will be instructed to taper their LCM dose as appropriate. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.

Has been changed to:

Lacosamide will be administered orally bid (at approximately 12-hour intervals in the morning and in the evening). **Administration of oral solution by feeding tube is permitted for subjects who are unable to swallow the oral solution.**

At the end of the Baseline Period **and** completion of Visit 2, subjects who meet the eligibility criteria will commence **a 6-week** Titration Period **(LCM dosing flexibility allowed based on tolerability)**.

As described in Section 5.1, subjects will initiate treatment with LCM oral solution at **2mg/kg/day, or LCM tablets at 100mg/day** based on body weight. The dose will be titrated to a level to optimize tolerability and seizure control, not to exceed **12mg/kg/day (oral solution) for subjects weighing <50kg, or 600mg/day (tablets/oral solution) in subjects weighing ≥50kg. Subjects will increase the LCM dose in a stepwise fashion on a weekly basis to optimize tolerability and seizure control (see Figure 5-1 and Figure 5-2). During the Titration Period only, back-titration is permitted.**

The planned doses for each week of the Titration Period for subjects taking the LCM oral solution and tablet formulations are displayed in Table 7-1.

Table 7-1 Lacosamide dose titration during the Titration Period

Body weight category (formulation)	Flexible doses for the Titration Period by study week					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
<50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/ day	12mg/kg/ day
≥50kg (tablets/oral solution)	100mg/day	200mg/day	300mg/day	400mg/day	500mg/day	600mg/day

Note: Subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead.

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. The flexible LCM dosing over the remainder of the Titration Period is outlined in Table 7-2.

Table 7-2: Flexible LCM dosing during the Titration Period

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

LCM=lacosamide; Max=maximum; Min=minimum
[a] Titration step to achieve a dose not previously administered
[b] Titration step subsequent to a back-titration
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)

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 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 LCM 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 LCM 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 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 dose for at least the final 3 days of Week 6

Body weight category (formulation)	LCM for at least the final 3 days of Week 6	
	Minimum	Maximum
<50kg (oral solution)	4mg/kg/day	12mg/kg/day
≥50kg (tablets/oral solution)	200mg/day	600mg/day

LCM=lacosamide

Eligible subjects (those who reach and maintain at least the minimum LCM dose for at least the final 3 days of the Titration Period) will enter a 12-week Maintenance Period at the dose they achieved at the last day of Week 6. The LCM dose will remain stable

throughout the Maintenance Period. Subjects who require a change in dose during the Maintenance Period will be withdrawn from the study. **Subjects who require a change in formulation during the Maintenance Period should consult the medical monitor to assess if the subject can continue in the study.** Subjects may be eligible for participation in the additional open-label study (SP848) **if they have completed** the Maintenance Period and **are** taking a minimum dose of **4mg/kg/day for subjects weighing <50kg, and 200mg/day (tablets/oral solution) for subjects weighing ≥50kg.** Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966. Subjects who do not complete the full 12 weeks of the Maintenance Period may still be eligible to enter the SP848 open-label study after consultation with the medical monitor.

Subjects who choose not to participate in the open-label study or subjects who **discontinue** due to other reasons will enter **a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.** The doses to be used during the Taper Period and the duration of the Taper Period will depend on the dose maintained during the Maintenance Period.

Table 7-4 and Table 7-5 display the recommended LCM dose reductions during the Taper Period for subjects <50kg and ≥50kg, respectively. A slower 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 exit 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 7-4: Recommended LCM dose taper for subjects <50kg receiving oral solution formulation

Maximum LCM dose achieved	Taper schedule			
	Week 19	Week 20	Week 21	Week 22
11-12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9-10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7-8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day
5-6mg/kg/day	4mg/kg/day	2mg/kg/day	2mg/kg/day	NA
3-4mg/kg/day	2mg/kg/day	2mg/kg/day	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: Subjects with doses <3mg/kg/day do not need to taper. End of Taper Visit will be at the end of Week 22 for subjects undergoing 4 weeks of taper, at the end of Week 21 for subjects undergoing 3 weeks of taper, and at the end of Week 20 for subjects undergoing 2 weeks of taper.
Note: Subjects not requiring taper will enter directly into the Safety Follow-Up Period and not attend any Taper Period visits.

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.

Table 7-5: Recommended LCM dose taper for subjects ≥50kg receiving oral solution or tablet formulation

Maximum LCM dose maintained	Taper schedule			
	Week 19	Week 20	Week 21	Week 22
550-600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
450-500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
350-400mg/day	300mg/day	200mg/day	100mg/day	100mg/day
250-300mg/day	200mg/day	100mg/day	100mg/day	NA
150-200mg/day	100mg/day	100mg/day	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: Subjects with doses <150mg/day do not need to taper. End of Taper Visit will be at the end of Week 22 for subjects undergoing 4 weeks of taper, at the end of Week 21 for subjects undergoing 3 weeks of taper, and at the end of Week 20 for subjects undergoing 2 weeks of taper.
Note: Subjects not requiring taper will enter directly into the Safety Follow-Up Period and not attend any Taper Period visits.
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.

Change #23

Section 7.5 Handling and storage requirements

Lacosamide is to be stored according to the instructions on the label. Lacosamide is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be frozen.

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

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) before further use of the IMP.

The CPM (or designee) will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature, if available) to the Drug Supply Coordinator. Based on discussion with a UCB Quality Assurance representative, the Drug Supply Coordinator will then provide the CPM (or designee) with instructions for the site regarding use of the IMP.

Has been changed to:

Lacosamide is to be stored according to the instructions on the label. Lacosamide is stable at room temperature and is to be stored at temperatures not exceeding 25°C (77°F). Lacosamide should not be **refrigerated or** frozen.

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. **Data should be available to support the temperature conditions maintained at the clinical site (eg manual temperature logs or automated chart recordings).**

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.

Change #24

Section 7.7 Procedures for monitoring subject compliance

At each visit after IMP is dispensed, subjects must return all unused IMP 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.

Has been changed to:

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.

Change #25

Section 7.8.1 Permitted and prohibited concomitant treatments (medications and therapies)

Subject must have been maintained on a stable dose regimen of up to 3 marketed AEDs for at least 4 weeks prior to Visit 1 (ie, prior to entry into the Baseline Period).

Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. Vagal nerve stimulation (implanted for at least 6 months and stable for at least 4 weeks before Visit 1) must be kept stable during the Baseline Period and the Maintenance Period.

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

- Neuroleptics
- Monoamine oxidase (MAO) inhibitors

- Barbiturates (except as anti-epileptic medications)
- Narcotic analgesics

Only stable use of amphetamines and sedative antihistamines is allowed during the study. Only stable, low doses of anxiolytics or once-daily hypnotics are allowed for non epilepsy indications.

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 less than 12 months are also excluded. Any subject who has been treated with felbamate for at least 12 months and has not experienced serious toxicity issues is eligible for the study.

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 at least 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).

Oral contraceptive use is allowed if ethinylestradiol dosage is at least 30µg per intake (50µg if associated with carbamazepine or other strong enzyme inducers [eg, phenobarbital, primidone, oxcarbazepine]).

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.

Has been changed to:

Subject must have been maintained on a stable dose regimen of **1 to 3** marketed AEDs for at least 4 weeks prior to Visit 1 (ie, prior to entry into the Baseline Period**); the dose regimen of the AEDs must be kept stable through the end of the Maintenance Period.**

Vagal nerve stimulation is allowed and will not be counted as a concomitant AED. **The VNS device must be implanted for at least 6 months before Visit 1, and the device settings must be stable for at least 4 weeks before Visit 1 and** be kept stable during the Baseline Period and **through the end of** the Maintenance Period**.**

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

- Neuroleptics
- **MAO** 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 less than 12 months are also excluded. Any subject who has been treated with felbamate for at least 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 are allowed 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 week (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.

Change #26

Section 7.8.2 Rescue medication

The 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) during study participation; more frequent use precludes subjects from study participation.

Has been changed to:

The use of benzodiazepines as rescue therapy for epilepsy is allowed if taken at a maximum frequency of 1 day per **week** (with up to 3 doses within 24 hours) during study participation; more frequent use precludes subjects from study participation.

Change #27

Section 8.1.1 Visit 1 (Week -6) Screening Visit

At Visit 1, subjects will be evaluated for their suitability for enrollment. The Screening Visit assessments will be conducted 6 weeks prior to the first administration of LCM. It is acceptable for the Screening assessments to be conducted over >1 day, although it should not extend over a period longer than 1 week. 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 (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved ICF. When possible, or as required by the local IRB/IEC, the subject will be requested to give assent 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 ICF 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 and Section 11 of this protocol):

- Contact IXRS to obtain unique subject identification number.
- Review seizure history. The subject or caregiver (including parent/legal guardian) will be asked how many seizures the subject has had over the past 4 weeks as a historical Baseline.
- Concomitant AED(s) assessment.
- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Medical history assessment.
- Complete physical examination.
- Complete neurological examination.
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings).
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight and height assessment.
- Epilepsy surgery assessment.
- C-SSRS (if applicable). The C-SSRS will be completed for all subjects ≥6 years of age.
- Blood sample for clinical chemistry, hematology, and endocrinology.

- Serum pregnancy test (if applicable).
- Urine sample for urinalysis (if applicable). Will be performed for subjects aged 5 to 17 years.
- Tanner Stage (if applicable). The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.
- Dispense subject diary.
- AE reporting.
- Health care resource use.

Eligible subjects will be scheduled to return to the clinic (Visit 2, Week 0) approximately 6 weeks ±2 days after the Screening Visit.

Has been changed to:

At Visit 1, subjects will be evaluated for their suitability for enrollment. The Screening Visit assessments will be conducted 6 weeks prior to the first administration of LCM. It is acceptable for the Screening assessments to be conducted over >1 day**.** 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 (when possible or as required according to local IRBs/IECs) and the subject's parent/legal **representative** by the investigator (or designee). The subject's parent/legal **representative** will be requested to sign and date the IRB/IEC-approved ICF. When possible, or as required by the local IRB/IEC, the subject will be requested to give assent to participate in the study.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature **on** an ICF 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 and Section 11 of this protocol):

- Contact IXRS to obtain unique subject identification number.
- Review seizure history. The subject or caregiver (including parent/legal **representative**) will be asked how many seizures the subject has had over the past 4 weeks as a historical Baseline.
- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Medical history assessment.
- Complete physical examination.
- Complete neurological examination.

- 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)**.
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight and height assessment.
- **Head circumference.**
- Epilepsy surgery assessment.
- C-SSRS (if applicable). The C-SSRS will be completed for all subjects ≥6 years of age.
- Blood sample for clinical chemistry, hematology, and endocrinology.
- Serum pregnancy test (if applicable).
- Urine sample for urinalysis (if applicable). Will be performed for subjects aged 5 to 17 years.
- Tanner Stage (if applicable). The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.
- Dispense subject diary **and remind subject to complete subject diary on a daily basis**.
- AE reporting.

Eligible subjects will be scheduled to return to the clinic (Visit 2, **Day 1**) approximately 6 weeks ±2 days after the Screening Visit.

Change #28

Section 8.1.2 Telephone contact (Week -3)

Three weeks before Visit 2, the investigator or designee should contact the subject's caregiver (including parent/legal guardian) by telephone. The investigator (or designee) should remind the subject's caregiver (including parent/legal guardian) to ensure the diary is completed. The following should be performed via telephone:

- Review inclusion/exclusion criteria
- Concomitant medications assessment
- Concomitant AEDs assessment
- Subject diary review
- Review withdrawal criteria
- AE reporting

Has been changed to:

Three weeks before Visit 2 **(±2 days),** the investigator or designee should contact the subject's caregiver (including parent/legal **representative**) by telephone. The investigator (or designee) should remind the subject's caregiver (including parent/legal **representative**) to ensure the diary is completed. The following should be performed via telephone:

- Review inclusion/exclusion criteria
- Concomitant medications assessment
- Concomitant AEDs assessment
- **Reminder to complete subject diary on a daily basis**
- Review withdrawal criteria
- AE reporting

Change #29

Section 8.1.3 Visit 2 (Week 0)

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 (end of Week 0) to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 2) for removal of the scalp electrodes and return of the recording device. At Visit 2 (end of Week 0), the investigator should determine whether the subject is still eligible and willing to continue in the study.

The following will be performed prior to the first dose of LCM:

- Review inclusion/exclusion criteria.
- Concomitant AED(s) assessment.
- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight and height assessment.
- C-SSRS (if applicable).

- Blood sample for clinical chemistry and hematology.
- Blood sample for LCM and concomitant AED plasma concentrations (before dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.
- Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III Scales) (if applicable). For pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (version consistent with age at the visit).
- PedsQL for subjects ≥1 month to ≤18 years of age (version consistent with age at the visit).
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).
- Subject diary return/review.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS to obtain bottle number(s).
- Dispense subject diary.
- Health care resource use.
- Dispense LCM. Subjects should take the first dose of LCM based on body weight in the clinic. The starting dose for subjects taking the oral solution formulation will be either 2mg/kg/day or 3mg/kg/day, and the starting dose for subjects taking the tablet formulation will be 100mg/day.

Has been changed to:

Section 8.2.1 Visit 2 (Day 1)

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 2 (end of Week 0) to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 2, **Day 1**) for removal of the scalp electrodes and return of the recording device. At Visit 2, the investigator should determine whether the subject is still eligible and willing to continue in the study.

The following will be performed prior to the first dose of LCM:

- Review inclusion/exclusion criteria.

- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.
- 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**. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight and height assessment.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Blood sample for LCM and concomitant AED plasma concentrations (before dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Achenbach CBCL (if applicable): CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.
- Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III Scales) (if applicable). For pediatric subjects <18 months of age at Baseline enrolled in English-speaking countries.
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) (version consistent with age at the visit).
- PedsQL for subjects ≥1 month to ≤18 years of age (version consistent with age at the visit).
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).
- Subject diary return/review.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.

- **Reminder to complete subject diary on a daily basis.**
- Health care resource use.
- Dispense LCM. Subjects should take the first dose of LCM **(**based on body weight**)** in the clinic. The starting dose for subjects taking the oral solution formulation will be **2mg/kg/day, and the starting dose for subjects taking the tablet formulation will be 100mg/day**.

Change #30

The following section has been added:

Section 8.2.2 Telephone contacts (Weeks 1 and 3)

At the end of Weeks 1 and 3 (±2 days), the investigator or designee should contact the subject's caregiver (including parent/legal representative) by telephone. The assessments for these telephone contacts are the same as those performed during the telephone contact at Week -3 in Section 8.1.2 with the exception that inclusion/exclusion criteria do not need to be checked at Weeks 1 and 3.

Change #31

Section 8.2.1 Visit 3 (Week 1)

At Visit 3 (end of Week 1), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight assessment.
- C-SSRS (if applicable).
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings).
- Subject diary return/review.
- LCM return.
- AE reporting.

- Review withdrawal criteria.
- Contact IXRS to obtain bottle number(s).
- Dispense subject diary.
- Health care resource use.
- Dispense LCM. The subject's LCM dose can be titrated based on body weight to either 4mg/kg/day or 6mg/kg/day (oral solution) or 200mg/day (tablets), if clinically appropriate.

Has been changed to:

Section 8.2.3 Visit 3 (Week 2)

At Visit 3 **(end of Week 2 ±2 days),** subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight assessment.
- **Urine pregnancy test (if applicable).**
- C-SSRS (if applicable).
- 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).**
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- **Contact IXRS**.
- Dispense subject diary.
- **Reminder to complete subject diary on a daily basis.**
- Health care resource use.
- **Dispense LCM.**

Change #32

Section 8.2.2 Visit 4 (Week 2)

Assessments for Visit 4 (end of Week 2) are the same as those described for Visit 3 (end of Week 1) in Section 8.2.1, with the following additions:

- A blood sample for clinical chemistry and hematology
- A urine sample for urinalysis (if applicable)

The subject's LCM dose can be titrated based on body weight to either 6mg/kg/day or 9mg/kg/day (oral solution) or 300mg/day (tablets), if clinically appropriate.

Has been changed to:

Section 8.2.4 Visit 4 (Week 4)

Assessments for Visit 4 (end of **Week 4 ±2 days**) are the same as those described for Visit 3 (end of Week **2**) in Section **8.2.3**. **This visit is optional and will only be required if a subject requires further LCM dose adjustment.**

Change #33

Section 8.2.3 Visit 5 (Week 3)

Assessments for Visit 5 (end of Week 3) are the same as those described for Visit 3 (end of Week 1) in Section 8.2.1.

The subject's LCM dose can be titrated based on body weight to either 8mg/kg/day or 12mg/kg/day (oral solution) or 400mg/day (tablets), if clinically appropriate.

Has been changed to:

Section 8.2.5 Visit 5 (Week 5)

Assessments for Visit 5 (end of **Week 5 ±2 days**) are the same as those described for Visit 3 (end of Week **2**) in Section **8.2.3. This visit is optional and will only be required if a subject requires further LCM dose adjustment.**

Change #34

Section 8.2.4 Visit 6 (Week 4)

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 6 (end of Week 4) to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 6) for removal of the scalp electrodes and return of the recording device.

At Visit 6 (end of Week 4), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight assessment.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS to obtain bottle number(s).
- Dispense subject diary.
- Health care resource use.
- Dispense LCM.

Has been changed to:

Section 8.2.6 Visit 6 (Week 6, End of Titration)

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 6 (end of **Week 6 ±2 days**) to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 6) for removal of the scalp electrodes and return of the recording device.

At Visit 6 (end of **Week 6**), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- 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.** Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight assessment.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age **(same version that was used at Visit 2).**
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.
- **Reminder to complete subject diary on a daily basis.**
- Health care resource use.

- Dispense LCM **for the first 4 weeks of the Maintenance Period.**

Change #35

Section 8.3.1 Telephone contacts (Weeks 6, 10, and 14)

At the end of Weeks 6, 10, and 14, the investigator or designee should contact the subject's caregiver (including parent/legal guardian) by telephone. The assessments for these telephone contacts are the same as those performed during the telephone contact at Week -3 in Section 8.1.2 with the exception that inclusion/exclusion criteria do not need to be checked at Weeks 6, 10, and 14.

Subjects must titrate to at least 6mg/kg/day for subjects weighing ≤30kg, 4mg/kg/day for subjects weighing >30kg to ≤50kg, or 200mg/day (tablets/oral solution) for subjects weighing >50kg in order to enter the Maintenance Period.

Has been changed to:

Section 8.3.1 Telephone contacts (Weeks 8, 12, and 16)

At the end of Weeks **8, 12, and 16 (±2 days),** the investigator or designee should contact the subject's caregiver (including parent/legal **representative**) by telephone. The assessments for these telephone contacts are the same as those performed during the telephone contact at Week -3 in Section 8.1.2 with the exception that inclusion/exclusion criteria do not need to be checked at Weeks **8, 12, and 16.**

Subjects must titrate to at least **4mg/kg/day for subjects weighing <50kg, or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg** in order to enter the Maintenance Period.

Change #36

Section 8.3.2 Visit 7 (Week 8)

At Visit 7 (end of Week 8), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight assessment.

- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings).
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Urine sample for urinalysis (if applicable).
- Urine pregnancy test (if applicable).
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS to obtain bottle number(s).
- Dispense subject diary.
- Health care resource use.
- Dispense LCM.

Has been changed to:

Section 8.3.2 Visit 7 (Week 10)

At Visit 7 (end of **Week 10 ±2 days**), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight assessment.
- 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).**
- C-SSRS (if applicable).
- Blood sample for clinical chemistry and hematology.
- Urine pregnancy test (if applicable).
- Subject diary return/review.

- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS.
- Dispense subject diary.
- **Reminder to complete subject diary on a daily basis.**
- Health care resource use.
- Dispense LCM.

Change #37

Section 8.3.3 Visit 8 (Week 12)

Assessments for Visit 8 (end of Week 12) are the same as those described for Visit 7 (end of Week 8) in Section 8.3.2 with the exception of there being no urinalysis assessment at Visit 8.

Has been changed to:

Section 8.3.3 Visit 8 (Week 14)

Assessments for Visit 8 (end of **Week 14 ±2 days**) are the same as those described for Visit 7 (end of **Week 10**) in Section 8.3.2 **with the addition of:**

- **Brief physical examination.**
- **Brief neurological examination.**

For the assessment of clinical chemistry and hematology, if no abnormality is observed in the laboratory blood samples from the previous visit, the assessment does not have to be performed.

Change #38

Section 8.3.4 Visit 9 (Week 16)/Early Termination Visit

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 9 (end of Week 16)/Early Termination to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 9/Early Termination Visit) for removal of the scalp electrodes and return of the recording device.

At Visit 9 (end of Week 16) or the Early Termination Visit (if applicable), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.

- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.
- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings. Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight and height assessment.
- C-SSRS (if applicable).
- Blood sample for clinical chemistry, hematology, and endocrinology.
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Urine sample for urinalysis (if applicable).
- Serum pregnancy test (if applicable).
- Clinical Global Impression of Change assessment.
- Caregiver's Global Impression of Change assessment.
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age.
- BRIEF-P (≥2 years to ≤5 years of age)/BRIEF (≥5 years of age) (version consistent with age at Visit 2).
- PedsQL for subjects ≥1 month to ≤18 years of age (version consistent with age at Visit 2).
- Tanner Stage (if applicable). The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- Contact IXRS to obtain bottle number(s).
- Dispense subject diary (for subjects entering Taper Period and not SP848).

- Health care resource use.
- Dispense LCM (for subjects entering Taper Period and not SP848).

Subjects may be eligible for participation in the open-label study (SP848) if they have been maintained on a dose of at least 6mg/kg/day (oral solution) for subjects weighing ≤30kg, 4mg/kg/day (oral solution) for subjects weighing >30kg to ≤50kg, and 200mg/day (tablets/oral solution) in subjects weighing >50kg in the Maintenance Period. Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966.

Subjects who choose not to participate in the open-label study, subjects who are only able to tolerate the lowest LCM dose (100mg/day for the tablet formulation, 3mg/kg/day or 2mg/kg/day for the oral solution formulation), or subjects discontinuing due to other reasons will enter up to a 4-week Taper Period followed by a 1-week study drug-free Safety Period and Final Safety telephone contact.

Has been changed to:

Section 8.3.4 Visit 9 (Week 18)/Early Termination Visit

Subjects will be asked to return to the clinic on the morning of the day prior to Visit 9 (end of Week **18 ±2 days**)/Early Termination to begin 24-hour ambulatory EEG recordings. Scalp electrodes will be attached, and subjects will receive a recording device. Subjects will be asked to return approximately 24 hours later (for Visit 9/Early Termination Visit) for removal of the scalp electrodes and return of the recording device.

At Visit 9 (end of Week **18**) or the Early Termination Visit (if applicable), subjects will return for a clinic visit, and the following will be performed:

- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Complete physical examination.
- Complete neurological examination.
- 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.** Recordings should be performed at least 15 minutes after removal of scalp electrodes used for the 24-hour ambulatory EEG recording).
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight and height assessment.
- **Head circumference.**
- C-SSRS (if applicable).

- Blood sample for clinical chemistry, hematology, and endocrinology.
- Blood sample for LCM and concomitant AED plasma concentrations (at any time post-dosing with LCM). Blood sample will be drawn along with clinical chemistry and hematology samples.
- Urine sample for urinalysis (if applicable).
- Serum pregnancy test (if applicable).
- Clinical Global Impression of Change assessment.
- Caregiver's Global Impression of Change assessment.
- Achenbach CBCL (if applicable); CBCL/1½-5 or CBCL/6-18 for pediatric subjects ≥18 months of age **(same version that was used at Visit 2).**
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) **(same version that was used at Visit 2).**
- PedsQL for subjects ≥1 month to ≤18 years of age **(same version that was used at Visit 2).**
- Tanner Stage (if applicable). The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study.
- Subject diary return/review.
- LCM return.
- AE reporting.
- Review withdrawal criteria.
- **Contact IXRS.**
- Dispense subject diary (for subjects entering Taper Period and not SP848).
- **Reminder to complete subject diary on a daily basis (if applicable).**
- Health care resource use.
- Dispense LCM (for subjects entering Taper Period and not SP848).

Subjects may be eligible for participation in the open-label study (SP848) if they have been maintained on a dose of at least **4mg/kg/day (oral solution) for subjects weighing <50kg, or 200mg/day (tablets/oral solution) for subjects weighing ≥50kg in the Maintenance Period.** Subjects will begin SP848 on the LCM dose they were taking in the Maintenance Period in SP0966.

Subjects who choose not to participate in the open-label study or subjects who discontinue due to other reasons will enter a 2- to 4-week Taper Period followed by a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Investigators should discuss treatment options with the subject and/or his/her parent/legal representative 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 representative. These subjects should complete Visit 9/Early Termination Visit and then complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The End of Taper Visit is not required for subjects who complete or withdraw from the study and who do not undergo taper of LCM.

Change #39

Section 8.4 End of Study Period

The following paragraph has been added:

For subjects who enter the open-label study (SP848), the end of the study will be the date of the subject's last assessment in SP0966 (end of Maintenance Period or Early Termination Visit). Subjects who do not enroll in SP848 will enter a Taper Period followed by a Safety Follow-Up Period as described below, and the end of the study will be the date of the last Safety Follow-Up Telephone Contact.

Change #40

Section 8.4.1 Taper Period (Weeks 17 to 20)/End of Taper Visit

For subjects who do not enroll in the open-label study (SP848), a Taper Period will be scheduled. For subjects completing the full duration of the Maintenance Period, the Taper Period will begin at Week 17. For subjects who do not complete the full duration of the Maintenance Period, the Taper Period will begin earlier, at the time that they end the Maintenance Period. Please refer to Section 7.2 for details of the taper schedule.

The following will be performed at the End of Taper Visit at the end of the last week of the Taper Period:

- Concomitant AED(s) assessment.
- Changes in VNS settings.
- Concomitant medication(s) assessment.
- Brief physical examination.
- Brief neurological examination.
- Vital signs (BP and pulse, including orthostatic assessments).
- Body weight assessment.

- 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment and collection of blood samples, and, if possible, with the subject in the supine position for 5 minutes preceding the ECG recordings).
- C-SSRS (if applicable).
- Blood sample for clinical chemistry, hematology, and endocrinology. If no abnormality is observed in the laboratory blood samples from the previous visit, the End of Taper assessment does not have to be performed.
- Urine sample for urinalysis (if applicable). If no abnormality is observed in the 2 previous urinalysis tests, the End of Taper assessment does not need to be performed.
- Serum pregnancy test (if applicable).
- Subject diary return/review.
- LCM return.
- AE reporting.
- Health care resource use.

Has been changed to:

Section 8.4.1 Taper Period

For subjects who do not enroll in the open-label study (SP848), a **2- to 4-week (depending on dose achieved)** Taper Period will be scheduled. For subjects completing the full duration of the Maintenance Period, the Taper Period will begin at Week **19 (±2 days).** For subjects who do not complete the full duration of the Maintenance Period, the Taper Period will begin earlier, at the time that they end the Maintenance Period. Please refer to Section 7.2 for details of the taper schedule. **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. These subjects should complete Visit 9/Early Termination Visit and then complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM and a Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.**

Section 8.4.1.1 Telephone Contact (Week 19)

At the end of Week 19 (±2 days) during the first week of the Taper Period, the investigator or designee should contact the subject's caregiver (including parent/legal representative) by telephone. The following assessments will be performed:

- **Concomitant AED(s) assessment**
- **Concomitant medication(s) assessment**
- **Reminder to complete subject diary on a daily basis**
- **AE reporting**
- **Review withdrawal criteria**

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.

Section 8.4.1.2 End of Taper Visit (Weeks 20 to 22)

The End of Taper Visit is not required for subjects who complete or withdraw from the study and who do not undergo taper of LCM. Each subject will have only 1 Taper Visit. The Taper Visit will be scheduled at the end of the Taper Period (Week 20, Week 21, or Week 22, depending on dose level achieved; see Table 7-4 and Table 7-5). A time window of ±2 days relative to Visit 2 (Titration Period) is applicable.

The following will be performed at the End of Taper Visit at the end of the last week of the Taper Period:

- **Concomitant AED(s) assessment.**
- **VNS assessment (for subjects with an implanted VNS device).**
- **Concomitant medication(s) assessment.**
- **Brief physical examination.**
- **Brief neurological examination.**
- **Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).**
- **Body weight assessment.**
- **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).**
- **C-SSRS (if applicable).**
- **Blood sample for clinical chemistry, hematology and endocrinology.**
- **Urine sample for urinalysis (if applicable).**
- **Serum pregnancy test (if applicable).**
- **Subject diary return/review.**
- **LCM return.**
- **AE reporting.**
- **Review withdrawal criteria.**
- **Contact IXRS.**
- **Health care resource use.**

Section 8.4.2 Safety Follow-up

Safety Follow-up is required only for subjects who do not enroll in the open-label study (SP848).

Section 8.4.2.1 Safety Follow-Up Visit (Weeks 22 to 24)

The Safety Follow-Up Visit will occur 2 weeks (±2 days) after the final dose of LCM.

The following assessments will be performed:

- **Concomitant AED(s) assessment.**
- **VNS assessment (for subjects with an implanted VNS device).**
- **Concomitant medication(s) assessment.**
- **Complete physical examination.**
- **Complete neurological examination.**
- **Vital signs (BP and pulse rate, including orthostatic assessments in ambulatory subjects).**
- **Body weight and height assessment.**
- **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) (only for subjects with an abnormal reading at the previous visit).**
- **C-SSRS (if applicable).**
- **Blood sample for clinical chemistry, hematology and endocrinology (only for subjects with an abnormal value at the previous visit).**
- **Urine sample for urinalysis (if applicable) (only for subjects with an abnormal value at the previous visit).**
- **Urine pregnancy test (if applicable) (only if blood is not collected for another assessment).**
- **AE reporting.**
- **Health care resource use.**

Section 8.4.2.2 Safety Follow-Up Telephone Contact (Weeks 24 to 26)

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

- **Concomitant AED(s) assessment**
- **Concomitant medication(s) assessment**
- **AE reporting**

Change #41

Section 8.5 Unscheduled Visit

Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. During an Unscheduled Visit, the following assessments are required:

- Concomitant AED(s) assessment.
- Changes in VNS settings
- Concomitant medication(s) assessment
- Vital signs (BP and pulse, including orthostatic assessments)
- Body weight assessment (height is not required)
- Contact IXRS to obtain bottle number(s)
- Subject diary return/review
- AE reporting
- Review withdrawal criteria
- Health care resource use

If the Unscheduled Visit is due to an AE, then the C-SSRS is required.

In addition to the required assessments listed above, further assessments can be completed as needed and may include ECG, laboratory tests, physical examination, neurological examination, etc.

Has been changed to:

Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. During an Unscheduled Visit, the following assessments are required:

- Concomitant AED(s) assessment.
- **VNS assessment (for subjects with an implanted VNS device).**
- Concomitant medication(s) assessment.
- Vital signs (BP and pulse **rate**, including orthostatic assessments **in ambulatory subjects**).
- Body weight assessment (height is not required).
- Subject diary return/review.
- **Reminder to complete subject diary on a daily basis.**
- AE reporting.
- Review withdrawal criteria.

If the Unscheduled Visit is due to an AE, then the C-SSRS is required.

In addition to the required assessments listed above, **the investigator can perform further assessments based on his/her clinical judgment and the medical needs of the subject (eg, assessments of ECG, laboratory tests, physical examination, neurological examination, etc).**

Change #42

Section 9.1 Seizure frequency

At the Screening Visit (Visit 1), seizure history will be based on the subject or caregiver (including parent/legal guardian) being asked how many seizures the subject has had over the past 4 weeks.

During the study, subjects will keep a diary to record daily seizure activity from the Screening Visit until the end of the study. The subject should be reminded to bring the diary with them to each clinic visit. The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

Has been changed to:

At the Screening Visit (Visit 1), seizure history will be based on the subject or caregiver (including parent/legal **representative**) being asked how many seizures the subject has had over the past 4 weeks.

During the study, subjects will keep a diary to record daily seizure activity from the Screening Visit until the end of the study. **At each visit and telephone contact the subject and/or legal representative should be reminded to complete the subject diary on a daily basis and** to bring the diary with them to each clinic visit **(including Unscheduled Visits)**. The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

The investigator should discuss the possibility of the emergence of other seizure types with parents and caregivers, and advise that all seizures should be recorded in the diary.

Change #43

Section 9.3 Pediatric Quality of Life Inventory

The multidimensional PedsQL scale encompasses the essential core domains for pediatric HRQoL measurement: 1) Physical Functioning/Symptoms, 2) Emotional Functioning, 3) Social Functioning, and 4) Cognitive/School Functioning. The PedsQL assessment is retrospective to the prior month, and individual items are scored using a 5-point Likert scale

(never, almost never, sometimes, often, or always). A total health summary score is calculated from the sum of the raw scores of the individual items, with higher scores indicating higher HRQoL.

Has been changed to:

The multidimensional PedsQL **generic core scales encompas** 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 of the individual items, with higher scores indicating higher HRQoL.

Change #44

Section 10 ASSESSMENT OF PK

Blood samples for the determination of LCM and concomitant AED plasma concentrations will be collected at Visits 2, 6, and 9 (at any time after dosing with the exception of the sample at Visit 2, which should be predose) along with clinical chemistry and hematology samples (according to the tabular schedule of study procedures in Section 5.2). In each case, the time the subject took the most recent dose of LCM and concomitant AEDs and the time of blood sampling must be recorded. Actual sampling times will be recorded in the eCRF to the minute.

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

Has been changed to:

Section 10 ASSESSMENT OF PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Blood samples for the determination of LCM and concomitant AED plasma concentrations will be collected at Visits 2 and 9 (at any time after dosing with the exception of the sample at Visit 2, which should be predose) along with clinical chemistry and hematology samples (according to the tabular schedule of study procedures in Section 5.2). In each case, the time the subject took the most recent dose of LCM and concomitant AEDs and the time of blood sampling must be recorded. Actual sampling times will be recorded in the eCRF to the minute.

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

Change #45

Section 11.1.6 Pregnancy

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 the Early Termination 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 be scheduled 2 weeks after the subject has discontinued her IMP.

Has been changed to:

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 the Early Termination 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 IMP.**
- **A Safety Follow-Up Telephone Contact should occur 30 days (-1/+3 days) after the subject has discontinued IMP**.

Change #46

Section 11.7.3 12-lead ECG

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

Has been changed to:

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in the supine position **for approximately** 5 minutes **before the ECG recordings and** during **the recordings, if possible.**

Change #47

Section 11.7.5 Physical examination

The physical examination should be performed by a medically qualified clinician licensed to perform the examination, according to the tabular schedule of study procedures in Section 5.2. If possible, the same clinician should conduct all physical examinations for the

same subject during the study. Clinically significant physical examination findings that have emerged or worsened since baseline are to be reported as AEs.

Has been changed to:

The physical examination should be performed by a medically qualified clinician licensed to perform the examination, according to the tabular schedule of study procedures in Section 5.2. If possible, the same clinician should conduct all physical examinations for the same subject during the study. **Subsequent to Visit 1, clinically significant physical examination findings should be reported as AEs.**

Change #48

Section 11.7.5.1 Complete physical examination

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

Has been changed to:

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**.

Change #49

Section 11.7.11 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures in Section 5.2.

The "Since Last Visit" version of the C-SSRS will be used, with the following exceptions:

- The "Baseline/Screening" version of the C-SSRS should be completed at Visit 1.
- If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.

Has been changed to:

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures in Section 5.2.

The "Since Last Visit" version of the C-SSRS will be used, with the following exceptions:

- The "Baseline/Screening" version of the C-SSRS should be completed at Visit 1.
- If a subject turns 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be completed at the first visit after the sixth birthday.

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.

Change #50

Section 13.1 Definition of analysis sets

The analysis set for the preliminary efficacy variables will be the Full Analysis Set and will include all subjects in the SS having at least 1 post-Baseline efficacy related assessment.

Has been changed to:

The analysis set for the preliminary efficacy variables will be the Full Analysis Set and will include all subjects in the SS having **had a Baseline and** at least 1 post-Baseline efficacy related assessment.

Change #51

Section 13.3.1 Analysis of the primary safety variables

The actual change in the count of generalized spike-wave discharges on 24-hour ambulatory EEG from Visit 2 (Baseline Period) to Visit 6 (start of Maintenance Period) will be calculated and summarized descriptively.

Has been changed to:

The actual change in the count of generalized spike-wave discharges on 24-hour ambulatory EEG from **Visit 2 to Visit 6** will be calculated and summarized descriptively.

Change #52

Section 13.3.2 Secondary safety variables

The actual change in the count of 3Hz spike-wave discharges on 24-hour ambulatory EEG from Visit 2 (Baseline Period) to Visit 6 (start of Maintenance Period) will be calculated and summarized descriptively.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Summary tables for number and percentage of subjects reporting at least 1 TEAE tabulated by System Organ Class and preferred term will be presented. Furthermore, TEAEs that lead to early discontinuation from the study and serious TEAEs will be tabulated. Treatment-emergent AEs will be defined as those events which start on or after the date of first LCM administration, or whose severity worsens on or after the date of first LCM administration. Adverse events occurring within 30 days after last dose of LCM will also be considered treatment emergent.

Has been changed to:

The actual change in the count of 3Hz spike-wave discharges on 24-hour ambulatory EEG from **Visit 2 to Visit 6** will be calculated and summarized descriptively.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Summary tables for number and percentage of subjects reporting at least 1 TEAE tabulated by System Organ Class and preferred term will be presented. Furthermore, TEAEs that lead to early discontinuation from the study and serious TEAEs will be tabulated. **Treatment-emergent AEs will be defined as those events which start on or after the date of first LCM administration and within 30 days following the date of last LCM administration, or whose severity worsens within this time frame.**

Change #53

Section 13.4.1 Preliminary efficacy analyses

The actual change in the count of generalized and 3Hz spike-wave discharges on 24-hour ambulatory EEG from Visit 2 (Baseline Period) to Visit 9 (end of Maintenance Period) or Early Termination will be calculated and summarized descriptively.

Has been changed to:

The actual change in the count of generalized and 3Hz spike-wave discharges on 24-hour ambulatory EEG from Visit 2 to Visit 9 or Early Termination will be calculated and summarized descriptively.

Change #54

Section 13.4.2 Pharmacokinetic analyses

A listing of LCM and AED plasma concentrations will be presented.

Has been changed to:

A listing of LCM and AED plasma concentrations will be presented. **A statistical analysis of the effect of LCM on AED concentrations will be performed.**

Change #55

Section 13.5 Handling of protocol deviations

After all eCRFs have been retrieved and entered, all queries issued and answered to the extent possible, and prior to locking the clinical database, a Data Review Meeting will be held. Important protocol deviations (ie, those considered to have an impact on eg, primary safety or study conduct) will be identified and reviewed by a panel consisting of the Clinical Project Manager, the study biostatistician, study physician, a representative of the monitoring team, and other appropriate team members. Important protocol deviations will be listed.

Has been changed to:

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

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

Change #56

Section 13.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC. The DMC will oversee the safety of the study by convening to review safety data after 15 subjects have completed Visit 6 or withdrawn from the study, then again after 30 subjects have completed Visit 6 or withdrawn from the study. The DMC will consist of UCB neurologists, a drug safety physician, a biostatistician, and an independent medical expert. Study enrollment will not be halted during planned DMC review of the safety data. The Sponsor can convene an ad hoc DMC meeting to review the data and make recommendations on the continuation or modification of the study. The objectives and procedures for the DMC will be detailed in the DMC Charter.

Has been changed to:

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC. The DMC will oversee the safety of the study by convening to review safety data after 15 subjects have completed Visit 6 or withdrawn from the study, then again after 30 subjects have completed Visit 6 or withdrawn from the study. **The DMC will consist of a UCB neurologist, a neurologist from the European region, a drug safety physician, a biostatistician, and an independent medical expert.** Study enrollment will not be halted during planned DMC review of the safety data. The Sponsor can convene an ad hoc DMC

meeting to review the data and make recommendations on the continuation or modification of the study. The objectives and procedures for the DMC will be detailed in the DMC Charter.

Change #57

Section 13.8 Determination of sample size

A total of 50 evaluable subjects are planned for enrollment for this study across 2 age cohorts. The first cohort will consist of approximately 40 subjects between 4 years and <18 years of age. The second cohort will consist of at least 10 subjects between 1 month and <4 years of age. Since the primary objective of this open-label exploratory study is to assess the safety and preliminary efficacy of LCM in subjects with generalized seizures and other epilepsy syndromes, a sample size of 50 evaluable subjects is deemed adequate for meeting the objectives of the study. No formal sample size calculations were performed.

Has been changed to:

A total of 50 evaluable subjects are planned for enrollment for this study across 2 age **groups**. The first **age group** will consist of approximately 40 subjects between 4 years and <18 years of age. The second **age group** will consist of at least 10 subjects between 1 month and <4 years of age. Since the primary objective of this open-label exploratory study is to assess the safety and preliminary efficacy of LCM in subjects with generalized seizures and other epilepsy syndromes, a sample size of 50 evaluable subjects is deemed adequate for meeting the objectives of the study. No formal sample size calculations were performed.

Change #58

Section 16 REFERENCES

The following citations have been added:

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

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

17.5 Protocol Amendment 4

Rationale for the amendment

The present amendment has been issued to open enrollment of subjects ≥1 month to <2 years of age in SP0966. A weight-based dosing scheme has been established for pediatric subjects down to ≥1 month of age, which is consistent with the current SP0966 dosing scheme. This dosing scheme is based on safety and PK modeling using data from previous pediatric and adults studies.

In addition, the exclusion of subjects with primary generalized tonic-clonic seizures (PGTCS) with a diagnosis of idiopathic generalized epilepsy (IGE) from the SP0966 study population is removed in this amendment. In the original SP0966 protocol dated 30 May 2012, these

subjects were planned to be included in the exploratory evaluation of LCM treatment in pediatric epilepsy syndromes with generalized seizures. However, after finalization of the SP0966 protocol, UCB decided that pediatric subjects ≥4 years of age with PGTCS and a diagnosis of IGE would instead be evaluated along with adults in a confirmatory double-blind, placebo-controlled Phase 3 study. Thus, SP0966 Protocol Amendment 1 (19 Oct 2012) excluded pediatric subjects in this patient population from SP0966. Due to postponement of initiation of the above-mentioned planned confirmatory study in subjects ≥4 years of age, UCB considers it appropriate to start investigating pediatric subjects with PGTCS with a diagnosis of IGE in the SP0966 exploratory study as originally planned.

Following additional feedback from regulatory agencies, Withdrawal Criterion #6 and Exclusion Criterion #16 have been modified.

It is also clarified that head circumference is to be measured only in subjects <4 years of age.

Modifications and changes

Global changes

The following key changes were made throughout the protocol:

- Subjects with PGTCS with a diagnosis of IGE are not excluded from the study population.
- Subjects ≥1 month to <2 years of age can now be enrolled into SP0966.
- Subjects with second- or third-degree heart block are excluded from SP0966, without the requirement of being at rest.
- The AV block withdrawal criterion was modified to second or third degree AV block, without the requirement of being awake.
- Head circumference is to be measured only in subjects <4 years of age.
- Administrative changes: the name and details of the Clinical Project Manager and the SAE Reporting Email address were updated.

Specific changes

Change #1

SPONSOR DECLARATION

Clinical Project Manager

[redacted], MD

Has been changed to:

Clinical Project Manager

[redacted]

Change #2

STUDY CONTACT INFORMATION

Clinical Project Manager

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

Has been changed to:

Clinical Project Manager

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

Change #3

SERIOUS ADVERSE EVENT REPORTING

Email	**Global (except Japan):** DS_ICT@ucb.com

Has been changed to:

Email	**Global (except Japan): DSICT**@ucb.com

Change #4

Section 1 SUMMARY, paragraph 2

The primary variables in this study are changes in the count of generalized spike-wave discharges and change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) from the Baseline Period to the Maintenance Period. The above variables reference partial seizures evolving to secondarily generalized seizures. While these partial seizures will be summarized as a part of the analysis, subjects must have a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1) to possibly be eligible for study participation. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are also not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type. Other variables to be assessed include measures of efficacy, plasma concentrations, and other measures of safety.

Has been changed to:

The primary variables in this study are changes in the count of generalized spike-wave discharges and change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and partial evolving to secondarily generalized) from the Baseline Period to the Maintenance Period. The above variables reference partial seizures evolving to secondarily generalized seizures. While these partial seizures will be summarized as a part of the analysis, subjects must have a diagnosis of uncontrolled epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981) (see Section 17.1) to possibly be eligible for study participation. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Other variables to be assessed include measures of efficacy, plasma concentrations, and other measures of safety.

Change #5

Section 2 INTRODUCTION, last paragraph

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized (Type II) seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥2 years of age will be included in this study. Once the LCM dose range has been defined for subjects <2 years of age based on SP847, enrollment of subjects in this age group will begin in SP0966.

Has been changed to:

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes

associated with generalized (Type II) seizures in pediatric subjects ≥1 month to <18 years of age.

Change #6

Section 5.1 Study description, paragraphs 1 and 2

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age. Initially, only subjects ≥2 years of age will be included in this study. Once the LCM dose range has been defined for subjects <2 years of age based on confirmation of supportive PK, safety, and tolerability dosing data from SP847, enrollment of subjects in this age group will begin in SP0966.

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are also not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.

Has been changed to:

SP0966 is a Phase 2, multicenter, open-label exploratory study designed to assess the safety and preliminary efficacy of oral LCM as adjunctive therapy for epilepsy syndromes associated with generalized seizures in pediatric subjects ≥1 month to <18 years of age.

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible.

Change #7

Section 5.2 Schedule of study assessments, Table 5-1

Assessments
Head circumference

Has been changed to:

Assessments
Head circumference **(subjects <4 years)**

Change #8

Section 6.1 Inclusion criteria, criterion 3

3. Subject is male or female, ≥1 month to <18 years of age. (Note, until the LCM dose range has been defined in subjects <2 years of age based on SP847, only subjects ≥2 years of age will be enrolled.) For preterm infants <1 year old, the corrected gestational age should be used when determining eligibility. The generally accepted definition of corrected gestational age, which is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age, will be used for this study.

Has been changed to:

3. Subject is male or female, ≥1 month to <18 years of age. For preterm infants <1 year old, the corrected gestational age should be used when determining eligibility. The generally accepted definition of corrected gestational age, which is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age, will be used for this study.

Change #9

Section 6.2 Exclusion criteria, criterion 6

6. Subject has primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy.

Has been removed

Change #10

Section 6.2 Exclusion criteria, criterion 17

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

Has been changed to:

17. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second- or third-degree heart block or a corrected QT interval [QTc] greater than 450ms).

Change #11

Section 6.3 Withdrawal criteria, criterion 6

6. Subject develops a second degree AV block while awake or develops a third degree AV block.

Has been changed to:

6. Subject develops second- or third-degree AV block.

Change #12

Section 8.1.1 Visit 1 (Week -6) Screening Visit

- Head circumference.

Has been changed to:

- Head circumference **in subjects <4 years of age**.

Change #13

Section 8.3.4 Visit 9 (Week 18)/Early Termination Visit

- Head circumference.

Has been changed to:

- Head circumference **in subjects <4 years of age**.

17.6 Protocol Amendment 5

Rationale for the amendment

The present amendment has been issued to exclude subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy from the SP0966 study population. A confirmatory study (SP0982) to investigate the effect of LCM in this population is being conducted and, therefore, this population will not be included in SP0966.

As per the recommendations made by the USA FDA, the creatinine clearance has been changed from less than 50mL/min to less than 30mL/min.

In addition, minor administrative changes and edits were made.

Modifications and changes

Global changes

The following key changes were made throughout the protocol:

- Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy were excluded from the study population.
- Exclusion criterion for creatinine clearance rate has changed from <50mL/min to <30mL/min.
- Exclusion criterion number 20 has been reworded to clarify that the excluded sodium channelopathies are cardiac.
- Administrative changes: the name of the Study Physician and the name of the CRO have been updated, and the Sponsor Declaration has been updated for electronic signature.
- Russia has been removed as a participating country.

Specific changes

Change #1

SPONSOR DECLARATION

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.

Clinical Project Manager
[redacted]

_____
Date/Signature

Clinical Trial Biostatistician
[redacted]**, MA**

_____
Date/Signature

Study Physician
[redacted]**, MD**

_____
Date/Signature

Clinical Program Director
[redacted]**, BS**

_____
Date/Signature

Has been revised and moved to Section 19:

19. SPONSOR DECLARATION

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current GCP.

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:	

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]
Fax:	[redacted]

Change #3

Clinical Monitoring Contract Research Organization

Name:	PRA International
Address:	4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612 UNITED STATES
Phone:	+1 919 786 8200
Fax:	+1 919 786 8201

Has been changed to:

Name:	**PRA Health Sciences**
Address:	4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612 UNITED STATES
Phone:	+1 919 786 8200
Fax:	+1 919 786 8201

Change #4

Section 1 SUMMARY, paragraph 3

Approximately 50 subjects will be enrolled in this study across approximately 50 sites in Europe, Russia, and North America, and other regions as deemed necessary.

Has been changed to:

Approximately 50 subjects will be enrolled in this study across approximately 50 sites in Europe and North America, and other regions as deemed necessary.

Change #5

Section 5.1 Study description, Paragraph 2

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible.

Has been changed to:

Subjects should have a current diagnosis of epilepsy with generalized seizures (Type II) according to the International Classification of Epileptic Seizures (1981), see Section 17.1. The diagnosis should have been established by clinical history and an EEG with generalized spike-wave discharges. In addition to the Type II seizures, subjects with a current diagnosis of mixed seizure disorder(s), including both Type I and Type II seizures, are also eligible. Subjects with exclusively absence (Type IIA1) or atypical absence (Type IIA2) seizures are not eligible. **Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy are not eligible for this study as there is a confirmatory (Phase 3) study evaluating this seizure type.**

Change #6

Section 5.1.3 Anticipated regions and countries

This study will be conducted at approximately 50 sites in Europe, Russia, and North America, and other regions as deemed necessary.

Has been changed to:

This study will be conducted at approximately 50 sites in Europe and North America, and other regions as deemed necessary.

Change #7

Section 6.1 Inclusion criteria and Section 6.2 Exclusion criteria

Inclusion criterion 2

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

Has been changed to:

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

Exclusion criterion 6

The following exclusion criterion has been added:

6. **Subject has primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy.**

Exclusion criterion 15

15. Subject has impaired renal function (ie, creatinine clearance is lower than 50mL/min) at Visit 1.

Has been changed to:

15. Subject has impaired renal function (ie, creatinine clearance is lower than **3**0mL/min) at Visit 1.

Exclusion criterion 20

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

Has been changed to:

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

Change #8

Section 7.2 Treatment(s) to be administered

Table 7-1: Lacosamide dose titration during the Titration Period

Body weight category (formulation)	Flexible doses for the Titration Period by study week					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
<50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/ day	12mg/kg/ day
≥50kg (tablets/oral solution)	100mg/day	200mg/day	300mg/day	400mg/day	500mg/day	600mg/day

Note: Subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead.

Has been changed to:

Table 7-1: Lacosamide dose titration during the Titration Period

Body weight category (formulation)	Flexible doses for the Titration Period by study week					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
<50kg (oral solution)	2mg/kg/day	4mg/kg/day	6mg/kg/day	8mg/kg/day	10mg/kg/ day	12mg/kg/ day
≥50kg (tablets/oral solution)	100mg/day	200mg/day	300mg/day	400mg/day	500mg/day	600mg/day

LCM=lacosamide
Note: Subjects weighing ≥50kg who are unable or unwilling to swallow tablets can be dispensed LCM oral solution instead.

Change #9

Section 11.1.4 Follow up of AEs

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

Has been changed to:

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

Change #10

Section 11.4 Immediate reporting of AEs

The following AEs must be reported immediately:

Has been changed to:

The following AEs must be reported immediately **by the investigator to the sponsor**:

Change #11

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.

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 GCP 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 understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current GCP.

SP0966 Protocol Amendment 5

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	26-Feb-2015 19:13 GMT+01
	Clinical Approval	02-Mar-2015 19:36 GMT+01