PROTOCOL SP0982 AMENDMENT 5

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY FOR UNCONTROLLED PRIMARY GENERALIZED TONIC-CLONIC SEIZURES IN SUBJECTS WITH IDIOPATHIC GENERALIZED EPILEPSY

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
bid	twice daily
BP	blood pressure
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
CBCL	Child Behavior Checklist
CDMS	Clinical Data Management System
CL_{cr}	creatinine clearance
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DMC	data monitoring committee
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
EI-AED	enzyme-inducing antiepileptic drug
EQ-5D-3L	EuroQol-5 Dimension
ET	Early Termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HLA	Human leukocyte antigen
HRQoL	health-related quality of life
ICH	International Council for Harmonisation

IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
iv	intravenous
KM	Kaplan-Meier
LCM	lacosamide
LFT	liver function test
MAO-A	monoamine oxidase A
MRI	magnetic resonance imaging
PDILI	potential drug-induced liver injury
PedsQL™	Pediatric Quality of Life Inventory
PET	polyethylene terephthalate
PGTC	primary generalized tonic-clonic
PK	pharmacokinetic
PPS	Per Protocol Set
PS	patient safety
QC	quality control
QOLIE-31-P	Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	treatment emergent adverse event
TFL	tables, figures, and listings
ULN	upper limit of normal
VNS	vagus nerve stimulation

1 SUMMARY

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of oral lacosamide (LCM) (VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) twice daily [bid]) vs placebo as adjunctive therapy for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects ≥4 years of age with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant antiepileptic drugs (AEDs) independent of the number of prior failed AEDs (see Section 7.8).

Up to 250 subjects across 150 to 180 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

The maximum duration of study drug administration is 28 weeks. The study will last a maximum of 36 weeks per subject.

The study is comprised of the following: a 4-week Prospective Baseline Period and a 6-week (minimum) to 24-week (maximum) Treatment Period, which includes a 6-week Titration Period and an 18-week (maximum) Maintenance Period. Eligible subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 10 (Week 24) or the Early Termination (ET) Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period.

The primary study objective is to demonstrate the efficacy of oral LCM vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE taking 1 to 3 concomitant AEDs (See Section 7.8).

The primary efficacy variable is the time to the second PGTC seizure (also defined as an event) during the 24-week Treatment Period. Once the 125th event occurs, the study will have met its protocol-defined endpoint or milestone; all subjects will transition into EP0012 or taper off study medication.

The key secondary efficacy variable is seizure freedom for PGTC seizures for the 24-week Treatment Period, which will use a gatekeeping strategy to assess statistical significance (see Section 13.3.1). The other secondary efficacy variable is time to the first PGTC seizure during the Treatment Period.

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the investigator. Other safety variables are withdrawal due to AEs; incidence of new seizure types, increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period; and changes in physical and neurological examination findings; changes in hematology, chemistry, endocrinology, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; for pediatric subjects <18 years of age, safety will be evaluated using a behavioral assessment (Achenbach Child Behavior Checklist [CBCL]) and a cognitive function assessment (Behavior Rating Inventory of Executive Function® [BRIEF®]/Behavior Rating Inventory of Executive Function Preschool Version [BRIEF-P]).

The plasma concentrations of LCM will also be assessed.

2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated to affect almost 70 million people worldwide (Ngugi et al, 2011). Epileptic seizures occur in the context of a wide range of epilepsy syndromes that may be of genetic, structural/metabolic, or of unknown origin. The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic (23%), absence (6%), and myoclonic (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

Generalized seizures are those in which the first clinical changes indicate initial involvement of both brain hemispheres. Consciousness may be impaired and this impairment may be the initial manifestation. Motor manifestations are typically bilateral. Generalized seizures typically occur with idiopathic generalized (genetic) or symptomatic generalized epilepsy syndromes. Idiopathic generalized epilepsy is a category of disorders defined by strict clinical and electroencephalogram (EEG) features proposed by the International League Against Epilepsy (ILAE) classification of epileptic syndromes (ILAE, 1989). Clinical experience has shown that IGEs represent a heterogeneous condition in which many factors interact (such as age at onset, external factors, role of medications, and sleep) (Jallon and Latour, 2005). Idiopathic generalized epilepsies are assumed to have a genetic etiology and onset almost always occurs during childhood or adolescence, although there are exceptions; some patients develop these kinds of epilepsies after the second decade of life or, rarely, even later.

Treatment of PGTC seizures is complex because the patient population with PGTC seizures is heterogeneous, as PGTC seizures can occur as an isolated seizure type or in association with other generalized seizure types.

Although some forms of epilepsy 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). 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).

Between 15% and 40% of patients with generalized epilepsy remain refractory to therapy or do not tolerate the currently available AEDs used in this population (phenobarbital, valproate, ethosuximide, lamotrigine, topiramate, and levetiracetam) (Bartolomei et al, 1997; Verrotti et al, 2007); some of these AEDs can induce serious, life-threatening AEs (eg, aplastic anemia, rash, hepatic failure). Generalized tonic-clonic seizures may respond to drugs that aggravate typical absences and/or myoclonic jerks (Genton, 2000; Verrotti et al, 2007). Two IGE seizure types, typical absences and myoclonic seizures, are particularly prone to aggravation by certain AEDs (carbamazepine, vigabatrin, tiagabine, phenytoin, phenobarbital, and lamotrigine).

Lacosamide belongs to a novel class of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. 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 bid dose

regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) as monotherapy or adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 4 years of age and older. Lacosamide has also been approved in the US (oral tablets, oral solution [syrup], and solution for iv infusion) as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older. The safety and efficacy of LCM has been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures. Excluding blinded ongoing studies and indications not currently pursued, as of the data cutoff of 31 Aug 2016, 4938 subjects have been exposed to LCM in the clinical development program.

Preliminary recent safety and PK data suggest that the exposure-response in pediatric and adult subjects treated with LCM will be similar. Lacosamide has been evaluated in 3 completed pediatric studies; 2 studies in subjects aged 1 month to 17 years, and in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled partial-onset seizures. Subjects who completed the Maintenance Period were offered the opportunity to participate in the open-label extension study.

In addition, LCM is being evaluated in the following ongoing pediatric efficacy and safety studies:

- SP0967 (ages ≥1 month to <4 years) as adjunctive therapy in partial-onset seizures
- EP0034, open-label extension study to SP0967 and SP0969
- SP0966 (ages ≥1 month to <18 years) as adjunctive therapy, exploratory study in subjects with epilepsy syndromes associated with generalized seizures

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

Considering the significant unmet medical need for new treatment options for patients with IGE and PGTC seizures, the efficacy and tolerability profiles for LCM were evaluated in a series of animal models followed by a Phase 2 pilot study of subjects with IGE and uncontrolled PGTC seizures.

Lacosamide demonstrated significant seizure protection in animal models of seizures and epilepsy mimicking generalized epilepsy in humans. Of particular relevance for the PGTC indication are the anticonvulsant properties of LCM treatment obtained against generalized tonic-clonic seizures induced by a maximal electroshock in both mice and rats, and sound-stimulation in audiogenic seizure-susceptible mice. In these models, LCM treatment significantly protected against generalized tonic-clonic seizures. The elevation of seizure threshold by LCM following iv infusion of pentylenetetrazol in mice may also be indicative of a potential efficacy against myoclonic seizures, where LCM treatment significantly delayed time to first myoclonic seizure. However, LCM had no protective effect in animal models of absence seizures in the Genetic Absence Epilepsy Rat from Strasbourg model of absence epilepsy.

The Phase 2, multicenter, open-label, pilot study (SP0961) designed to assess the safety of adjunctive LCM (400mg/day) for uncontrolled PGTC seizures in subjects aged 16 to 65 years

with IGE is complete. The results of this pilot study showed reductions in PGTC and myoclonic seizure frequencies, with a small reduction in absence seizure frequency. A minority of subjects (~10%) in SP0961 showed an increase in absence seizures (reported as treatment-emergent adverse events [TEAEs]) that, in this uncontrolled study, these changes cannot be distinguished between the drug vs the natural course of the disease. The AE profile was similar to what has been observed with adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

The purpose of this study (SP0982) is to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day for pediatric subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for adult subjects [≥18 years of age] and pediatric subjects [<18 years of age] weighing ≥50kg) (see Table 7–3) for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary study objective is to demonstrate the efficacy of oral LCM (Table 7–3) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8).

3.2 Secondary objective

The secondary study objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures.

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable is the time to the second PGTC seizure during the 24-week Treatment Period.

4.1.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variable is:

- Time to the first PGTC seizure during the Treatment Period

4.1.3 Other efficacy variables

Other efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline)

- The percent change in PGTC seizure frequency per 28 days during the first 12 weeks of the Treatment Period relative to the Combined Baseline
- The percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline
- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Prospective Baseline
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the Titration Period compared to Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the first 12 weeks of the Treatment Period compared to Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the Treatment Period compared to Combined Baseline
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale

(Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age

- Change from Baseline to end of treatment or ET in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject due to epilepsy
- Number of days with help from a caregiver due to epilepsy

4.2 Safety variables

The safety variable is:

- AEs as reported spontaneously by the subject and/or caregiver or observed by the investigator.

Other safety variables are:

- Subject withdrawal due to AE
- Incidence of new seizure types during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Changes in hematology, chemistry, endocrinology, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings
- Behavioral assessment (Achenbach CBCL/1½-5 or CBCL/6-18) for pediatric subjects only
- Cognitive function assessment (BRIEF-P or BRIEF) for pediatric subjects only

4.3 Pharmacokinetic variable

The plasma concentrations of LCM will be assessed.

5 STUDY DESIGN

5.1 Study description

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM (see Table 7–3) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE currently taking 1 to

3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8). This study will also assess the safety, tolerability, and PK of LCM use in this population.

Up to 250 subjects across 150 to 180 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

The study will last a maximum of 36 weeks per subject. The study is comprised of the following: a 4-week Prospective Baseline Period and a 6-week (minimum) to 24-week (maximum) Treatment Period, which includes a 6-week Titration Period and an 18-week (maximum) Maintenance Period. Eligible subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 10 (Week 24) or the Early Termination (ET) Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period.

Eligibility to enter SP0982 will be based on a 12-week Historical Baseline prior to screening at Visit 1. In rare cases where there is a gap between consenting and Visit 1 procedures, the 12-week Historical Baseline will be calculated from the date of Informed Consent/Assent.

Prior to randomization, the following 3 criteria concerning PGTC seizure frequency must be met:

- The subject must have experienced at least 3 PGTC seizures during the 16-week Combined Baseline Period,
- The subject must have experienced at least 2 PGTC seizures during the 12-week Historical Baseline Period,
- Of the above seizures, at least 1 PGTC seizure should have occurred during the first 8 weeks and at least 1 PGTC seizure should have occurred during the second 8 weeks of the 16-week Combined Baseline Period.

Examples of different scenarios and the subjects´ eligibility in terms of Baseline Period seizures are presented in a table in Inclusion Criterion 5. A schematic diagram for the Combined Baseline Period seizure eligibility is provided in Figure 5-1.

At Visit 1, subjects and/or caregivers will be given a seizure diary to document all types of seizures, concomitant AEDs, and any other pertinent health status information. Seizure frequency and type eligibility will be verified by reliably documented seizure history collected (eg, in a seizure diary) 12 weeks prior to Visit 1. In addition, prior to Visit 1, subjects are required to have had an EEG showing discharges consistent with IGE (eg, generalized ≥3Hz epileptiform discharges and a normal EEG background). A confirmatory EEG may be performed during the Prospective Baseline, if approved by the Central Reviewer. Investigators will send a copy of the EEG report to the Central Reviewer. The report should include a detailed description of the background activity and abnormalities in the EEG as well as a clinical interpretation. The information provided will be reviewed and any questions regarding the subject's eligibility will be discussed with the investigator prior to the subject being randomized.

The Prospective Baseline begins with subject screening at Visit 1 (Week -4) and will last 4 weeks. Visit 1 will be conducted to evaluate subject eligibility for enrollment into the study. It is acceptable for this visit to be conducted on more than 1 day; although, it should not extend over a period longer than 7 consecutive days. Seizure count eligibility will be verified by data collected in a study seizure diary during the 4-week Prospective Baseline. Subjects and/or

caregivers will be contacted via telephone 2 weeks following Visit 1 to assess continued eligibility and will be reminded of the importance of accurate seizure diary completion. At Visit 2, subjects who complete the Prospective Baseline and meet all entry criteria except the minimum PGTC seizure criteria required for randomization (Baseline failures) may choose to enter EP0012. In this case, at the end of the Prospective Baseline, Visit 1 of EP0012 will be performed.

At the end of the Prospective Baseline (Visit 2), eligible subjects will be randomized to receive LCM or placebo (see Table 7–1) in a 1:1 fashion (active:placebo) and stratified by Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) and by age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age, and ≥18 years of age). The Treatment Period starts at the time of the Randomization Visit (Visit 2).

At the Randomization Visit (Visit 2) eligible subjects will complete the Visit 2 assessments and take the first dose of study drug at the clinic and enter a 6-week Titration Period. The recommended LCM (or matching placebo) dosing during the Titration Period to achieve the target Maintenance Period doses is provided in Table 7–1. All subjects should follow the recommended dosing schedule, unless dose adjustments based on tolerability are needed. Table 7–2 provides LCM (or matching placebo) dosing with flexibility based on tolerability during the Titration Period. During the Titration Period, subjects must achieve a target Maintenance Period dose range (see Table 7–3).

During the Maintenance Period, a single dose reduction of study drug or placebo is permitted as long as the minimum target dose is maintained (Table 7–3). No other dose reductions are allowed. If a dose reduction is required, an (un)scheduled visit, either telephone or clinic visit, is required. If the subject is not able to tolerate the study drug after 1 dose reduction, the subject must enter the Taper Period and be withdrawn from the study. All dose reductions should be discussed with the Medical Monitor. Once the dose has been reduced, it cannot be increased.

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures
- The 125th event occurs in the study. A second PGTC seizure is defined as an event.

Subjects who experience >2 PGTC seizures and who also complete ≥6 weeks (ie, ≥42 days) of the treatment period after randomization will be required to exit and complete the ET Visit (Section 6.3). The seizures may occur on the same day, but the initiation and completion of each individual seizure must be distinguishable allowing reliable counting of individual seizures.

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period or if the 125th event occurs in the study (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. The Final Clinic Visit is the same as Visit 1 of EP0012 (see Section 7.2.3). During the 4-week blinded transition, subjects receiving placebo during SP0982 will have their dose titrated to LCM (see Table 7–4).

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. Following the End of Taper Visit, there will be a 30-day Safety Follow-up Period (see Section 7.2.4). In case the 125th event occurs in the study, the subjects discontinuing treatment will complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. However, the End of Taper Visit will be the same as Visit 1 of EP0012. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

Unscheduled visits may be performed at any time after Visit 1 at the discretion of the investigator.

Schematic diagrams of the study are provided in Section 5.3.

5.1.1 Study duration per subject

The maximum duration of study drug administration is 28 weeks. The study will last a maximum of 36 weeks per subject, consisting of the following study periods:

- 4-week Prospective Baseline Period
- 6-week (minimum) to 24-week (maximum) Treatment Period (including a 6-week titration)
- 4-week End of Study Period consisting of either:
  - 4-week blinded transition (required for subjects participating in EP0012)
  - Up to 4-week blinded taper followed by a 30-day Safety Follow-up Period (required for subjects not participating in EP0012)
  - Subjects can enter EP0012 after the completion of Visit 10 (Week 24) or ET Visit and a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period (see Section 7.2.4).

Titration Period

In case the 125th event occurs in the study while subjects are still in their 6-week Titration Period, these subjects will not have to proceed to Week 6 prior to initiating the Transition/Taper Period; these subjects will also be invited for their ET Visit at the next scheduled visit.

Maintenance Period

In case the 125th event occurs in the study while subjects are in their Maintenance Period, these subjects will also be invited for their ET Visit at the next scheduled visit and enter the Transition/Taper Period.

Transition Period

In case the subject is in the Transition/Taper Period, these subjects will proceed to their scheduled completion visit.

Screening Period

In case the 125th event occurs while a subject is in screening, the subject may proceed to the scheduled Baseline Visit if they are eligible or are a Baseline failure; these subjects will be able to enter EP0012 and will not proceed to randomization in SP0982 but will enter EP0012. For the subjects entering EP0012, their next visit will be Visit 1.

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

5.1.2 Study completers

The following subjects will be considered study completers:

- Subjects who meet any of the predetermined exit criteria (Section 6.3)
- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period

Further information is provided in Section 6.3.

5.1.3 Planned number of subjects and sites

The number of screened subjects may vary according to the observed screen failure rate. Up to 250 subjects (100 to 125 per treatment arm) will be randomized to achieve a total of 125 events, where an event is defined as the occurrence of the second PGTC seizure.

Subjects will be randomized in the following age categories:

- (a) ≥4 years of age to <12 years of age
- (b) ≥12 years of age to <18 years of age
- (c) ≥18 years of age category

There will be approximately 150 to 180 sites in order to recruit the required subjects; additional sites will be added if deemed necessary. A target of at least 40 of the randomized subjects should consist of subjects <18 years of age.

5.1.4 Anticipated regions and countries

The study is planned to be conducted in the US, Europe, Asia, and Australia, with possible extension to other countries and regions.

5.2 Schedule of study assessments

The schedule of study assessments is provided in Table 5–1, Table 5–2, and Table 5–3.

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Assessments	Prospective Baseline 4 weeks			Treatment Period[a]											Unscheduled[b]
				6 to 24 weeks (maximum)											NA
				Titration Period (6 weeks)[e]					Maintenance Period (18 weeks)						
Visit[c]	V1[bb]	TC	V2[d]	TC[e]	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ET[f]	Visit
Study week	-4	-2		1	2	3	4	5	6	8	12	16	20	24	NA
Informed consent/assent	X														
Inclusion/Exclusion criteria	X	X	X												
Subject ID card dispensing	X														
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/Epilepsy history	X														
Physical exam (complete)[g]	X		X											X	
Physical exam (brief)[h]					X		X		X	X	X	X	X		
Neurological exam (complete)[i]	X		X											X	
Neurological exam (brief)[j]					X		X		X	X	X	X	X		
12-lead ECG[k]	X		X		X		X		X		X		X	X	
Vital signs (BP and pulse) including orthostatic assessments[l]	X		X		X		X		X	X	X	X	X	X	
Body weight	X		X		X		X		X	X	X	X	X	X	
Height	X													X	
EEG[m]	X														
Tanner Stage[n]			X											X	
Laboratory tests:															
Chemistry/hematology	X		X		X				X		X		X	X	
Endocrinology[aa]			X											X	
Urinalysis[o]	X		X		X				X		X		X	X	
Pregnancy test[p]	X		X		X		X		X	X	X	X	X	X	
LCM plasma concentration[q]									X					X	
Contact IRT[r]	X		X		X		X		X	X	X	X	X	X	X
Randomization			X												
Dispense subject diary[s]	X		X		X		X		X	X	X	X	X	X	
Subject diary return/review[s]			X		X		X		X	X	X	X	X	X	
Dispense study drug[t]			X[u]		X		X		X	X	X	X	X	X	
Study drug review/return					X		X		X	X	X	X	X	X	
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Assessments	Prospective Baseline 4 weeks			Treatment Period[a]											Unscheduled[b]
				6 to 24 weeks (maximum)											NA
				Titration Period (6 weeks)[e]					Maintenance Period (18 weeks)						
Visit[c]	V1[bb]	TC	V2[d]	TC[e]	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ET[f]	Visit
Study week	-4	-2		1	2	3	4	5	6	8	12	16	20	24	NA
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Achenbach CBCL[v]			X											X	
BRIEF-P/BRIEF[w]			X											X	
EQ-5D-3L[x]			X											X	
QOLIE-31-P/PedsQL[y]			X											X	
C-SSRS[z]	X		X		X		X		X	X	X	X	X	X	
Healthcare resource use			X		X		X		X	X	X	X	X	X	
Work/school days lost due to epilepsy			X		X		X		X	X	X	X	X	X	
Days with help from a caregiver due to epilepsy			X		X		X		X	X	X	X	X	X	
Socio-professional data			X		X		X		X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; bid=twice daily; BP=blood pressure; exam=examination; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EEG=electroencephalogram; EQ-5D-3L=EuroQol-5D; ET=Early Termination; ID=identification; IEC=Independent Ethics Committee; IGE=idiopathic generalized epilepsy; IRB=Institutional Review Board; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; PEDsQL=Pediatric Quality of Life Inventory; PGTC=primary generalized tonic-clonic; QOLIE-31-P=Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31; TC=telephone contact; V=Visit

[a] The Treatment Period starts at the time of the Randomization Visit (Visit 2). The Treatment Period continues until 1 of the following occurs (whichever occurs first): completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures, or completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or TCs, at the discretion of the investigator. In addition to the required assessments indicated above, depending on the type of visit (clinic or telephone), further assessments can be completed as needed and may include ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed (for subjects ≥6 years of age) if the unscheduled visit is due to an AE.

[c] A window of ±2 days relative to Visit 1 is applicable for all protocol specified visits and TCs. During the Treatment Period, each visit should occur at the end of the week indicated in accordance with this time window.

[d] All assessments at Visit 2 should be conducted prior to the first dose of study drug. At the end of the Prospective Baseline, subjects will be randomized at Visit 2 to receive LCM or placebo in a 1:1 fashion (active:placebo) and commence the Treatment Period with a 6-week, double-blind, flexible dose titration (see Section 7.2.1).

[e] Subjects and/or caregivers will receive TCs throughout titration (Study Weeks 1, 3, and 5) to discuss titration dosing options.

[f] Once the subject has experienced 2 PGTC seizures, the site may contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure (Section 6.3).

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

[h] The brief physical examination will include review of the following body systems: cardiovascular, pulmonary, abdominal (hepato-gastrointestinal), and dermatologic.

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

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

[k] The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

[l] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

[m] Subjects are required to have had an EEG showing discharges consistent with IGE prior to Visit 1. A confirmatory EEG may be performed during the Prospective Baseline, if approved by the Central Reviewer. Investigators will send a copy of the EEG report to the Central Reviewer. The information provided will be reviewed and any questions regarding the subject's eligibility will be discussed with the investigator prior to the subject being randomized.

[n] The Tanner Stage will be performed only for subjects who are pubescent at Visit 2 or who enter puberty during the course of the study.

[o] Urinalysis will be required for all subjects.

[p] Serum pregnancy tests will be conducted at the following visits: Visit 1, Visit 10/ET Visit. At Visit 2, a urine dipstick pregnancy test should be performed prior to IRT contact. The result of the urine dipstick test must be negative prior to administration of the first dose of study drug. All other pregnancy tests (ie, Visits 3 through Visit 9) will be urine dipstick. Pregnancy tests will be performed for female subjects of childbearing potential only.

[q] Blood samples for analysis of LCM plasma concentrations will be collected at any time between 2 successive bid doses.

[r] An IRT will be used to control all drug distribution and inventory for this study.

[s] At all visits, subjects and/or caregivers will be reminded to report the occurrence of all seizure types, including days without seizures.

[t] During the Maintenance Period, a single dose reduction is allowed as long as the minimum target dose is maintained (see Table 7–3). Once the dose has been reduced, it cannot be increased. Subjects who are not able to tolerate the minimum target dose during the Maintenance Period will be withdrawn from the study. All dose reductions should be discussed with the Medical Monitor.

[u] At Visit 2, subjects should take the first dose of study drug in the clinic.

[v] The Achenbach CBCL/1½-5 is for children <5 years and 11 months of age and the CBCL/6-18 is for children ≥6 years to <18 years of age; the questionnaire is 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.

[w] The BRIEF-P should be used for subjects who are <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.

[x] The EQ-5D-3L will be performed in subjects who are ≥12 years of age.

[y] The QOLIE-31-P will be performed for subjects who are ≥18 years of age and the PedsQL will be performed for subjects <18 years of age. The version of the PedsQL used should be consistent with the subject's age at Visit 2 and should be maintained for each subject for the duration of the study.

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

[aa] Thyroid function will be required in subjects <18 years of age only.

[bb] Participation in the study starts from the time of signing the approved Informed Consent/Assent form. However, sites may conduct prescreening EEGs and prior to this, subjects will read and sign a separate Informed Consent form that has been approved by an IRB/IEC and the Sponsor, and which complies with regulatory requirements.

Table 5–2: Schedule of study assessments for SP0982 (Transition Period)

Assessment	Transition Period (4 weeks)[a]	
	Transition TC or Visit[b]	Final Clinic Visit (EP0012 Visit 1)
	2 weeks after Visit 10/ET	
Concomitant medications and AED(s)	X	X
Body weight		X
Height		X
Physical exam (complete)[d]		X
Neurological exam (complete)[e]		X
12-lead ECG[f]		X
Vital signs (BP and pulse) including orthostatic assessments[c]		X
Laboratory tests:		
Chemistry/hematology		X
Urinalysis[i]		X
Endocrinology[k]		X
Pregnancy test[j]		X
Contact IRT		X
Subject diary return/review[g]		X
Study drug review/return		X
Withdrawal criteria	X	X
AE reporting	X	X
C-SSRS[h]		X
Healthcare resource use		X
Work/school days lost due to epilepsy		X
Days with help from a caregiver due to epilepsy		X
Socio-professional data		X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Early Termination; IRT=interactive response technology; TC=telephone contact

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

[a] At the end of Visit 10/ET, subjects who complete the study may be eligible to participate in an open-label extension study (EP0012). Subjects who choose to enroll in the open-label extension study will proceed to a blinded 4-week Transition Period.

[b] A Transition TC is required. A Transition Clinic Visit is optional, at the discretion of the investigator. Subjects requiring a clinic visit will have the same assessments conducted as an Unscheduled Visit.

[c] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

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

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

[f] The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

[g] The subject diary will be dispensed at Visit 1. At all subsequent visits, subjects and or caregivers will be reminded to report the occurrence of all seizure types, including days without seizures.

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

[i] Urinalysis will be required for all subjects.

[j] Urine pregnancy tests will be performed for female subjects of childbearing potential only.

[k] Thyroid function will be required in subjects <18 years of age only.

Table 5–3: Schedule of study assessments for SP0982 (Taper Period and Safety Follow-up Period)

Assessment	Taper Period[a] (up to 4 weeks)	Safety Follow-up Period[c]	
		Safety Follow-up Visit	Safety Follow-up TC
	End of Taper Visit[b]	2 weeks (±2 days) after last dose of study drug	30 days (-1/+3 days) after last dose of study drug
Concomitant medications and AED(s)	X	X	X
Physical exam (complete)[k]	X	X	
Neurological exam (complete)[l]	X	X	
12-lead ECG[h]	X	X[i]	
Vital signs (BP and pulse) including orthostatic assessments[j]	X	X	
Body weight	X	X	
Laboratory tests:			
Chemistry/hematology	X	X[i]	
Endocrinology[m]		X[i]	
Urinalysis[f]	X	X	
Pregnancy test[g]	X	X	
Contact IRT	X		
Subject diary return/review[d]	X		
Study drug review/return	X		
Withdrawal criteria	X		
AE reporting	X	X	X
C-SSRS[e]	X	X	
Healthcare resource use	X	X	
Work/school days lost due to epilepsy	X	X	
Days with help from a caregiver due to epilepsy	X	X	
Socio-professional data	X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IRT=interactive response technology; TC=telephone contact

[a] Subjects completing Visit 10 (Week 24) or the ET Visit who choose not to continue in EP0012 must complete a blinded taper followed by the End of Taper Visit.

[b] An End of Taper Visit will be scheduled at the end of the Taper Period (up to 4 weeks) depending on dose level achieved; see Table 7–5. Of note, for subjects who enter the Taper Period at ≤2mg/kg/day (oral solution) or 100mg/day (tablets), the End of Taper Visit will take the place of the ET Visit.

[c] There will be a 30-day (-1/+3 days) Safety Follow-up Period for subjects who complete the End of Taper Visit. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed 2 weeks later by a TC. After the 125th event occurs, the 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

[d] The last subject diary will be returned at the End of Taper Visit.

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

[f] Urinalysis will be required for all subjects.

[g] Urine pregnancy tests will be performed for female subjects of childbearing potential only.

[h] The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[j] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

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

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

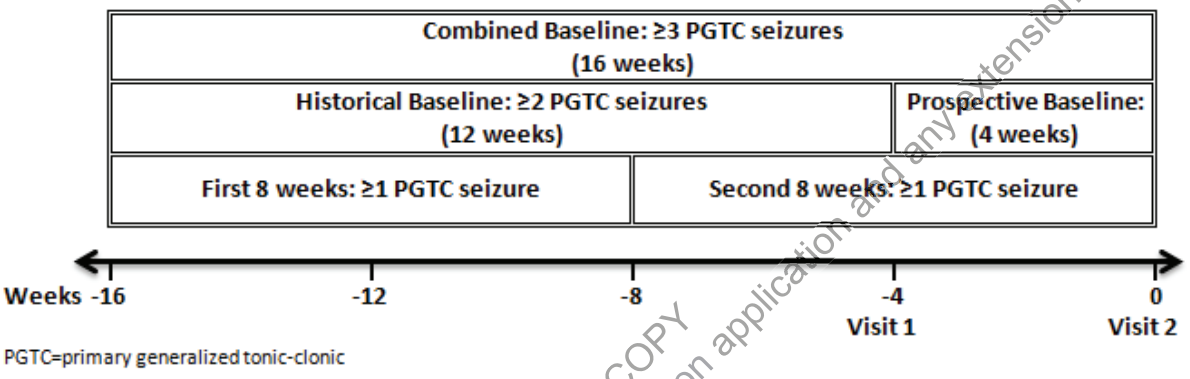
[m] Thyroid function will be required in subjects <18 years of age only.

5.3 Schematic diagrams for SP0982

The schematic diagram for the Combined Baseline Period eligibility is provided in Figure 5-1.

A schematic diagram for the Prospective Baseline Period through the Taper Period with successive panels for pediatric subjects weighing <30kg, pediatric subjects weighing ≥30kg to <50kg, and adult subjects and pediatric subjects weighing ≥50kg is provided in Figure 5–2. The schematic diagram for the Transition Period is provided in Figure 5–3.

Figure 5-1: Combined Baseline Period seizure eligibility for SP0982



PGTC=primary generalized tonic-clonic

Figure 5–2: SP0982 Prospective Baseline Period through the Taper Period schematic diagram

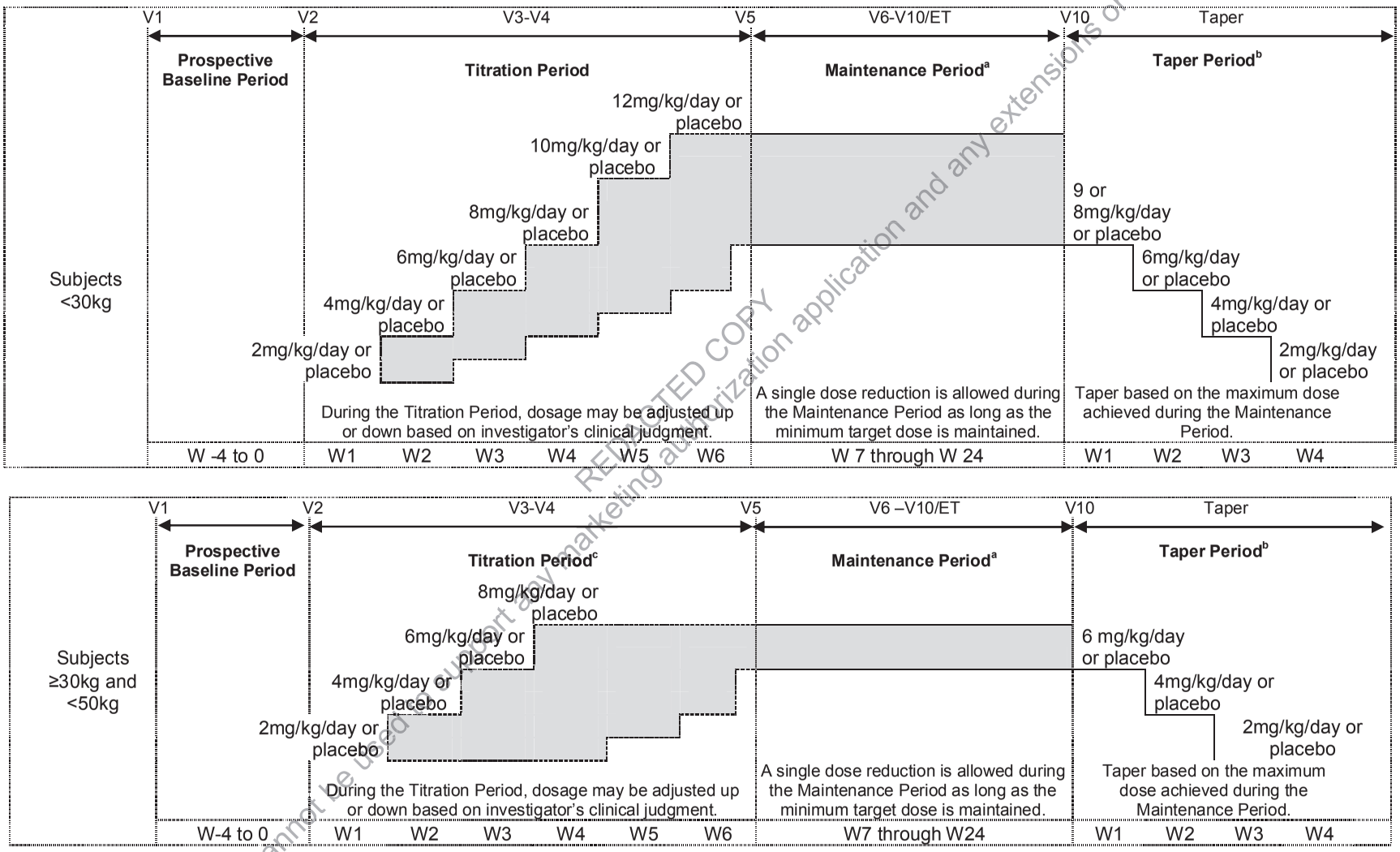
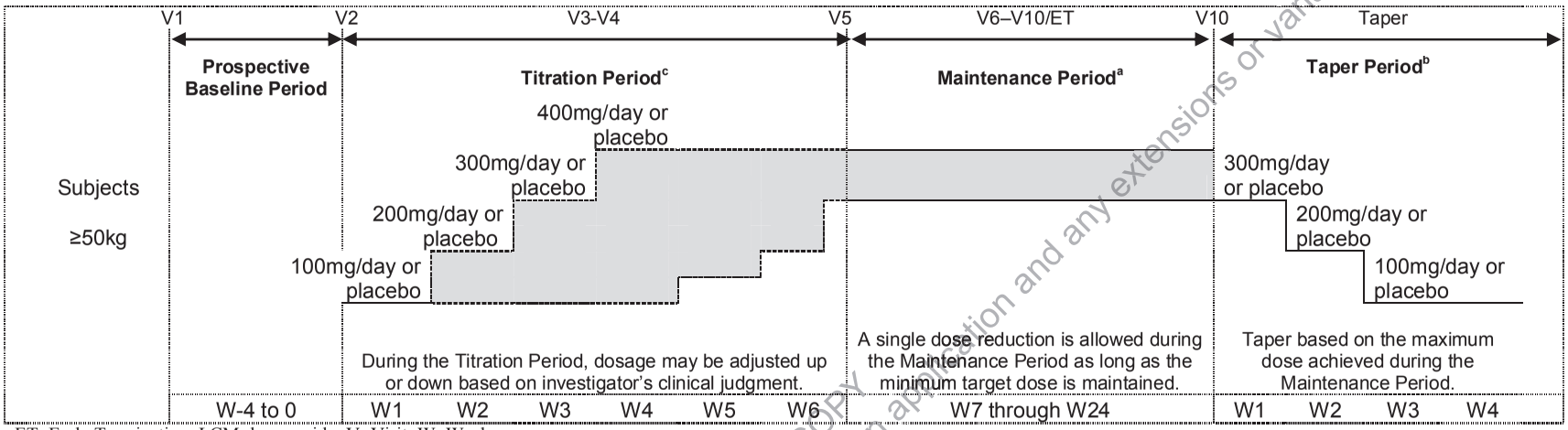


Figure 5–2: SP0982 overall schematic diagram



ET=Early Termination; LCM=lacosamide; V=Visit; W=Week

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

[a] Subjects will be required to achieve and maintain a minimum LCM (or matching placebo) dose for at least the final 3 days of Week 6 to be eligible for entry into the Maintenance Period.

[b] If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit. There will be a 30-day Safety Follow-up Period for subjects who complete the End of Taper Visit. After the 125th event occurs, the 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

[c] If the subject is in the Titration Period when the 125th event occurs, the subject will proceed to the Transition/Taper period directly after their ET/V10 Visit.

Figure 5–3: SP0982 Transition Period schematic diagram

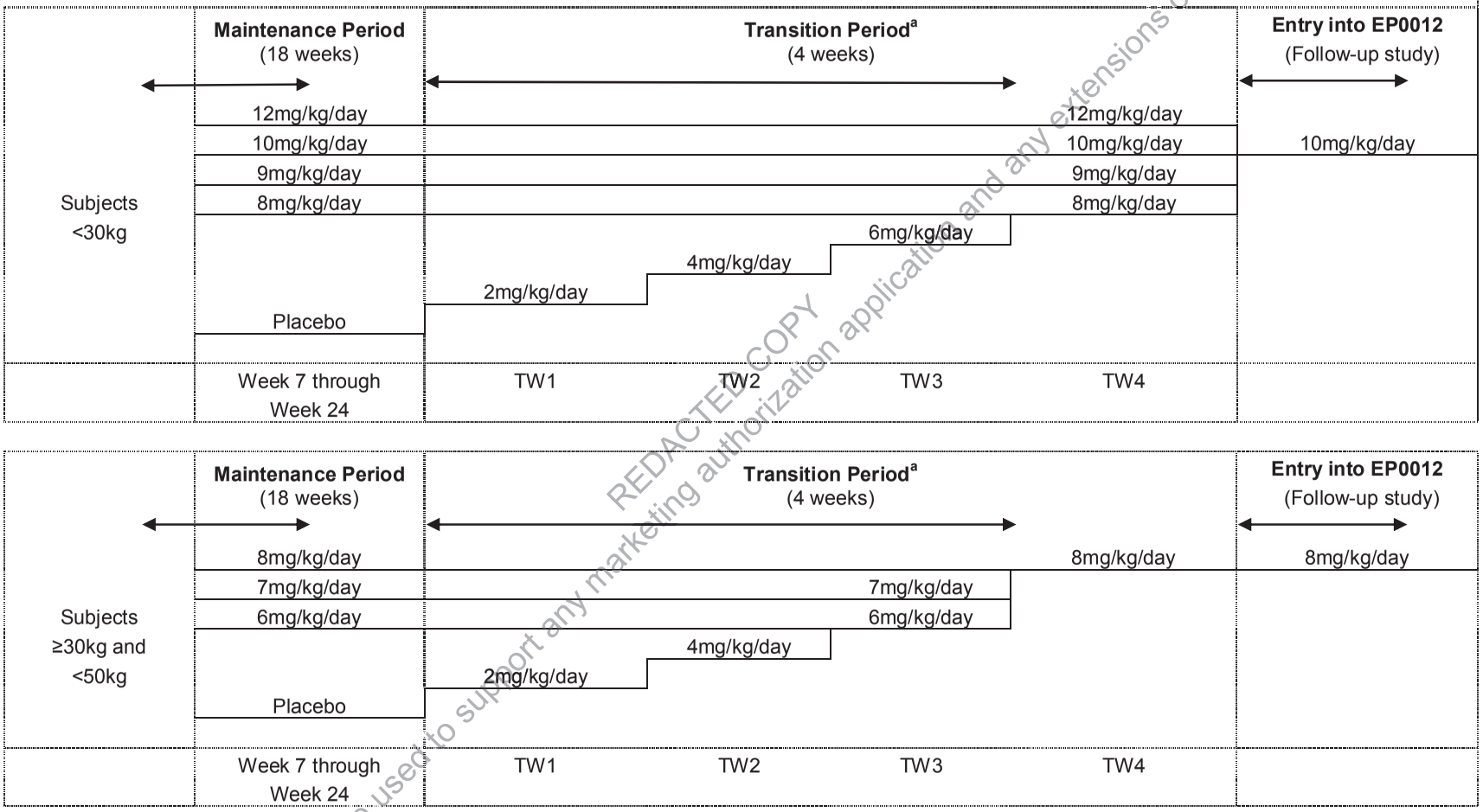
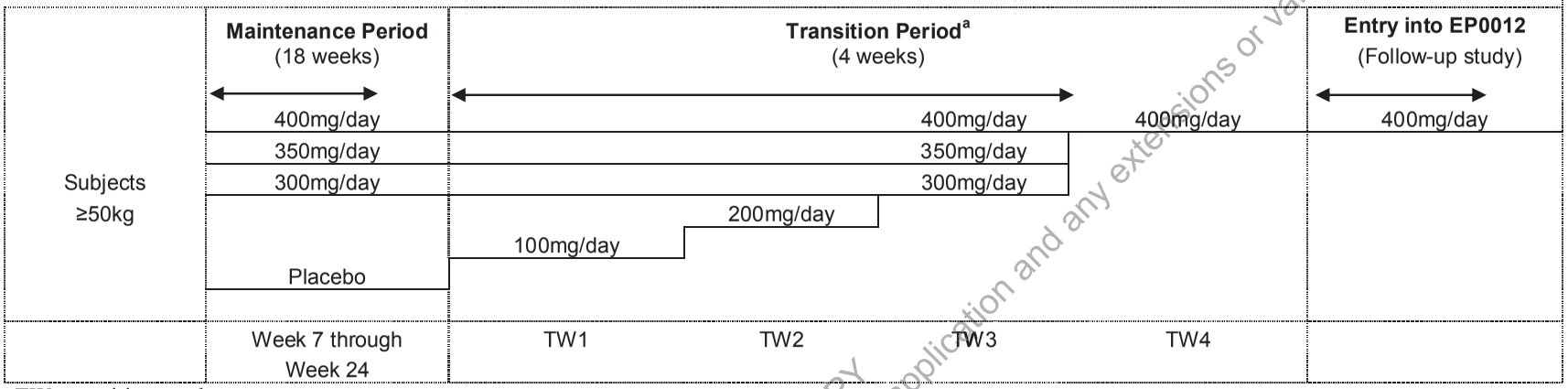


Figure 5–3: SP0982 Transition Period schematic diagram



TW=transition week

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

[a] If a subject is in the Titration Period and the next scheduled visit after the 125th event is not until Week 6, the subject will enter the Transition/Taper Period, and the escalation will be adapted accordingly.

5.4 Rationale for study design and selection of dose

Clinical experience has shown that up to 30% of patients with PGTC seizures who are treated with currently available AEDs have insufficient seizure control or unacceptable drug tolerability. Thus, there is a significant unmet medical need for new treatment options in this patient population.

In 3 primary efficacy studies (SP667, SP754, and SP755), adjunctive LCM treatment has demonstrated efficacy and was well tolerated in the treatment of secondary generalized seizures in subjects with uncontrolled partial-onset seizures. In these studies, LCM dose titration was initiated at 100mg/day (in 2 divided doses) and escalated to the randomized dose (LCM 200mg/day, LCM 400mg/day, or LCM 600mg/day) in 100mg/day per week increments. These 3 primary efficacy studies were the basis of the approval of LCM as adjunctive therapy in the treatment of partial-onset seizures in subjects 16 years and older in the EU and 17 years and older in the US, with an established therapeutic dose range of 200mg/day to 400mg/day.

Additionally, the safety of LCM in subjects (16 to 65 years of age) with uncontrolled PGTC seizures with IGE was assessed in a clinically complete, Phase 2, multicenter, open-label, pilot study (SP0961). In this study, LCM dose titration was initiated at 100mg/day (in 2 divided doses) and increased to a maximum dose of LCM 400mg/day at weekly increments, as deemed clinically appropriate. Although evaluation of changes in PGTC seizure frequency was not intended for evaluation of efficacy, an assessment was made for exploratory purposes and a reduction in PGTC seizure frequency was observed. In addition, the AE profile was similar to that observed with adjunctive LCM for the treatment of subjects with partial-onset seizures, with the exception of seizure-related AEs.

5.4.1 Rationale for dose

For adult subjects, the LCM 100mg/day dose was selected to be the starting dose for this study to ensure a safe and well-tolerated up-titration scheme. The LCM 400mg/day maintenance dose was well tolerated and demonstrated efficacy in 3 primary efficacy studies as adjunctive therapy in subjects with partial-onset seizures. In SP0961 (the Phase 2 pilot study) and SP0962 (the open-label extension study) in subjects with uncontrolled PGTC seizures with IGE, the 400mg/day dose was also well tolerated. Generally, the doses of AEDs used for the treatment of partial-onset seizures are similar to those used to treat generalized seizures. Thus, the 300mg/day to 400mg/day target dose range is considered the optimal maintenance dose for the population with uncontrolled PGTC seizures with IGE.

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 pediatric dosing recommendations for SP0982 are to achieve LCM plasma concentrations similar to the average steady-state LCM plasma concentration reached after a LCM 400mg/day dose administration in adult studies.

A population PK model (CL0177) was developed using plasma concentration data and demographic information from all pediatric subjects in SP847 and SP1047. The data consisted of 402 LCM plasma concentration-time records obtained in 79 children, with a balanced distribution of 14, 22, 25, and 18 subjects in the age groups 6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years, respectively. Body weights ranged from 6kg to 76kg.

Different pediatric dosing adaptation schemes were simulated with the aim of reaching the range of average steady-state plasma concentration ($C_{SS,ave}$) obtained in adults receiving LCM 400mg/day, which is approximately 8µg/mL (90% prediction interval: 5µg/mL to 12µg/mL). This was achieved with a dosing scheme of 12mg/kg/day in children weighing <30kg, 8mg/kg/day in children weighing from 30kg to <50kg, and 400mg/day in children weighing ≥50kg. The proportional pediatric dose adaptation corresponding to 300mg/day in adults and in children weighing ≥50kg, are 8mg/kg/day in children weighing <30kg, and 6mg/kg/day in children weighing from 30kg to <50kg.

5.4.2 Rationale for second PGTC seizure

The primary efficacy variable, the time to the second PGTC seizure, has several advantages from a clinical and methodological perspective. In traditional adjunctive study designs, the primary endpoint is percent reduction in seizure frequency over the entire Treatment Period; which requires a higher frequency of seizures at entry. Using the time to second seizure, the frequency of Baseline seizures and the duration of the Prospective Baseline can be reduced as the endpoint is time to reach an event (second seizure), rather than a percentage decrease in the number of events (seizures). This expands the patient population under study and allows for enrollment of subjects more representative of the broader PGTC seizure population. Furthermore, subjects are treated for up to 24 weeks in a traditional adjunctive design, depending upon the titration schedule of the active treatment. Subjects must remain on treatment as they continue to experience seizures. In the time to n^{th} seizure design, subjects are required to remain in the study for a minimum of 6 weeks. If a subject experiences ≥2 seizures while on treatment, then after 6 weeks the subject exits the study, rather than continuing to have PGTC seizures, while remaining eligible to receive LCM in the open-label extension study (EP0012).

The rationale for time to second seizure was established by using data from an adjunctive study in subjects with PGTC seizures, using an 8-week Baseline, 7-week Titration, and 12-week Maintenance Period comparing lamotrigine and placebo (French et al, 2007). This posthoc analysis using a Cox proportional hazards model revealed that time to third seizure was statistically significant with a hazard ratio of 0.533 (lamotrigine 48.2%, placebo 25.4%). Lamotrigine requires a long Titration Period, where a minimally effective dose is not reached until the fifth week of the Titration Period (100mg/day). Lacosamide, by comparison, reaches a minimally effective dose in the second week (200mg/day) for a majority of trial subjects. Since a majority of the events in the lamotrigine study occurred before Day 21, it is likely that fewer events would occur using LCM as it reaches an effective dose earlier; therefore, time to second seizure was chosen as a reasonable endpoint from a clinical and statistical perspective.

5.4.3 Rationale for minimum duration of treatment

The minimum duration of the Treatment Period for each subject will be 6 weeks. There are 3 reasons for the requirement of a minimum Treatment Period duration:

- To collect a minimum of placebo-controlled safety data for the entire study population
- To allow for the analysis of reduction in seizure days for non-PGTC seizures (eg, absence or myoclonic seizures)
- To allow for increased flexible dosing during titration

Primary generalized tonic-clonic seizures are sparse but severe clinical events that profoundly affect the lives of patients. Should the minimum duration of the study be longer (eg, 12 weeks), this would prolong the time subjects randomized to placebo (or subjects randomized to LCM who do not respond to the treatment) have to stay on a nonefficacious treatment. By allowing subjects to exit the study after completing 6 weeks of the Treatment Period, sufficient double-blind safety data can be collected from a high proportion of subjects to be meaningful. Moreover, additional safety data will be available from the open-label, long-term, extension study (EP0012).

5.4.4 Rationale for selected age range

Idiopathic generalized epilepsies are assumed to have a genetic etiology and onset almost always occurs during childhood or adolescence, although there are exceptions; some patients develop these kinds of epilepsies after the second decade of life or, rarely, even later.

There are a number of different epilepsy syndromes within the group of IGEs. Patients with the most common IGE syndromes (ie, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand mal seizures on awakening) may experience generalized tonic-clonic seizures. Onset of these syndromes normally occurs during childhood and adolescence.

The ≥4-year age cutoff was established based on the difficulty of establishing a clear diagnosis of IGE in younger subjects with PGTC seizures. This is further supported by epidemiology data, which indicates that the incidence and prevalence of generalized epilepsies is lower in preschoolers compared to older children (Olafsson et al, 2005).

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent/Assent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.
3. Male and female subjects ≥4 years of age.
4. Subject with a confirmed diagnosis at least 24 weeks prior to Visit 1 and a disease onset prior to 30 years of age, consistent with IGE experiencing PGTC seizures (Type IIE) that are classifiable according to the ILAE Classification of Epileptic Seizures (ILAE, 1981).
5. Subject has ≥3 PGTC seizures during the 16-week Combined Baseline (12-week Historical Baseline plus 4-week Prospective Baseline) distributed as described below:
   - at least 3 PGTC seizures should have occurred during the 16-week Combined Baseline Period,

– at least 2 PGTC seizures should have occurred during the 12-week Historical Baseline Period,

– of the above seizures, at least 1 PGTC seizure should have occurred during the first 8 weeks and at least 1 PGTC seizure should have occurred during the second 8 weeks of the 16-week Combined Baseline Period.

The schematic diagram for the Combined Baseline Period eligibility is provided in Figure 5-1. Examples of PGTC seizure frequency and eligibility are provided in the table below:

Number of PGTC seizures			**Is subject eligible?** (In terms of Inclusion Criterion 5)
Historical Baseline Weeks -16 to -8	**Historical Baseline Weeks -8 to -4**	**Prospective Baseline Weeks -4 to 0** (Visit 1 to Visit 2)	
2	1	0	Yes
3	0	0	No*
1	1	1	Yes
0	2	1	No
1	2	0	Yes
2	0	1	Yes
1	0	2	No
1	1	0	No*

Screening Visit

*Eligible to roll over to EP0012 if all other inclusion criteria are also met.
PGTC=primary generalized tonic-clonic

6. If a brain magnetic resonance imaging (MRI)/computed tomography (CT) scan has been performed, there must be no evidence of any progressive abnormality or any lesion likely to be associated with partial-onset seizures.

7a. Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs with no benzodiazepine AEDs **OR** 1 benzodiazepine marketed AED with 1 to 2 non-benzodiazepine marketed AEDs (see examples in the table below) for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS (see Section 7.8).

Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

Benzodiazepine AEDs	Non-Benzodiazepine AEDs	Total AEDs	Is subject eligible? (In terms of Inclusion Criterion 7)
0	1	1	Yes
0	2	2	Yes
1	1	2	Yes
1	2	3	Yes
1	0	1	**No**
0	3	3	**No**
2	1	3	**No**

AED=antiepileptic drug

8. Subjects are required to have had an EEG report consistent with IGE (eg, generalized ≥3Hz epileptiform discharges and a normal EEG background) confirmed by a Central Reviewer.

6.2 Exclusion criteria

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

1. Subject has previously been randomized in this study or subject has previously been assigned to treatment in a clinical study of LCM.
2. Subject has participated in another study of an investigational medicinal product (IMP) or an experimental medical device within the last 30 days or is currently participating in another study of an IMP or a medical device.
3. Subject has a history of partial-onset seizures or EEG findings indicative of partial-onset seizures.

4a. Subject has symptomatic generalized epilepsy ([ILAE, 1989] (eg, Lennox-Gastaut Syndrome typically presenting with seizures including tonic seizures), some other related syndrome like Doose's syndrome (typically presenting with myoclonic-atonic seizures), or evidence of both focal and generalized epilepsy.

5. Subject has a history of convulsive status epilepticus 1 year prior to screening.
6. Subject has a current or previous diagnosis of pseudoseizures, conversion disorders, or other nonepileptic ictal events which could be confused with seizures.
7. Subject has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate in this study.
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.
9. Subject has a known hypersensitivity to any components of the investigational product(s).

10. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
11. Subject has multiple drug allergies or severe drug allergy.
12. Subject has any history of alcohol, opioid, or other drug use disorder, as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), within the previous 2 years.

    Note: previous sporadic cannabis use is not exclusionary as long as subject is requested and agrees not to use cannabis during the study.
13. Subject has an acute or sub-acutely progressive central nervous system disease.
14. Subject with a known history of severe anaphylactic reaction or serious blood dyscrasias.
15. At Visit 1, subject has ≥2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

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

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

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes re-screening.
16. Subject has impaired renal function (ie, creatinine clearance [CLcr] is <30mL/min) at Screening (see Section 10.2).
17. Subject has a known cardiac channelopathy, such as Brugada syndrome.
18. Subject has sick sinus syndrome without a pacemaker, or second- or third-degree atrioventricular (AV) block, or subject has any other clinically significant ECG abnormalities.
19. Subject has experienced a myocardial infarction in the last 3 months prior to Visit 1.

20. Subject has New York Heart Association Class III or Class IV heart failure.

New York Heart Association Criteria:	
Class I	Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association, 1994

21. Female subject who is pregnant or nursing and/or a woman of childbearing potential who is not surgically sterile, 2 years postmenopausal, or does not practice 1 highly effective method of contraception (according to International Council for Harmonisation [ICH] guidance, defined as those that result in a failure rate of <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, 2 years postmenopausal, 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 taking 1 or more of the following medications on a regular basis within 28 days prior to Visit 1: monoamine oxidase A (MAO-A) inhibitors, barbiturates (for indications other than epilepsy), or clozapine.

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 <12 months are excluded. Subjects treated with felbamate for ≥12 months prior to Visit 1 and who have not experienced serious toxicity issues are eligible.

24. Subject has taken vigabatrin in the preceding 6 months. Note: A subject with a history of vigabatrin treatment must have had a visual perimetry test at least 6 months following conclusion of treatment. The results of the visual perimetry test must have shown either no damage or a visual field defect associated with 1 of the following 2 conditions: 1) there was no change from a visual field test done at some point while the subject was taking vigabatrin, or 2) there was no change from a visual field test done shortly after stopping vigabatrin administration.

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

Subjects may be rescreened with prior consultation and permission of the Medical Monitor. If the investigator has any doubts concerning the subject's eligibility, he/she should consult the UCB Study Physician or representative for clarification.

6.3 Exit criteria

Subjects will be required to exit the study if either of the following events occurs:

- Subject completes the first 6 weeks of the Treatment Period (after randomization) and experiences ≥2 PGTC seizures during that time
- Subject experiences a second PGTC seizure after the first 6 weeks of the Treatment Period
- The 125th event occurs in the study

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within **1 week** of the subject's second seizure, with the following exception: if the 2 PGTC seizures occur during the first 6 weeks of the Treatment Period (after randomization), the subject should continue the Titration Period visits and wait for the end of the first 6 weeks of the Treatment Period to complete the ET Visit.

6.4 Withdrawal criteria

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

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

- The subject is unable to attain at least the minimum Maintenance Period target dose (Table 7–3).
- The subject requires a subsequent dose increase after dose reduction during the Maintenance Period or the subject requires more than 1 dose reduction during the Maintenance Period.
- Subject develops a second- or third-degree AV block.
- The subject becomes pregnant, as evidenced by a positive pregnancy test.
- The sponsor or a regulatory agency requests withdrawal of the subject.
- The subject is unwilling or unable to continue and withdraws consent.
- In the case of liver function test (LFT) results of transaminases (AST and/or ALT) ≥3xULN to <5xULN and total bilirubin ≥2xULN or transaminases (AST and/or ALT) ≥5xULN, 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 more than 1 week later.
- Subject ≥6 years of age 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:

- The subject requires a medication that is not permitted.
- The subject requires a modification to concomitant AED dose(s) during the study (see Section 7.8).
- The subject is unable to manage the completion of the diary, demonstrates a questionable diary, or is noncompliant with the study procedures or medications in the opinion of the investigator.
- An episode of status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new seizure type considered by the investigator to require intervention.
- Subject develops a clinically relevant change in medical condition (or ECG or laboratory parameter) as determined by the investigator, and the investigator feels it is in the interest of the subject to withdraw.
- Subject develops an intolerable AE during the course of the study.
- Discontinuation criteria for potential drug-induced liver injury (PDILI) are described in Section 6.4.1.

Investigators should attempt to obtain information on subjects, in the case of withdrawal. For subjects considered as lost to follow up, the investigator should make 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.

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

6.4.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with PDILI must be assessed to determine if IMP must be immediately and permanently discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

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

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

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

Evaluation of PDILI must be initiated as described in Section 10.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal product

Investigational medicinal product will be provided as LCM oral solution (syrup) (LCM 10mg/mL), LCM tablets (LCM 50mg), and matching placebos.

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

The LCM 50mg tablets and matching placebo are white, oval tablets debossed with "SP" on one side. Tablets will be packaged in high-density polyethylene (HDPE) bottles.

7.2 Treatments to be administered

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

At Visit 2, subjects will be randomized to receive either LCM (oral solution for pediatric subjects [≥4 to <18 years of age] weighing <50kg or tablets for adult subjects [≥18 years of age] and pediatric subjects weighing ≥50kg) or matching placebo. At the end of Visit 2, subjects should take the first dose of study drug while in the clinic. Treatment assigned will be determined by the subject's weight at Visit 2.

Tablets are 50mg and **must not be broken**; instead unequal dosing is allowed – if subjects are taking an odd number of tablets per day (eg, 7 tablets totaling 350mg), they should take the lower dose in the morning (eg, 150mg [3 tablets]) and the higher dose in the evening (eg, 200mg [4 tablets]).

SP0982 will target Maintenance Period doses of LCM or matching placebo as presented in Table 7–3.

7.2.1 Titration Period

Table 7–1 provides the recommended LCM (or matching placebo) dosing during the Titration Period for subjects to reach the target doses for the Maintenance Period. All subjects should

follow this recommended dosing schedule, unless dose adjustments based on tolerability are needed.

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

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

LCM=lacosamide
[a] The oral solution formulation is for pediatric subjects weighing <50 kg.
[b] The tablet formulation is for adult subjects (≥18 years of age) and pediatric subjects weighing ≥50kg.

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

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

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

LCM=lacosamide; Max=maximum; Min=minimum
Note: Asymmetrical dosing with no more than 50mg difference between morning and evening doses will be allowed for subjects who require back titration in a 50mg increment.
[a] Titration step to achieve a dose not previously administered.

All subjects are required to complete Week 1 dosing before study drug dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further study drug dose increase or whether a subject should hold the dose for a longer duration. There is no limit to the number of back-titration steps or dose holds allowed and all are at the investigator's discretion; however, subjects must achieve the minimum LCM (or matching placebo) target dose by the end of the Titration Period (Table 7–3). If it becomes apparent that a subject is unable to attain at least the minimum Maintenance Period target dose, then the subject must enter the Taper Period and be withdrawn from the study.

Subjects who titrate to a next higher dose level should remain at that dose prior to a dose increase for ≥7 days unless a back-titration step is required based on tolerability. Subjects who have their study drug back titrated must remain on the lower dose for ≥3 days (in order to reach steady state) before a subsequent dose increase.

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

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

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

LCM=lacosamide; Max=maximum; Min=minimum

7.2.2 Maintenance Period

Subjects will enter an 18-week Maintenance Period at the dose they received on the last day of the Titration Period in accordance with targeted Maintenance Period dosing (Table 7–3).

During the Maintenance Period, a single dose reduction is allowed as long as the minimum target dose is maintained. Once the dose has been reduced, it cannot be increased. Subjects who are not able to tolerate the minimum target dose during the Maintenance Period (Table 7–3) will be withdrawn from the study and enter an up to 4-week blinded Taper Period. All dose reductions should be discussed with the Medical Monitor.

7.2.3 Transition Period (for subjects who enter EP0012)

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period or when the 125th event occurs in the study (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. Two weeks after Visit 10 (Week 24) or the ET Visit, a Transition telephone contact is required; a subsequent Clinic Visit is at the discretion of the investigator (Table 5–2). The background AED may be adjusted during the Transition Period at the discretion of the investigator. The Final Clinic Visit is the same as Visit 1 of EP0012.

The following schematic displays the scenario for subject dispensation:

ET=Early Termination; TC=telephone contact

[a] A Transition TC is required. A Transition Clinic Visit is optional, at the discretion of the investigator.

Subjects will transition in a double-blind fashion to LCM dosing as described Table 7–4. At the completion of the Transition Period, subjects eligible to enter EP0012 will be placed on a common dose (see Figure 5–3).

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

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

LCM=lacosamide

Note: If a subject is in the Titration Period and the next scheduled visit after the 125th event occurs, dosing will be adapted to reach the target dosing at Week 4.

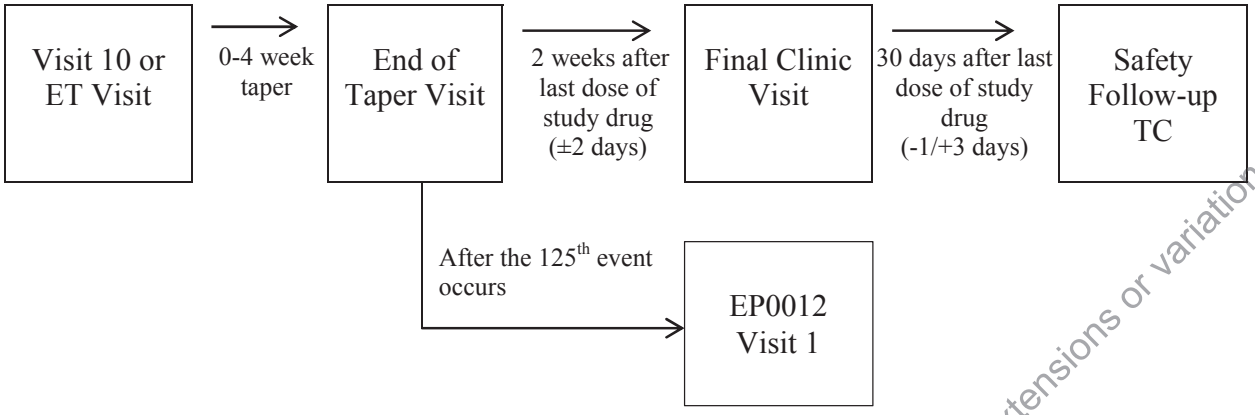
7.2.4 Taper Period

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit (Table 7–5).

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.

Following the End of Taper Visit, there will be a 30-day Safety Follow-up Period. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-up telephone contact 30 days after the last dose of study drug. In case the 125th event occurs in the study, the subjects discontinuing treatment will complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. However, the End of Taper Visit will be the same as Visit 1 of EP0012. The 30-day Safety Follow-up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

The following schematic displays the scenario for subject dispensation:



ET=Early Termination; TC=telephone contact
Note: An End of Taper Visit will be scheduled at the end of the Taper Period (up to 4 weeks) depending on the dose level achieved; see Table 7-5. Of note, for subjects who enter the Taper Period at 2mg/kg/day (oral solution) or 100mg/day (tablets), the End of Taper Visit will take the place of the ET Visit.

Table 7–5 summarizes the Taper Period dosing for each treatment dose for subjects not entering EP0012.

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

LCM (or matching placebo) dose achieved	LCM (or matching placebo) doses for the Taper Period			
	Week 1	Week 2	Week 3	Week 4
11 or 12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9 or 10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7 or 8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	NA
5 or 6mg/kg/day	4mg/kg/day	2mg/kg/day	NA	NA
3 or 4mg/kg/day	2mg/kg/day	NA	NA	NA
≤2mg/kg/day	NA	NA	NA	NA
350 or 400mg/day	300mg/day	200mg/day	100mg/day	NA
250 or 300mg/day	200mg/day	100mg/day	NA	NA
150 or 200mg/day	100mg/day	NA	NA	NA
100mg/day	NA	NA	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: The oral solution is dosed as "mg/kg/day" and tablets are dosed as "mg/day."
Note: Dosing for the Taper Period will be adapted depending on the dose subjects reached during the Titration Period when the 125th event occurs.

7.3 Packaging

Lacosamide (tablets and oral solution) and matching placebos are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or

regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

Lacosamide tablets and matching placebos will be packaged in HDPE bottles.

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

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the 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 according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log (showing actual and minimum/ maximum temperatures reached over the time interval) in accordance with local requirements on a regular basis.

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

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

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor'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 or destroyed.

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

The investigator must ensure that IMP is used only in accordance with the protocol.

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

7.7 Procedures for monitoring subject compliance

At each visit after IMP is dispensed, subjects must return all unused IMP and empty IMP kits. Drug accountability must be completed in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

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

Timely completion of the subject diary is essential for evaluation of safety and efficacy. Subject diary completion, including AED usage, will be evaluated at each clinic visit and telephone contact. Sites are encouraged to call subjects to inquire about their diary completion. Investigators should advise subjects and/or caregivers about the importance of reporting non-PGTC seizures. Subjects should be reminded that diaries must include daily entries even if no seizures have occurred.

7.8 Concomitant medication/treatment

7.8.1 Permitted concomitant treatments (medications and therapies)

Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 2 to 3 AEDs (with 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period with or without additional concurrent stable VNS.

- Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and must remain unchanged during the course of the study.
- The chronic (daily dose) use of a benzodiazepine is allowed regardless of indication and will be counted as 1 of the 3 allowed AEDs.
- Intermittent use of benzodiazepines (limited to 2 doses per 28 days) is allowed only for epilepsy indications if established at least 28 days prior to Visit 1. Intermittent use of benzodiazepines for any other indication is prohibited during the study.

Contraceptive treatment is allowed as described in in Section 6.2 (Exclusion Criterion 21). Recommended contraception methods for subjects on enzyme-inducing antiepileptic drugs (EI-AEDs) or not on EI-AEDs are detailed in Section 17.9.

Stable use of amphetamines and sedative antihistamines is allowed during the study.

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

7.8.2 Prohibited concomitant treatments (medications and therapies)

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

- Clozapine.
- Any MAO inhibitors.

- Barbiturates (except as antiepileptic medications).
- Patients taking non-benzodiazepine anxiolytics or once-daily hypnotics must remain on stable doses of these medications throughout the study.
- Herbal medicines for epilepsy

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.

7.9 Blinding

UCB Global Clinical Trial Supply will create a packaging list using a validated application. The packaging list will be provided to the interactive response technology (IRT) vendor and to the packaging vendor who will prepare the kits accordingly.

The treatment randomization schedule will be generated by UCB (or designee) in a manner that will ensure that the study team remains blinded, in accordance with current standard operating procedures (SOPs). The randomization schedule will be maintained in a secure location until the study is unblinded for the final statistical analysis.

All sponsor, investigator sites, and contract research organization (CRO) staff involved with the study will be blinded to the treatment code with the following exceptions:

- Sponsor personnel and its subcontractors directly involved in the packaging of the IMP or in the management of the IRT.
- Sponsor Patient Safety (PS) staff will receive separate access to the IRT in order to meet their requirements for serious adverse event (SAE) reporting to regulatory authorities.
- Central laboratory staff assaying study drug. However, no randomization list will be provided.

An interim futility assessment is planned to allow UCB to consider terminating the study should the likelihood of a positive outcome be unacceptably low based on an unblinded assessment of interim data by an independent data monitoring committee (IDMC). Such an interim assessment will be conducted in a manner that ensures that blinding is not compromised for individuals involved with operational aspects of the study or individuals involved with the planning and conduct of the final statistical analyses. The 3 planned interim safety assessments will be conducted similarly to assure that blinding is maintained.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

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

7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IRT. All sites will be provided with details of

how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding whenever possible.

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

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB. The randomization schedule will be produced by the IRT Vendor who is otherwise not involved in this study. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

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

To randomize a subject (Visit 2), the investigator (or designee) will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the investigator (or designee) of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the eCRF.

8 STUDY PROCEDURES BY VISIT

All visits occur at the end of the respective week in the study and a window of ±2 days relative to Visit 1 is applicable for all visits and telephone contacts.

A detailed schedule of study assessments is provided in Table 5–1, Table 5–2, and Table 5–3.

8.1 Prospective Baseline Period

8.1.1 Visit 1 (Week -4)

At Visit 1 (Week -4), subjects will be evaluated for their suitability for enrollment. The Visit 1 assessments will be conducted up to 4 weeks (±2 days) prior to the first administration of study drug.

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 and the subject's parent/legal guardian (for subjects <18 years of age) by the investigator (or designee). The IRB/IEC-approved Informed Consent/Assent form must be signed and dated by the subject, or his/her legal representative, and by the person who conducted the informed consent/assent discussion (investigator or designee). Participation in the study starts from the time of signing the IRB/IEC-approved Informed Consent/Assent form.

Sites may conduct prescreening EEGs and prior to this, subjects will read and sign a separate Informed Consent form that has been approved by an IRB/IEC and the Sponsor, and which complies with regulatory requirements.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature of an informed consent/assent prior to any study-related procedures or evaluations, and the results of the following assessments:

- Subject ID card dispensed
- Medical history and/epilepsy history
- EEG report
- Body weight and height
- Physical examination (complete)
- Neurological examination (complete)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Dispense subject diary
- AE reporting
- Concomitant medications and AEDs
- Contact IRT

8.1.2 Telephone contact (Week -2)

The investigator (or designee) should contact the subject by telephone 2 weeks following Visit 1 to assess continued eligibility and will remind the subject of the importance of accurate seizure diary completion. During the telephone contact, the following assessments will be performed:

- Inclusion/exclusion criteria
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

8.2 Treatment Period

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures
- The 125th event occurs in the study

8.2.1 Visit 2 (Day 0) Randomization

All assessments at Visit 2 (Day 0) should be conducted prior to the first dose of study drug. During Visit 2 (Day 0), the following assessments will be performed:

- Inclusion/exclusion criteria
- Randomization
- Body weight
- Physical examination (complete)
- Neurological examination (complete)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Achenbach CBCL
- BRIEF-P/BRIEF
- EQ-5D-3L
- QOLIE-31-P/PedsQL
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- Tanner Stage (will be performed only for subjects who are pubescent at Visit 2 or who enter puberty during the course of the study)
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

The subject will take the first dose of study drug in the clinic.

8.2.2 Titration Period

8.2.2.1 Week 1 to Week 6

Both clinic visits and telephone contacts will be conducted during the Titration Period, beginning with a telephone contact at the end of Week 1 and continuing through clinic Visit 5 at the end of Week 6.

At each clinic visit and telephone contact, the investigator, in conjunction with the subject and/or parent(s)/legal representative(s), will decide how to proceed with study drug dosing based on tolerability (including vital signs, body weight, 12-lead ECG, and AE reporting, as applicable to the type of visit contact). If the withdrawal of study drug is required during the Titration Period, the subject will enter the blinded Taper Period (Table 7–5).

8.2.2.1.1 Telephone contact (Week 1, Week 3, Week 5, and unscheduled)

The following assessments will be performed during telephone contacts (both scheduled [Week 1, Week 3, and Week 5] and unscheduled) during the Titration Period:

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

8.2.2.1.2 Visit 3 (end of Week 2)

During Visit 3 (end of Week 2), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.2.1.3 Visit 4 (end of Week 4)

During Visit 4 (end of Week 4), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Urine pregnancy test (for women of childbearing potential)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.3 Maintenance Period

8.2.3.1 Visit 5 (end of Week 6)

During Visit 5 (end of Week 6), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)

- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, a urine pregnancy test [for women of childbearing potential], and LCM plasma concentration)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.3.2 Visit 6 (end of Week 8)

During Visit 6 (end of Week 8), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Urine pregnancy test (for women of childbearing potential)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy

- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.3.3 Visit 7 (end of Week 12)

During Visit 7 (end of Week 12), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.3.4 Visit 8 (end of Week 16)

During Visit 8 (end of Week 16), the following assessments will be performed:

- Body weight
- Physical examination (brief)

- Neurological examination (brief)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Urine pregnancy test (for women of childbearing potential)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.3.5 Visit 9 (end of Week 20)

During Visit 9 (end of Week 20), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy

- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.2.3.6 Visit 10/ET Visit (end of Week 24)

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure. Once the 125th event occurs subjects will return to the site at the next scheduled visit and the ET/Visit 10 will be performed (see Section 6.3).

During the Visit 10/ET Visit (end of Week 24), the following assessments will be performed:

- Body weight
- Height
- Physical examination (complete)
- Neurological examination (complete)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, urinalysis, a serum pregnancy test [for women of childbearing potential], and LCM plasma concentration)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Achenbach CBCL (same version used at Visit 2)
- BRIEF/ BRIEF-P (same version used at Visit 2)
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P/PedsQL (same version used at Visit 2)
- Healthcare resource use
- Work/school days lost due to epilepsy

- Days with help from a caregiver due to epilepsy
- Tanner Stage (will be performed only for subjects who are pubescent at Visit 2 or who enter puberty during the course of the study)
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.3 End of Study Period

8.3.1 Transition Period

8.3.1.1 Transition Clinic Visit/telephone contact

A Transition telephone contact is required. The following assessments will be performed during the Transition telephone contact:

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

A Transition Clinic Visit is optional, at the discretion of the investigator. Subjects requiring a clinic visit will have the same assessments conducted as an Unscheduled Visit (see Section 8.4).

8.3.1.2 Final Clinic Visit

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period or the 125th event occurs in the study (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. The Final Clinic Visit is the same as Visit 1 of EP0012. Subjects choosing to enter EP0012 must sign and date the EP0012 extension IRB/IEC-approved informed consent prior to receiving EP0012 study drug.

During the Final Clinic Visit, the following assessments will be performed:

- Body weight
- Height
- Physical examination (complete)
- Neurological examination (complete)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)

- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Study drug return/review
- Withdrawal criteria
- Contact IRT

8.3.2 Taper and Safety Follow-up Period

8.3.2.1 End of Taper Visit

Subjects completing Visit 10 (Week 24) or the ET Visit who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by the End of Taper Visit. At the End of Taper Visit, the following assessments will be performed:

- Body weight
- Physical examination (complete)
- Neurological examination (complete)
- ECG 12-lead assessment (see Section 10.3.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Study drug review/return
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting

- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

8.3.2.2 Safety Follow-up Visit

Following the End of Taper Visit, the subject will return 2 weeks (±2 days) after the last dose of study drug for a Safety Follow-up Visit. In case the 125th event occurs in the study, the subjects discontinuing treatment will complete a 30-day Safety Follow-up Period in the EP0012 study. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

During the Safety Follow-up Visit, the following assessments will be performed:

- Body weight
- Physical examination (complete)
- Neurological examination (complete)
- ECG 12-lead assessment (see Section 10.3.1) (required only for subjects with an abnormal reading at the previous clinic visit)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology [required only for subjects with an abnormal value at the previous clinic visit], urinalysis, and a urine pregnancy test [for women of childbearing potential]).
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs

8.3.2.3 Safety Follow-up telephone contact

Thirty days (-1/+3 days) after the last dose of study drug, the subject will receive a Safety Follow-up telephone contact. In case the 125th event occurs in the study, the subjects discontinuing treatment will complete a 30-day Safety Follow-up Period in the EP0012 study. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

During the Safety Follow-up telephone contact, the following assessments will be performed:

- AE reporting
- Concomitant medications and AEDs

8.4 Unscheduled Visit

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

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IRT

If an Unscheduled Visit is due to an AE, then the C-SSRS (for subjects ≥6 years of age) is required.

In addition to the required assessments listed above, depending on the type of visit (clinic or telephone), further assessments can be completed as needed and may include ECG, vital signs, laboratory tests, dispense study drug, diary review, etc.

9 ASSESSMENT OF EFFICACY

9.1 Primary efficacy variable

The primary efficacy variable is the time to the second PGTC seizure during the 24-week Treatment Period.

9.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline)
- The percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline
- Time to the first PGTC seizure during the Treatment Period

9.3 Other efficacy variables

Other efficacy variables are:

- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline

- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Period) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Prospective Baseline
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the first 12 weeks of the Treatment Period compared to Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the Treatment Period compared to Combined Baseline
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period
- Change from Baseline in QOLIE-31-P subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the PedsQL subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- Change from Baseline to end of treatment or ET in the EQ-5D-3L VAS score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject due to epilepsy
- Number of days with help from a caregiver due to epilepsy

9.3.1 Seizure variables

Subjects will keep a diary to record daily seizure activity from Visit 1 until the end of study participation. Efficacy and safety variables will be assessed using the seizure count information recorded on the subject diaries. Subjects should be reminded that diaries must include daily entries even if no seizures have occurred. The subject should be reminded to bring the diary to each clinic visit.

9.3.1.1 PGTC seizures

The following information will be recorded on a daily basis as applicable:

- Seizure type
- Number of PGTC seizures

If more than 1 PGTC seizure occurs on a single day, each seizure should be counted separately, provided there is a complete recovery of consciousness between seizures.

9.3.1.2 Absence and myoclonic seizures

In the subject diary, the following information will be recorded on a daily basis:

- Seizure type
- Number of seizures to be recorded although for the purpose of data analysis, only the number of days with seizure will be analyzed.

Investigators should advise subjects and/or caregivers about the importance of reporting absence and myoclonic seizures.

9.3.2 Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P)

The QOLIE-31-P Version 2 will be used to evaluate the health-related quality of life (HRQoL) of study subjects ≥18 years of age (Cramer and Van Hammée, 2003).

The QOLIE-31-P is an adaptation of the original QOLIE 31 instrument (Cramer et al, 1998) that includes 30 items grouped into 7 multi-item subscales (Seizure Worry [5 items], Overall Quality of Life [2 items], Emotional Well-being [5 items], Energy/Fatigue [4 items], Cognitive Functioning [6 items], Medication Effects [3 items], and Daily Activities/Social Functioning [5 items]) and 1 health status item.

In addition to the 31 items, the QOLIE-31-P contains 7 items assessing the degree of "distress" associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

9.3.3 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). The version of the PedsQL used at Visit 2 should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Section 5.2).

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects ≥2 years to ≤4 years, ≥5 years to ≤7 years, ≥8 years to ≤12 years, and ≥13 years to

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

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

9.3.4 EQ-5D-3L Quality of Life Assessment

The EQ-5D-3L (EuroQol Group, 2011) is a self-administered questionnaire designed to measure health status in subjects ≥12 years of age. The EQ-5D-3L defines health in terms of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is divided into 3 levels:

- No problem=1
- Some or moderate problems=2
- Extreme problems=3

The EQ-5D-3L also captures a self-rating of health status on a 20cm vertical visual analog scale, anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

9.3.5 Healthcare resource use

Healthcare resource use will include concomitant medical procedures, hospitalizations, and healthcare provider visits.

9.3.6 Number of working or school days lost due to epilepsy

The number of working or school days lost due to epilepsy by the subject will be recorded, as applicable.

9.3.7 Number of days with help from a caregiver due to epilepsy

The number of days with help from a caregiver due to epilepsy will be recorded, as applicable.

9.3.8 Socio-professional data

Socio-professional data, such as highest level of education, current professional status, housing status, and regular assistance will be collected throughout the study, as applicable.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with

this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent/Assent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP 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 IMP 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.

10.1.1.2 Serious adverse event

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

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include potential Hy's Law [see Section 10.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if 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 criterion. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

10.1.1.2.1 Anticipated serious adverse events

Table 10–1 provides a list of anticipated SAEs which have been identified as events that are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the investigator's obligation to report all serious AEs (including anticipated SAEs) as detailed in Section 10.1.2.

Table 10–1: Anticipated SAEs for the epilepsy population

System Organ Class	Preferred Term
Congenital, Familial and Genetic Disorders	Teratogenicity
General disorders and Administration Site Conditions	Sudden unexplained death in epilepsy
Nervous System Disorders	Convulsion
	Incontinence
	Status epilepticus
Pregnancy, Puerperium and Perinatal Disorders	Abortion spontaneous
Psychiatric Disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder
Reproductive System and Breast Disorders	Menstrual disorder
	Impotence

SAE=serious adverse event

10.1.1.3 Adverse events of special interest

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

The following are AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second degree, Type I and II, and third degree), and marked bradycardia (<45 bpm)
- Syncope or loss of consciousness (other than seizure related)
- Serious suspected multiorgan hypersensitivity reactions

Serious suspected multiorgan hypersensitivity cases may be identified and reported to the sponsor by the investigator using the following algorithm as agreed with the Food and Drug Administration:

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

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

- Eosinophils % ≥10%
- Eosinophils absolute ≥0.5G/L
- Neutrophils absolute <1.5G/L
- Platelets ≤100G/L
- ALT ≥2xULN
- AST ≥2xULN

- Emergence of non-preexisting or worsening of any existing epileptic seizure types
- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

10.1.2 Procedures for reporting and recording adverse events

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.

10.1.2.1 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (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 study drug) are described in the eCRF Completion Guidelines.

10.1.2.2 Rule for repetition of an adverse event

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

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

10.1.2.3 Additional procedures for reporting serious adverse events

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

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

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

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

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the investigational product), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any 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.

10.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events are provided in Section 10.2.1.4.

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 subjects have discontinued their IMP.

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

10.1.4 Pregnancy

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an ET Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the ET Visit.
- A Safety Follow-up Visit (Final Clinic Visit) should be scheduled 2 weeks after the subject has discontinued her IMP.

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

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. Every reasonable attempt should be made to follow the health of the child 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. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/CRO contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

10.1.5 Suspected transmission of an infectious agent via a medicinal product

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

10.1.6 Overdose of investigational medicinal product

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

10.1.7 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 PS 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.

10.2 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis parameters will be collected according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3. A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.2.2). The procedures for handling and shipping these specimens will be provided to the sites.

The laboratory tests to be performed are presented in Table 10–2.

Table 10–2: Laboratory measurements

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

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

[a] Thyroid function will be required in subjects <18 years of age only.

[b] Urinalysis will be required for all subjects.

10.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.2.1.4).

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

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

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

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

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued. Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 10-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes				
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation - immediate IMP discontinuation not required (see Section 10.2.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 10.2.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values[d]

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

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

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

[c] Details provided in Section 10.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

10.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 10.2.1.3) and SAE report (if applicable).

10.2.1.2 Immediate action: determination of IMP discontinuation

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

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.4.1 and Table 10-3 for details).

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

10.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 10–4 (laboratory measurements) and Table 10–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

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

The following measurements are to be assessed:

Table 10–4: PDILI laboratory measurements

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

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

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

The following additional information is to be collected:

Table 10–5: PDILI information to be collected

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

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

10.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10-3.

Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

10.2.2 Pregnancy testing

Females of childbearing potential (who have not been surgically sterilized or who are not at least 2 years postmenopausal) will have serum and urine dipstick pregnancy testing performed according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

10.3 Other safety measurements

10.3.1 12-lead ECG

Standard 12-lead ECGs will be performed according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

10.3.1.1 Overall ECG interpretation

Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader. If the reading identifies a second- or third-degree AV block or another abnormal ECG finding that is assessed by the investigator to be clinically significant, then the ECG should be repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study (see Section 6.4). The investigator may consult with a cardiologist 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.

10.3.2 Vital signs, body weight, and height

Noninvasive BP (systolic and diastolic) and pulse rate will be measured at clinic visits in a supine position after at least 3 minutes at rest, according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3. Assessment of orthostatic changes will be as follows: after the 3-minute measurement in a supine position, the subject is asked to stand and BP and pulse rate are taken approximately 1 minute and approximately 3 minutes after the subject stands up, as feasible. Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

Body weight will be determined without shoes and wearing light clothing and height will be measured without shoes. Body weight and height will be measured using equipment that is age appropriate and assessed according to the tabular schedule of study assessments (Table 5–1, Table 5–2, and Table 5–3).

10.3.3 New seizure types

Incidence of new seizure types, and increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period will be assessed using the seizure count information recorded on the subject diaries (see Section 9.3.1).

10.3.4 Physical examination

Physical examinations will be performed by a medically qualified clinician licensed to perform the examination, according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3. Clinically significant physical examination findings are to be reported as AEs.

10.3.4.1 Complete physical examination

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

10.3.4.2 Brief physical examination

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

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

10.3.5 Tanner Stage

At Visit 2 and Visit 10/ET Visit, the investigator or qualified designee will evaluate the subject's sexual development using the 3-item Tanner scale, according to the tabular schedules of study procedures (Section 5.2). The investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 2 or who will enter puberty during the course of the study).

10.3.6 Neurological examination

Neurological examinations will be performed by a medically qualified clinician with documented training in the conduct of neurological examinations, according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3. 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 IGE with PGTC seizures.

10.3.6.1 Complete neurological examination

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

10.3.6.2 Brief neurological examination

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

10.3.7 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2012). 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 schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age, and the "Since Last Visit" version should be used at subsequent visits.

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than

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

10.3.8 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)/legal representative(s).

The Achenbach CBCL/1½ -5 is for children <5 years and 11 months of age, and the CBCL/6-18 is for children ≥6 years to <18 years of age; the questionnaire is to be completed by the parent(s)/legal representative(s). For each subject, the same version of the scale that is completed at Visit 2 should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Table 5–1) and should be completed by the same parent/legal representative. The completion of the Achenbach CBCL will require approximately 45 minutes.

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

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

Eight syndrome scores will be calculated from these questionnaires, which will in turn be summarized by 2 composite scores. Additionally, for each score on the questionnaire, 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.

10.3.9 BRIEF

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each subject, the same version (BRIEF-P or BRIEF) that is used at Visit 2 should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Table 5–1).

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

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

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

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

11 ASSESSMENT OF PHARMACOKINETICS

Blood samples for analysis of LCM plasma concentrations will be collected at any time between 2 successive bid doses, according to the schedule of study assessments in Table 5–1. The time the subject took the most recent dose of IMP and the time of blood sampling must be recorded. Actual dosing and sampling times will be recorded in the eCRF to the minute.

The central laboratory will store the plasma samples at -20°C until analysis. Blood draws for these assessments will coincide with the blood collection times for assessment of the hematology and clinical chemistry parameters. Time and date of each blood draw will be documented on the eCRF.

Instructions on blood sample collection, processing, storage, and labeling/shipping are provided in the laboratory manual for this study.

12 STUDY MANAGEMENT AND ADMINISTRATION

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.

12.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring 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 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). Printouts of eCRF screens are not considered acceptable source documents.

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

If the source documents are maintained by the investigator in a computerized system, the monitor should ensure that electronic records are ALCOA (attributable, legible, contemporaneous, original, and accurate) compliant and that there is proper access control, validation, and audit trail available upon request. If the monitor has no direct access to the original electronic medical records, the certified copies should be generated by the investigator and used for the study purposes. Accuracy and completeness of data on the certified copies should be verified by the monitor to maintain ongoing compliance.

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 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. This study is performed using electronic data capture (EDC); 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/assent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

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 IMP 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/Assent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

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

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 Informed Consent/Assent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned

arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH/GCP, and applicable regulatory requirements.

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

12.7 Good Clinical Practice

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

13 STATISTICS

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

13.1 Definition of analysis sets

13.1.1 Screened Set

The Screened Set consists of all subjects who have entered screening at Visit 1, have a signed Informed Consent/Assent form, and have at least basic demographic data available.

13.1.2 Randomized Set

The Randomized Set (RS) is a subset of the Screened Set and consists of all subjects who were randomized at the Randomization Visit (Visit 2).

13.1.3 Safety Set

The Safety Set (SS) is a subset of the RS and consists of all subjects who have been treated with at least 1 dose of study drug, either LCM or placebo. This population will serve as the primary population for assessing safety endpoints.

13.1.4 Full Analysis Set

The Full Analysis Set (FAS) is a subset of the SS consisting of all subjects with at least 1 seizure diary assessment during the Treatment Period. This population will serve as the primary population for assessing efficacy endpoints.

13.1.5 Per Protocol Set

The Per Protocol Set (PPS) is a subset of the FAS excluding subjects who completed fewer than 6 weeks of treatment or subjects with important protocol violations affecting the interpretation of the primary efficacy analysis. Important protocol violations will be determined prior to unblinding.

13.2 General statistical considerations

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.

13.3 Planned efficacy analyses

13.3.1 Analysis of the primary efficacy variable

The primary efficacy variable, time to second PGTC seizure during the 24-week Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the 16 weeks prior to randomization) and age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age). Pooling strategies for strata with a low number of events will be defined in the SAP prior to unblinding. Subjects who prematurely discontinue from the study will be censored on the date of last dose of study drug during the Treatment Period.

Additionally, a Kaplan-Meier (KM) plot for time to second PGTC seizure as well as the KM estimate for the median time to second PGTC seizure will be provided. This analysis will be performed using the FAS population.

Testing for the primary endpoint will be done at the 5% level (2-sided). A gatekeeping strategy (Marcus et al, 1996) will be used to test the key secondary efficacy variable provided that the primary endpoint is statistically significant (See Section 13.3.2 for additional details). No additional adjustments for multiplicity are required as all additional inferences will be hypothesis-generating only.

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

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy, consent withdrawn, or lost to follow-up will be analyzed as treatment failures (ie, events at the time of discontinuation).
- Repeat the primary analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy or AEs only will be analyzed as treatment failures.
- Repeat the primary analysis using the FAS, comparing the event rates at each interim analysis to examine possible operational bias due to unblinding.

13.3.2 Secondary efficacy analyses

13.3.2.1 Key secondary efficacy variable

Analysis of the key secondary efficacy variable, seizure freedom for PGTC seizures for the 24-week Treatment Period, will be analyzed in the same manner as the primary endpoint using the FAS. The percentage of seizure-free subjects at 24 weeks will be estimated from the KM estimates of time to first seizure using 2-sided 95% confidence intervals. A gatekeeping strategy will be employed to control the Type I error (Marcus et al, 1976). If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

13.3.2.2 Other secondary efficacy variables

All safety analyses will be described in the SAP. Analyses of the other secondary efficacy variables will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described in Section 13.3.2.1) will be exploratory only.

Time to the first PGTC seizure for the Treatment Period will be analyzed in the same manner as the primary endpoint using the FAS.

Further approaches for the analysis of the secondary variable will be described in a detailed SAP.

13.3.3 Other efficacy analysis

Analysis of the other efficacy endpoints listed in Section 4.1.3 of the protocol will be presented descriptively. Additional details will be provided in the SAP.

13.4 Planned safety and other analyses

Analyses of other variables, eg, safety or plasma concentration data, will be descriptive in manner only. Lacosamide plasma concentrations will be summarized and evaluated by population PK; details will be provided in a separate analysis plan.

The incidence and frequency of TEAEs will be summarized for each treatment group and study period. The incidence of SAEs and TEAEs leading to premature discontinuation from study drug will also be summarized for each treatment group and study period. Additional summaries will be provided by maximum intensity and relationship to study drug. All tables for AEs will be displayed by MedDRA® primary System Organ Class and Preferred Term. Further details on the analysis of AE data will be given in the SAP.

Observed values and changes from Baseline in vital signs, body weight, continuous laboratory parameters, and 12-lead ECG measurements will be summarized using continuous descriptive statistics. The number and percentage of subjects in each category will be summarized for the categorical outcomes. Shift tables summarizing the number and percentage of subjects having a different status (eg, abnormal laboratory result) post-Baseline compared to Baseline will be provided.

Incidence of new seizure types, and increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period will be summarized for each treatment group.

13.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on 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 (DCP). 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 in a blinded manner a part of the ongoing data cleaning process prior to database lock to confirm exclusion from analysis sets.

13.6 Handling of dropouts or missing data

All data will be used to the maximum possible extent, but without any imputations for missing data for any parameter, unless otherwise specified in the SAP. Sections 13.3.1 and 13.3.2 provide additional sensitivity analyses for the primary efficacy and key secondary efficacy endpoints, respectively.

13.7 Planned interim analysis and data monitoring

Some AEDs with sodium channel blocking properties can exacerbate some generalized seizure types, such as absence and myoclonic seizures. To enhance safety monitoring, 3 interim analyses are planned when 25%, 50%, and 75% of subjects experience an event (31, 62, and 93 events, respectively) or 24 weeks after 50, 100, and 150 subjects have been randomized, respectively, whichever comes first. An event is defined as the occurrence of the second PGTC seizure during the Treatment Period.

Three interim analyses for safety will be performed by the IDMC with a single futility assessment planned at the second interim analysis. The IDMC will oversee the safety of the study by reviewing safety data periodically. Details will be provided in an IDMC charter. Both safety and futility will be assessed in a manner that ensures that blinding is not compromised for individuals involved with operational aspects of the study, or individuals involved with the planning and conduct of the final statistical analyses. Analysis of the primary endpoint (time to second PGTC seizure) will only be examined at the planned futility assessment; an unblinded, descriptive review of safety, PGTC seizure frequency, and changes in days with absence and/or myoclonic seizures will be provided for all IDMC meetings.

Additional details, including the methods used for assessing futility, will be provided in the interim SAP. Neither futility or the IDMC safety assessments are expected to have any impact on the Type 1 error as there will be no stopping rule for success in place; however, the significance level will be set using a Haybittle-Peto boundary at alpha=0.0001 so as not to require any adjustment to the overall alpha level for the final analysis.

The IDMC will consist of 3 voting members, none of whom will be involved with the conduct of the study, either by management or participation. In addition, there will be an independent reporting team, consisting of an independent statistician and statistical programmers, who will be completely independent from the blinded reporting team. The blinded reporting team will be responsible for all operational aspects of the study, including routine monitoring and cleaning of the data, programming, and quality control (QC) of all analyses defined in the interim SAP on blinded data.

The blinded study team will actively monitor the number of events in the study. Once the required number of events (or subjects) has been met and the blinded reporting team has completed the QC of the IDMC tables, figures, and listings (TFLs), the programs will be passed to the independent reporting team. The independent statistician will request unblinded treatment codes from the IRT randomization coordinator and the TFLs will be re-run and QC'd using the actual treatment codes. Additional TFLs or ad hoc analyses can be requested by the IDMC based on their data review.

Any changes to predefined TFLs or new requests will be handled by the independent reporting team.

The actual randomization codes and the unblinded outputs will be stored in a secure location which will be accessible only to the independent reporting team. A secure, restricted-access directory will hold electronic copies of documents such as meeting minutes, interim reports, emails, and periodic data deliveries. Only the independent reporting team will have access to this secure location.

13.8 Determination of sample size

Observing 125 events (subjects who had a second PGTC seizure during the 24-week Treatment Period) will provide 90% power to observe a hazard ratio of 0.56 at the 2-sided 5% level, assuming a dropout rate of 15%. The observed hazard ratio was based on a 25.4% survival rate for placebo and 48.2% for lamotrigine from a previous study comparing lamotrigine and placebo (French et al, 2007). The observed hazard ratio in the lamotrigine study was 0.533; however, in order to account for the possibility of an increased placebo response, as has been documented in recent clinical studies of AEDs, the hazard ratio was increased by 5% to 0.56 for estimating a sample size for this study. The rationale for the increase in the hazard ratio included the following considerations: different active compounds (LCM and lamotrigine) and a choice of time to second seizure as the primary efficacy endpoint (in the lamotrigine study, percent change in PGTC seizure frequency was the primary endpoint) (see rationale for second PGTC seizure in Section 5.4.2).

This is an event-driven study. Enrollment in the study will continue up to 125 events occurring or a maximum of 250 subjects randomized, whichever comes first.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent/assent

Subject's Informed Consent/Assent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

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

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

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

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

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

14.2 Subject identification cards

Prior to study participation at Visit 2, upon signing the Informed Consent/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 them at all times.

14.3 Institutional Review Boards and Independent Ethics Committees

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

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, Informed Consent/Assent form (including Informed Consent/Assent form for prescreening EEG, if applicable), 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 the IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the sponsor, as specified by the

applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

14.4 Subject privacy

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

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

14.5 Protocol amendments

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

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

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

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17.3 Protocol Amendment 1

Rationale for the amendment

The primary purpose of this substantial amendment is to identify significant changes to the study design including inclusion and exclusion criteria, as well as the addition of an IDMC. In addition, study secondary variables were changed to more accurately represent the study design.

The protocol has been updated to include randomization stratified by age at informed consent (≥12 to <18 years of age vs ≥18 years of age). This is in order to maintain balance within each treatment arm and within the existing baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) as well as provide greater control for variability when analyzing the primary efficacy variable (time to second seizure).

An inclusion criterion was added to include subjects of normal intelligence for age in the judgment of the investigator. Exclusion criteria were added or modified to further exclude subjects who have a diagnosis of developmental delay or mental retardation or a history of status epilepticus. The rationale for adding the inclusion/exclusion criteria is that subjects with developmental delay or mental retardation are more likely to have symptomatic rather than idiopathic seizures.

The inclusion criterion regarding the lower limit body weight for male and female subjects ≥12 years of age was changed from ≥30kg to ≥50kg. This was based on the observations collected to date from pediatric PK/tolerability studies.

The text regarding the use of benzodiazepines was revised to clarify that up to 3 marketed AEDs are allowed for study inclusion provided at least 1 of the 3 AEDs is a benzodiazepine regardless of indication. The intermittent use of a benzodiazepine is permitted for epilepsy indications only and limited to 2 doses per 28 days; intermittent use for non-epilepsy indications is prohibited. The rationale for this change was based on data from SP0961 in which approximately 20% of PGTC seizure subjects with IGE used benzodiazepines. Subjects should not be excluded from the study due to benzodiazepine use unless they are using benzodiazepines intermittently for indications other than epilepsy. This change is consistent with other PGTC seizure studies in regards to benzodiazepine use.

The secondary efficacy endpoint time to first PGTC seizure during the 24-week Treatment Period was added as a key secondary endpoint as UCB considers that LCM will improve the rate of seizure freedom in this difficult to treat population. A gatekeeping strategy will be used to control Type I error (Section 13.3.2).

For the assessment of the effect of LCM on quality of life in pediatric subjects, the SP0982 protocol has been updated to include the PedsQL. The PedsQL is widely used in epilepsy and other therapeutic areas, and may allow for comparison with other diseases. In addition, the PedsQL also allows for consistency across age groups and development programs, and is available in many languages for global clinical studies.

For the assessment of neurobehavior and cognition in pediatric subjects, the SP0982 protocol has been updated to include the Achenbach CBCL and the BRIEF, respectively. The addition of these assessments also allows for consistency across age groups and development programs.

To ensure subject safety, interim assessments for safety and futility will be performed using an IDMC due to the novel study design and primary endpoint in this patient population. Furthermore,

a minority of subjects (~10%) in SP0961 showed an increase in absence seizures that, in this uncontrolled study, could not be distinguished between the drug vs the natural course of the disease and required additional examination in the current study.

SP0982 is an event-driven study where the statistical properties are based upon the number of events, not the number of subjects as is typical in most epilepsy studies (the primary efficacy variable is time to second PGTC seizure). As a result, the protocol was amended to reflect this focus. Furthermore, a maximum sample size of 250 subjects was introduced if 125 events were not observed on or before the 200th subject randomized. This is standard for event-driven studies and represents an approximate 25% increase from the projected sample size, in case the event rate is lower than anticipated.

Other changes made in this amendment are to provide clarification or administrative in nature.

Modifications and changes

Global changes

The following global changes were made within the protocol:

- Study contact information was updated.
- Additional sites and countries were added.
- PedsQL, BRIEF, and Achenbach CBCL assessments were added.
- Vital signs were updated to include orthostatic assessments.
- Subject age range for the QOLIE-31-P (subjects ≥18 years of age) and the PedsQL (for subjects <18 years of age) was added.
- The maximum study duration and the maximum duration of study drug administration were increased by 1 week as a result of the change to the End of Study Period.
- Baseline failures and study completers were defined.
- Section renumbering was done as needed when sections were added or removed.
- Minor editorial/administrative/organizational changes were made throughout the protocol.
- Assessments by visit were updated throughout text and the Schedule study of assessments (Table 5–1).

Specific changes

Change #1

Title page:

The title was updated from “Protocol SP0982” to “Protocol SP0982 Amendment 1.”

The information below was revised to include Protocol Amendment 1 and the type of protocol amendment:

Protocol/Amendment Number	Date	Type of Amendment
Final Protocol	05 Aug 2011	N/A

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	05 Aug 2011	Not applicable
Protocol Amendment 1	25 Sep 2012	Substantial

Change #2

Section 1 Summary

First paragraph

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multi-center study designed to assess the efficacy of adjunctive lacosamide (LCM, VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) 400mg/day (200mg, twice daily [bid]) compared to placebo for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects with idiopathic generalized epilepsy (IGE) in prolonging the time to second PGTC) seizure, despite treatment with 1 to 2 concomitant antiepileptic drugs (AEDs).

Has been changed to:

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of oral lacosamide (LCM) (VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) 400mg/day (200mg, twice daily [bid]) vs placebo as adjunctive therapy for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects ≥12 years of age with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant antiepileptic drugs (AEDs) independent of the number of prior failed AEDs (see Section 7.8)

Seventh through ninth paragraphs

The primary efficacy variable is the time to the second PGTC seizure during the 24 week Evaluation Period.

Secondary efficacy variables include the percent change in PGTC seizure frequency per 28 days from Baseline (combined historical and prospective) to the first 5 weeks of the Evaluation Period and to the 24-week Evaluation Period.

Other efficacy variables include percent change in days with absence seizures, percent change in days with myoclonic seizures, seizure free status for PGTC seizures and for all seizure types, 50% response for PGTC seizures, 50% response for days with absence seizures, and 50% response for days with myoclonic seizures, change from Baseline in Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), EuroQol 5Dimension (EQ 5D) Quality of Life Assessment items, healthcare resource use, number of working or school days lost by subject and/or caregiver, and socio-professional data.

Have been changed to:

The primary efficacy variable is the time to the second PGTC seizure during the 24-week Treatment Period. The key secondary efficacy variable is the time to the first PGTC seizure during the 24-week Treatment Period, which will use a gatekeeping strategy to assess statistical

significance (see Section 13.3.2). Other secondary efficacy variables include 1) the percent change in PGTC seizure frequency per 28 days from the Combined Baseline (Combined 12-week Historical and 4-week Prospective Baseline) to the first 5 weeks of the Treatment Period, 2) from the Combined Baseline to the full Treatment Period and 3) seizure-free status for PGTC seizures during the 24-week Treatment Period.

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs); withdrawal due to AEs; changes in hematology, chemistry, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; changes in neurological examination findings. In addition for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]), and quality of life assessments (Pediatric Quality of Life Inventory [PedsQL]).

Change #3

Sections 3.1 Primary objective

The primary study objective is to demonstrate the efficacy of adjunctive LCM at the dose of 400mg/day (200mg bid) compared to placebo in subjects with IGE with uncontrolled PGTC seizures despite treatment with 1 to 2 concomitant AEDs.

Has been changed to:

The primary study objective is to demonstrate the efficacy of oral LCM (400mg/day [200mg bid]) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8).

Change #4

Sections 4.1 Efficacy variables

The following sections have been updated.

Sections 4.1.2 Secondary efficacy variables

Secondary efficacy variables include:

- Percent change in PGTC seizure frequency per 28 days from Baseline (combined historical and prospective) to the first 5 weeks of the Evaluation Period.
- Percent change in PGTC seizure frequency per 28 days from Baseline (combined historical and prospective) to the 24-week Evaluation Period.

Have been changed to:

The key secondary variable is:

- Time to the first PGTC seizure during the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 5 weeks of the Treatment Period
- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period

Sections 4.1.3 Other efficacy variables

Other efficacy variables include:

- Percent change in days with absence seizures and days with myoclonic seizures, respectively, per 28 days from prospective Baseline to the first 5 weeks of the Evaluation Period and to the 24-week Evaluation Period.
- Seizure free status (yes, no) for PGTC seizures for the first 12 weeks of the Evaluation Period and for the 24-week Evaluation Period.
- Seizure free status (yes, no) for all seizure types for the first 12 weeks of the Evaluation and for the 24-week Evaluation Period.
- 50% response for PGTC seizures during the first 5 weeks of the Evaluation Period, the first 12 weeks of the Evaluation Period, and the 24-week Evaluation Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from Baseline (combined historical and prospective) to the respective period.
- 50% response for days with absence seizures and days with myoclonic seizures, respectively, during the first 12 weeks of the Evaluation Period and the 24-week Evaluation Period; a responder is a subject experiencing ≥50% reduction in days with absence seizures per 28 days from prospective Baseline to the first 12 weeks of the Evaluation Period.
- Change from Baseline in patient weighted QOLIE-31-P subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores.
- EQ-5D Quality of Life Assessment items.
- Healthcare resource use: medical procedures, hospitalizations and healthcare provider visits.
- Number of working or school days lost by subject and/or caregiver.
- Socio-professional data.

Has been changed to:

Other efficacy variables are:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- Percent change in days with absence seizures per 28 days from the Combined Baseline to the 24-week Treatment Period

- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period among subjects who completed the first 12 weeks of the Treatment Period.
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period among subjects who completed the 24-week Treatment Period
- Seizure-free status (yes, no) for all seizure types for the first 12 weeks of the Treatment Period among subjects who completed the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all seizure types for the 24-week Treatment Period among subjects who completed the 24-week Treatment Period
- 50% response for PGTC seizures during the first 5 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 12 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 12 weeks of the Treatment Period
- 50% response for PGTC seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the 24-week Treatment Period
- 50% response for days with absence seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in days with absence seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- 50% response for days with myoclonic seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in days with myoclonic seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the PedsQL subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- EuroQol-5 Dimension (EQ-5D-3L) items
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject
- Number of days with help from a caregiver

Change #5

Section 4.2 Safety variables

Safety variables include

- AEs as reported spontaneously by the subject and/or caregiver or observed by the investigator.
- Subject withdrawal due to AE.
- Changes in hematology, chemistry, and urinalysis parameters.
- Changes in 12-lead ECGs.
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight) and neurological examination findings.

Has been changed to:

Section 4.2 Safety variables

The safety variables are:

- AEs as reported spontaneously by the subject and/or caregiver or observed by the investigator.
- Subject withdrawal due to AE
- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs

Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings.

The following section was added.

Section 4.2.1 Other safety variables

Other safety variables are:

- Achenbach CBCL
- Cognitive function assessment BRIEF

Change #6

Section 5.1 Study description

Paragraph 1

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multi-center study designed to assess the efficacy of adjunctive LCM 400mg/day (200mg bid) compared to placebo for uncontrolled PGTC seizures in subjects with IGE in prolonging the time to second PGTC seizure, despite treatment with 1 to 2 concomitant AEDs.

Has been changed to:

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM (400mg/day [200mg bid]) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects ≥12 years of age with IGE currently taking 1 to

3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8). This study will also assess the safety, tolerability, and PK of LCM use in this population.

Paragraph 11

At the end of the Prospective Baseline, eligible subjects will be randomized at Visit 2 to LCM 400mg/day (200mg bid) or placebo in a 1:1 (active/placebo) fashion and begin the Evaluation Period with a double-blind 3-week titration.

Has been changed to:

At the end of the Prospective Baseline (Visit 2), eligible subjects will be randomized to receive LCM (400mg/day [200mg bid]) or placebo in a 1:1 fashion (active:placebo) and stratified by Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) and by age at informed consent (≥12 to <18 years of age vs ≥18 years of age). The Treatment Period starts at the time of the Randomization Visit (Visit 2).

Change #7

Section 6.1 Inclusion criteria

Inclusion criterion 4 was added and subsequent criteria were renumbered:

4. Subject is of normal intelligence for age in the judgment of the investigator.

Inclusion criterion 3, 4, 7, and 8:

3. Male and female subjects 12 years of age and older with a body weight≥30kg.
4. Subject with a confirmed diagnosis of at least 1 year prior to Visit 1 and a disease onset at 4 to 25 years, consistent with IGE experiencing PGTC seizures (type IIE) that are classifiable according to the International League Against Epilepsy Classification of Epileptic Seizures (Epilepsia, 1981)
7. Subject has been maintained on a stable dose regimen of 1 to 2 marketed AEDs for at least 28 days prior to Visit 1 and during the Prospective Baseline with or without additional concurrent stable VNS. Vagus Nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline. Stable daily doses of benzodiazepines will be counted as AEDs.
8. Subjects are required to have had an EEG report showing discharges consistent with IGE confirmed by an Independent Central Reviewer.

Has been changed to:

3. Male and female subjects 12 years of age and older with a body weight ≥50kg.
5. Subject with a confirmed diagnosis at least 24 weeks prior to Visit 1 and a disease onset at 5 to 30 years of age, consistent with IGE experiencing PGTC seizures (Type IIE) that are classifiable according to the ILAE Classification of Epileptic Seizures (ILAE, 1981).
8. Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs OR 1 to 3 AEDs (with at least 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS. (see Section 7.8).

- Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

9. Subjects are required to have had an EEG tracing and report showing discharges consistent with IGE (generalized >3Hz epileptiform discharges and a normal EEG background) confirmed by a Central Reviewer.

Change #8

Section 6.2 Exclusion criteria

Added exclusion criterion 4 and subsequent criteria were renumbered:

4. Subject has a diagnosis of developmental delay or mental retardation including mild forms.

Exclusion criteria 5 and 16:

5. Subject has a history of status epilepticus within the 12-month period prior to Visit 1 or experiences status epilepticus during the Prospective Baseline.

16. Subject has impaired renal function, ie, creatinine clearance (CLcr) is lower than 30mL/minute, at Visit 1. Creatinine clearance will be estimated as follows:

- Adult males: CLcr = (140-age) x weight in kg/(72 x serum creatinine in mg/dL)
- Adult females: CLcr = [(140-age) x weight in kg/(72 x serum creatinine in mg/dL)] x 0.85

Have been changed to:

6. Subject has a history of status epilepticus.

17. Subject has impaired renal function, ie, creatinine clearance (CLcr) is lower than 50mL/min.

Change #9

7.9 Concomitant treatments medications/therapies

Subject must have been maintained on a stable dose regimen of 1 to 2 marketed AEDs for at least 28 days prior to Visit 1 and must remain stable during the course of the study. Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and must remain unchanged during the course of the study.

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

- Neuroleptics
- 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.

- The chronic use of benzodiazepines is allowed for treatment of epilepsy. Benzodiazepines will be counted as one 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, are not allowed during the study.

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:

Section 7.8 Concomitant medication/treatment

7.8.1 Prohibited concomitant treatments (medications and therapies)

Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 1 to 3 AEDs (with at least 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period with or without additional concurrent stable VNS.

- Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and must remain unchanged during the course of the study.
- The chronic (daily dose) use of benzodiazepines is allowed regardless of indication and will be counted as 1 of the 3 allowed AEDs.
- Intermittent use of benzodiazepines (limited to 2 doses per 28 days) is allowed only for epilepsy indications if established at least 28 days prior to Visit 1. Intermittent use of benzodiazepines for any other indication is prohibited during the study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

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

- Neuroleptics.
- MAO inhibitors.
- Barbiturates (except as antiepileptic medications).
- Narcotic analgesics.
- Only stable use of amphetamines and sedative antihistamines is allowed during the study.
- Only stable, low doses of non-benzodiazepine anxiolytics or once-daily hypnotics 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. 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 #10

Section 7.10 Blinding

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

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

An interactive voice/web response system (IXRS) will be used to assign a treatment to subjects who meet eligibility criteria at Visit 1, based on a predetermined randomization schedule. The IXRS is used to control all drug distribution and inventory for this study.

Has been changed to:

Section 7.9 Blinding

UCB Global Clinical Trial Supply will create a packaging list using a validated application. The packaging list will be provided to the interactive voice/web response system (IVRS/IWRS) vendor and to the packaging vendor who will prepare the kits accordingly.

The treatment randomization schedule will be generated by UCB (or designee) in a manner that will ensure that the study team remains blinded, in accordance with current standard operating procedures (SOPs). The randomization schedule will be maintained in a secure location until the study is unblinded for the final statistical analysis.

All sponsor, investigator sites, and contract research organization (CRO) staff involved with the study will be blinded to the treatment code with the following exceptions:

- Sponsor personnel and its subcontractors directly involved in the packaging of the IMP or in the management of the IVRS/IWRS.
- Sponsor pharmacovigilance staff will receive separate access to the IVRS/IWRS in order to meet their requirements for serious adverse event (SAE) reporting to regulatory authorities.
- Central laboratory staff assaying study drug. However, no randomization list will be provided.

An interim futility assessment is planned to allow UCB to consider terminating the study should the likelihood of a positive outcome be unacceptably low based on an unblinded assessment of interim data by an independent data monitoring committee (IDMC). Such an interim assessment will be conducted in a manner that ensures that blinding is not compromised for individuals involved with operational aspects of the study nor individuals involved with the planning and conduct of the final statistical analyses. The 3 planned interim safety assessments will be conducted similarly to assure that blinding is maintained.

Change #11

The following section and text was added and subsequent sections were renumbered.

Section 9.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Time to the first PGTC seizure during the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 5 weeks of the Treatment Period
- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period

Change #12

Section 9.2 Other efficacy variables

Other efficacy variables include:

- Percent change in days with absence seizures and days with myoclonic seizures, respectively, per 28 days from prospective Baseline to the first 5 weeks of the Evaluation Period and to the 24-week Evaluation Period.
- Seizure free status (yes, no) for PGTC seizures for the first 12 weeks of the Evaluation Period and for the 24-week Evaluation Period.
- Seizure free status (yes, no) for all seizure types for the first 12 weeks of the Evaluation and for the 24-week Evaluation Period.
- 50% response for PGTC seizures during the first 5 weeks of the Evaluation Period, the first 12 weeks of the Evaluation Period, and the 24-week Evaluation Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from Baseline (combined Historical and Prospective) to the respective period.
- 50% response for days with absence seizures and days with myoclonic seizures, respectively, during the first 12 weeks of the Evaluation Period and the 24-week Evaluation Period; a responder is a subject experiencing ≥50% reduction in days with absence seizures per 28 days from prospective Baseline to the first 12 weeks of the Evaluation Period.
- Change from Baseline in patient weighted QOLIE-31-P subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores.
- EQ-5D Quality of Life Assessment items.
- Healthcare resource use: medical procedures, hospitalizations and healthcare provider visits.

- Number of working or school days lost by subject and/or caregiver.
- Socio-professional data

Has been changed to:

Section 9.3 Other efficacy variables

Other efficacy variables are:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- Percent change in days with absence seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period among subjects who completed the first 12 weeks of the Treatment Period.
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period among subjects who completed the 24-week Treatment Period
- Seizure-free status (yes, no) for all seizure types for the 12-week Treatment Period among subjects who completed the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all seizure types for the 24-week Treatment Period among subjects who completed the 24-week Treatment Period
- 50% response for PGTC seizures during the first 5 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 12 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 12 weeks of the Treatment Period
- 50% response for PGTC seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the 24-week Treatment Period
- 50% response for days with absence seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in days with absence seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- 50% response for days with myoclonic seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in days with myoclonic seizures per 28 days from the Combined Baseline to the 24-week Treatment Period

- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the PedsQL subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- EQ-5D-3L items
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject
- Number of days with help from a caregiver

Change #13

The following section number and text was added:

Section 9.3.3 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).

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects 12 years of age 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 HRQoL is measured for pediatric subjects ≥2 years to ≤18 years of age.

The multidimensional 23-item PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). 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 23 items, with higher scores indicating higher HRQoL.

Change #14

Section 10 Assessments of safety

The following section was updated.

Section 10.7.1 Vital signs and body weight

Noninvasive blood pressure (systolic and diastolic) and pulse rate will be measured at clinic visits in a sitting position after at least 3 minutes at rest, according to the schedule of study assessments in Table 5.1. Body weight will be determined without shoes and wearing light clothing, according to the schedule of study assessments in Table 5.1. Weight and height will be recorded according to the schedule of study assessments in Table 5.1.

Has been changed to:

Section 10.7.2 Vital signs and body weight

Noninvasive BP (systolic and diastolic) and pulse rate will be measured at clinic visits in a supine position after at least 3 minutes at rest, according to the schedule of study assessments in Table 5–1. Assessment of orthostatic changes will be as follows: after the 3-minute measurement in a supine position, the subject is asked to stand and BP and pulse rate are taken 1 minute and 3 minutes after standing up as feasible, Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

Body weight will be determined without shoes and wearing light clothing and height will be measured without shoes. Body weight and height will be measured using equipment that is age appropriate and assessed according to the tabular schedule of study assessments (Table 5–1).

The following sections were added.

Section 10.7.4 Tanner stage

At Visit 1 and Visit 9/ET Visit, the investigator or qualified designee will evaluate the subject's sexual development using a 3-item scale. The Tanner Stage will be performed for subjects who are <18 years of age at Visit 1. At Visit 9/ET Visit, if subject is >18years of age, a repeat assessment is not necessary.

Section 10.7.7 Achenbach CBCL

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. Behavioral problems will be scored by the parent(s)/legal representative(s). For subjects ≥12 years to <18 years of age, the CBCL/6 to 18 version will be used.

The same scale will be completed at Visit 2, Visit 4, and Visit 9/ET Visit by the parent(s)/legal representative(s). The completion of the Achenbach CBCL will require approximately 45 minutes.

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

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

Eight syndrome scores will be calculated from these questionnaires, which will in turn be summarized by 2 composite scores. Additionally, for each score on the questionnaire, 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 to 18 includes ratings related to performance in school, activities in leisure time, and special interests.

Section 10.7.8 BRIEF

The BRIEF is a validated tool that will be used for the evaluation of subjects ≥5 years of age. The BRIEF will be administered at the Visit 2, Visit 4, and Visit 9/ET Visit.

The BRIEF includes rating forms used by parents to assess subjects' executive functioning and include validity scales to measure negativity and inconsistency of responses.

The BRIEF Rating form contains items in nonoverlapping clinical scales and validity 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. Factor analytic studies and structural equation modeling provide support for the 2 factor model of executive functioning as encompassed by the 2 Indexes.

Change #15

Section 13.1.5 Per Protocol Set

The Per Protocol Set (PPS) is a subset of the FAS excluding subjects with important protocol violations affecting the interpretation of the primary efficacy analysis, to be determined during the Data Review Meeting.

Has been changed to:

The Per Protocol Set (PPS) is a subset of the FAS excluding subjects who completed fewer than 5 weeks of treatment or subjects with important protocol violations affecting the interpretation of the primary efficacy analysis. Important protocol violations will be determined during the Data Review Meeting prior to unblinding.

Change #16

Section 13.3 Planned efficacy analyses

The following sections were updated.

Section 13.3.1 Analysis of the primary efficacy variable

The primary analysis of the primary variable is performed using a cox regression on the dependent variable day of the occurrence of the second PGTC seizure during the Evaluation Period (after first intake of study medication) adjusted for the subject's Baseline PGTC seizure frequency per 28 days as covariate. Subjects who prematurely discontinue from the study during the Evaluation Period for reasons unrelated to occurrence of the 2nd PGTC seizure will be censored on the date of last dose of study medication during the Evaluation Period.

The treatment effect will be estimated and a confirmatory 1-sided 0.025-level test for superiority of LCM over placebo will be performed by reporting 2-sided p-values for the treatment effect and comparing to the level of 0.05. If and only if the p-value is below or equal to 0.05 and the point estimator for the treatment effect favors LCM, the hypothesis that "LCM does not positively influence the time until day of second PGTC seizure" will be declined and the alternative hypothesis of "LCM is superior compared to the treatment with placebo with respect to the duration until second PGTC seizure happens" will be accepted.

Additionally, Kaplan-Meier (KM) plot for time to second PGTC seizure as well as the KM estimate for the median time to second PGTC will be provided.

The above mentioned analyses will be performed using the FAS.

Sensitivity analyses will be conducted by repeating the same analysis using the PPS. Any p-values generated herein are of exploratory nature only.

Has been changed to:

The primary efficacy variable, time to second PGTC seizure during the Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the 16 weeks prior to randomization) and age at informed consent (≥12 to <18 years of age vs ≥18 years of age). Pooling strategies for strata with no events (ie, no subjects who had a second PGTC seizure) will be defined in the SAP prior to unblinding. Subjects who prematurely discontinue from the study will be censored on the date of last dose of study drug during the Treatment Period.

Additionally, a Kaplan-Meier (KM) plot for time to second PGTC seizure as well as the KM estimate for the median time to second PGTC seizure will be provided. This analysis will be performed using the FAS population.

Testing for the primary endpoint will be done at the 5% level (2-sided). A gatekeeping strategy (Marcus et al, 1996) will be used to test the key secondary efficacy variable provided that the primary endpoint is statistically significant (See Section 13.3.2 for additional details). No additional adjustments for multiplicity are required as all additional inferences will be hypothesis-generating only.

The following additional sensitivity analyses on the primary efficacy endpoint will be conducted in order to assess the effect of dropouts and protocol deviations on the primary endpoint:

- Repeat the primary analysis using the PPS.
- Repeat the primary analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy, consent withdrawn, or lost to follow-up will be analyzed as treatment failures (ie, events at the time of discontinuation).

Repeat the primary analysis using the FAS, except all subjects who prematurely discontinue due to lack of efficacy or AEs only will be analyzed as treatment failures.

Section 13.3.2 Secondary analysis and other efficacy analysis

Analyses on secondary efficacy variables will be performed on the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable as described in Section 13.3.1 will be exploratory only.

Any subject who is seizure-free with regard to PGTC seizure after the 12- the 24-week Treatment Period is regarded as a remitter. In one approach, Fisher's exact test will be used to evaluate any differences between the 2 treatment groups, ie, LCM and placebo. For seizure types other than PGTC seizures (ie, myoclonic absence, tonic, clonic, and atonic seizures), frequency counts per 28 days and changes as well as percent changes from Prospective Baseline will be provided for the Evaluation Period as well as for the first 12 weeks of treatment. An analysis of covariance of the changes from Prospective Baseline and log-transformed percent changes from Baseline will be applied as described for PGTC seizure evaluation, respectively. Further approaches of analyzing secondary variables will be described in a detailed SAP.

Has been changed to:

Analysis of the key secondary efficacy variable, time to first PGTC seizure during the Treatment Period, will be analyzed in the same manner as the primary endpoint using the FAS. A gatekeeping strategy will be employed to control the Type I error (Marcus et al, 1976). If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

The percent of subjects seizure-free at the end of the 24-week Treatment Period will be estimated from the Kaplan-Meier estimates of time to first seizure using 2-sided 95% confidence intervals.

Analyses of the other secondary efficacy variable will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described above), will be exploratory only.

The percent change in log-transformed PGTC seizure frequency during the first 5 weeks of the Treatment Period will be analyzed using analysis of covariance, controlling for Baseline seizure frequency. The percent change in log-transformed PGTC seizure frequency during the 24-week Treatment Period will be analyzed in a similar manner. Further approaches for the analysis of the secondary variable will be described in a detailed SAP.

Change #17

Section 13.7 Planned interim analysis and data monitoring

No interim analysis is planned for this study.

Has been changed to:

Some AEDs with sodium channel blocking properties can exacerbate some generalized seizure types, such as absence and myoclonic seizures. To enhance safety monitoring, 3 interim analyses are planned when 25%, 50%, and 75% of subjects experience an event (31, 62, and 93 events, respectively) or 24 weeks after 50, 100, and 150 subjects have been randomized, respectively, whichever comes first. An event is defined as the occurrence of the second PGTC seizure during the Treatment Period.

Three interim analyses for safety will be performed by the IDMC with a single futility assessment planned at the second interim analysis. Both safety and futility will be assessed in a manner that ensures that blinding is not compromised for individuals involved with operational aspects of the study, nor individuals involved with the planning and conduct of the final statistical analyses. Analysis of the primary endpoint (time to second PGTC seizure) will only be examined at the planned futility assessment; an unblinded, descriptive review of safety and seizure frequency data will be provided for all IDMC meetings.

Additional details, including the methods used for assessing futility, will be provided in the interim SAP. Neither futility nor the IDMC safety assessments are expected to have any impact on the Type 1 error as there will be no stopping rule for success in place; however, the significance level will be set using a Haybittle-Peto boundary at alpha=0.0001 so as not to require any adjustment to the overall alpha level for the final analysis.

The IDMC will consist of 3 voting members, none of whom will be involved with the conduct of the study, either by management or participation. In addition, there will be an independent reporting team, consisting of an independent statistician and statistical programmers, who will be completely independent from the blinded reporting team. The blinded reporting team will be responsible for all operational aspects of the study, including routine monitoring and cleaning of the data, programming, and quality control (QC) of all analyses defined in the interim SAP on blinded data.

The blinded study team will actively monitor the number of events in the study. Once the required number of events (or subjects) has been met and the blinded reporting team has completed the QC of the IDMC tables, figures, and listings (TFLs), the programs will be passed to the independent reporting team. The independent statistician will request unblinded treatment codes from the IVRS randomization coordinator and the TFLs will be re-run and QC'd using the actual treatment codes. Additional TFLs or ad hoc analyses can be requested by the IDMC based on their data review. Any changes to predefined TFLs or new requests will be handled by the independent reporting team.

The actual randomization codes and the unblinded outputs will be stored in a secure location which will be accessible only to the independent reporting team. A secure, restricted-access directory will hold electronic copies of documents such as meeting minutes, interim reports, emails, and periodic data deliveries. Only the independent reporting team will have access to this secure location.

Change #18

Section 13.8 Determination of sample size

When the sample size in both groups is 90, the log-rank test for equality of survival curves with a 0.025 one-sided significance level will have 90% power to detect the difference between the survival curves, when the assumed survival rate (based on time to second PGTC seizure) for placebo is 25.4% and for LCM is 48.2% (a constant hazard ratio of 0.533). This assumes no drop out during the study before the second PGTC seizure. These assumptions are derived from a lamotrigine (LTG) study, where after 3 months 30/58 subjects have encountered a third PGTC seizure under LTG and 44/59 subjects under placebo.

To adjust for a dropout rate of approximately 10% during the Evaluation Period for any other reason than the second PGTC seizure, sample sizes will be 100 per group.

Has been changed to:

Observing 125 events (subjects who had a second PGTC seizure during the 24-week Treatment Period) will provide 90% power to observe a hazard ratio of 0.56 at the 2-sided 5% level, assuming a nominal dropout rate of <10%. The observed hazard ratio was based on a 25.4% survival rate for placebo and 48.2% for lamotrigine from a previous study comparing lamotrigine and placebo (French et al, 2007). The observed hazard ratio in the lamotrigine study was 0.533; however, to provide a conservative margin, the hazard ratio was increased to 0.56 for estimating a sample size for the study. The rationale for the increase in the hazard ratio was 2-fold: different active compounds (LCM and lamotrigine) and a choice of time to second seizure as the primary efficacy endpoint (in the lamotrigine study, percent change in seizure frequency was the primary endpoint).

This is an event driven study. The study will be closed to enrollment once 125 events have been observed. If 125 events are observed prior to 200 subjects randomized, then enrollment will stop

and fewer than 200 subjects will be randomized. However, if 125 events are not observed after 200 subjects are randomized, then the study will continue to enroll up to a maximum of 250 subjects randomized or 125 events, whichever occurs first.

Change #19

Section 16 References

The following references were added.

Marcus R, Peritz E, Gabriel KR. On closed testing procedure with special reference to ordered analysis of variance. Biometrika. 1976;63:655-60.

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.

17.4 Protocol Amendment 2

Rationale for the amendment

The primary purpose of this substantial amendment is to identify significant changes to the study design and the inclusion of pediatric subjects (≥4 to 12 years of age).

In addition, the key study secondary efficacy variable was changed to more accurately represent the study design.

The protocol has been updated to include randomization stratified by age at informed consent for subjects ≥4 to <12 years of age. This is in order to maintain balance within each treatment arm and within the existing baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) as well as provide greater control for variability when analyzing the primary efficacy variable (time to second seizure).

An inclusion criterion was modified to include subjects ≥4 years of age. Exclusion criteria were modified in regards to subjects who have a diagnosis of developmental delay or mental retardation or a history of status epilepticus. The rationale for modifying the exclusion criteria is that subjects with developmental delay or mental retardation are more likely to have symptomatic rather than idiopathic seizures. The rationale for modifying the exclusion criteria for subjects with a history of status epilepticus is to align with the withdrawal criteria (ie, a subject may be withdrawn from the study due to an episode of status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new seizure type considered by the investigator to require intervention).

Other changes made in this amendment are to provide clarification or are administrative in nature.

Modifications and changes

Specific changes

Change #1

Title page:

The title was updated from "Protocol SP0982 Amendment 1" to "Protocol SP0982 Amendment 2."

IND 73809 was added.

The information below was revised to include Protocol Amendment 2 and the type of protocol amendment:

Protocol Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial

Change #2

SPONSOR DECLARATION

Clinical Project Manager
[redacted]
_____
Date/Signature

Clinical Study Biostatistician
[redacted]**, MS**
_____
Date/Signature

Study Physician
[redacted] **MD, PhD**
_____
Date/Signature

Associate Clinical Program Director
[redacted]**, PhD**
_____
Date/Signature

Has been changed to:

Clinical Project Manager
[redacted]**, MBA, MS**
_____
Date/Signature

Clinical Trial Biostatistician
[redacted]**, MA**
_____
Date/Signature

Study Physician
[redacted]**, MD, PhD**
_____
Date/Signature

Clinical Program Director
[redacted]**, MSc**
_____
Date/Signature

Change #3

SERIOUS ADVERSE EVENT REPORTING

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 Japan: +81 3 5283 1869
Email	Global (except Japan): DS_ICT@ucb.com Japan: JDSO@ucb.com

Has been changed to:

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	Europe and Rest of the World: +32 2 386 2421 USA: +1 770 970 8858 or +1 800 880 6949 or +1 866 890 3175 Canada: +1 877 582 8842
Email	Global: DSICT.-@ucb.com

Change #4

List of abbreviations

The following abbreviations have been added:

BRIEF®-P	Behavior Rating Inventory of Executive Function®-Preschool Version
EI-AED	Enzyme-inducing antiepileptic drug
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
PET	polyethylene terephthalate

Change #5

Section 1 Summary

Paragraph 1 through 7:

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of oral lacosamide (LCM) (VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) 400mg/day (200mg, twice daily [bid]) vs placebo as adjunctive therapy for

uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects ≥12 years of age with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant antiepileptic drugs (AEDs) independent of the number of prior failed AEDs (see Section 7.8).

Approximately 200 subjects across approximately 150 sites in the US, Canada, Europe, Asia, and Australia with possible extension to other countries and regions, will be randomized in this study.

The maximum duration of study drug administration is 28 weeks. The study will last a maximum of 32 weeks per subject. The study consists of a 4-week Prospective Baseline Period, a 5-week (minimum) to 24-week (maximum) Treatment Period (including a 3-week titration), and a 3- to 4-week End of Study Period.

Eligible subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 9 (Week 24) or the Early Termination (ET) Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete a 1-week blinded taper followed by a 2-week Safety Follow-up Period.

The primary study objective is to demonstrate the efficacy of oral LCM (400mg/day [200mg bid]) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE taking 1 to 3 concomitant AEDs (See Section 7.8).

The primary efficacy variable is the time to the second PGTC seizure during the 24-week Treatment Period. The key secondary efficacy variable is the time to the first PGTC seizure during the 24-week Treatment Period, which will use a gatekeeping strategy to assess statistical significance (see Section 13.3.2). Other secondary efficacy variables include 1) the percent change in PGTC seizure frequency per 28 days from the Combined Baseline (Combined 12-week Historical and 4-week Prospective Baseline) to the first 5 weeks of the Treatment Period, 2) from the Combined Baseline to the full Treatment Period, and 3) seizure-free status for PGTC seizures during the 24-week Treatment Period.

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs); withdrawal due to AEs; changes in hematology, chemistry, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; changes in neurological examination findings. In addition for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]), and quality of life assessments (Pediatric Quality of Life Inventory [PedsQL]).

Have been changed to:

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of oral lacosamide (LCM) (VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) twice daily [bid]) vs placebo as adjunctive therapy for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects ≥4 years of age with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant antiepileptic drugs (AEDs) independent of the number of prior failed AEDs (see Section 7.8).

Approximately 200 subjects across approximately 150 sites in the US, Canada, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

The maximum duration of study drug administration is 28 weeks. The study will last a maximum of 36 weeks per subject.

The study is comprised of the following: a 4-week Prospective Baseline Period and a 6-week (minimum) to 24-week (maximum) Treatment Period, which includes a 6-week Titration Period and an 18-week (maximum) Maintenance Period. Eligible subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 10 (Week 24) or the Early Termination (ET) Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period.

The primary study objective is to demonstrate the efficacy of oral LCM vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE taking 1 to 3 concomitant AEDs (See Section 7.8).

The primary efficacy variable is the time to the second PGTC seizure during the 24-week Treatment Period. The key secondary efficacy variable is seizure freedom for PGTC seizures for the 24-week Treatment Period, which will use a gatekeeping strategy to assess statistical significance (see Section 13.3.2). Other secondary efficacy variables include 1) the percent change in PGTC seizure frequency per 28 days from the Combined Baseline (Combined 12-week Historical and 4-week Prospective Baseline) to the first 6 weeks of the Treatment Period, 2) the percent change in PGTC seizure frequency per 28 days from the Combined Baseline to the full Treatment Period, and 3) time to the first PGTC seizure during the 24-week Treatment Period.

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs); withdrawal due to AEs; changes in hematology, chemistry, endocrinology, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; and changes in physical and neurological examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using a behavioral assessment (Achenbach Child Behavior Checklist [CBCL]) and a cognitive function assessment (Behavior Rating Inventory of Executive Function® [BRIEF®]/Behavior Rating Inventory of Executive Function-Preschool Version [BRIEF-P]).

Change #6

Section 2 Introduction

Paragraph 1:

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). The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic seizures (23%), absence seizures (6%), and myoclonic seizures (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

Has 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). Epileptic seizures occur in the context of a wide range of epilepsy syndromes that may be of genetic, structural/metabolic, or of unknown origin. The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic (23%), absence (6%), and myoclonic (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

Paragraph 2, fourth sentence:

Generalized epilepsies can be further classified as primary/idiopathic and secondary/symptomatic epilepsies.

Has been changed to:

Generalized seizures typically occur with idiopathic generalized (genetic) or symptomatic generalized epilepsy syndromes.

Paragraph 6 has been removed.

The following paragraph (after Paragraph 8) has been added:

Preliminary safety and PK data suggest that exposure-response in pediatric and adult subjects treated with LCM will be similar. Lacosamide is being evaluated in pediatric subjects 1 month to 17 years of age in 3 ongoing studies: SP847 (open-label, Phase 2, PK, tolerability, and safety study), SP848 (open-label long-term safety study), and SP1047 (PK study with a 1-day evaluation period).

Paragraph 9

Considering the significant unmet medical need for new treatment options for patients with PGTC seizures, the efficacy and tolerability profiles for LCM were evaluated in a series of animal models followed by a Phase 2 pilot study of subjects with uncontrolled PGTC seizures.

Has been changed to:

Considering the significant unmet medical need for new treatment options for patients with IGE and PGTC seizures, the efficacy and tolerability profiles for LCM were evaluated in a series of animal models followed by a Phase 2 pilot study of subjects with IGE and uncontrolled PGTC seizures.

Paragraph 11, first sentence:

The Phase 2, multicenter, open-label, pilot study (SP0961) designed to assess the safety of adjunctive LCM (400mg/day) for uncontrolled PGTC seizures in adult subjects, aged 16 to 65 years, with IGE is clinically complete.

Has been changed to:

The Phase 2, multicenter, open-label, pilot study (SP0961) designed to assess the safety of adjunctive LCM (400mg/day) for uncontrolled PGTC seizures in subjects, aged 16 to 65 years, with IGE is complete.

Paragraph 12:

The purpose of this study (SP0982) is to evaluate the efficacy and safety of LCM for uncontrolled PGTC seizures in subjects ≥12 years of age with IGE.

Has been changed to:

The purpose of this study (SP0982) is to evaluate the efficacy and safety of LCM (LCM 8mg/kg/day to 12mg/kg/day for pediatric subjects weighing <30kg, LCM 6mg/kg/day to 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 300mg/day to 400mg/day for adult subjects [≥18 years of age] and pediatric subjects [<18 years of age] weighing ≥50kg) (see Table 7-3) for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE.

Change #7

Section 3.1 Primary objective

The primary study objective is to demonstrate the efficacy of oral LCM (400mg/day [200mg bid]) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8).

Has been changed to:

The primary study objective is to demonstrate the efficacy of oral LCM (Table 7–3) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8).

Change #8

Section 4.1.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Time to the first PGTC seizure during the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 5 weeks of the Treatment Period
- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period

Has been changed to:

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures for the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 6 weeks of the Treatment Period

- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Time to the first PGTC seizure during the 24-week Treatment Period

Change #9

Section 4.1.3 Other efficacy variables

Bullets 1, 3, 9 and 15:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 5 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- EuroQol-5 Dimension (EQ-5D-3L) items

Have been changed to:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 6 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- Change from Baseline to end of treatment or ET in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)

Change #10

Section 4.2 Safety variables

Bullet 3:

- Changes in hematology, chemistry, and urinalysis parameters

Has been changed to:

- Changes in hematology, chemistry, endocrinology, and urinalysis parameters

Section 4.2.1 Other safety variables

Other safety variables are:

- Achenbach CBCL
- Cognitive function assessment BRIEF

Has been changed to:

Other safety variables are:

- Behavioral assessment (Achenbach CBCL/1½-5 or CBCL/6-18)
- Cognitive function assessment (BRIEF-P or BRIEF)

Change #11

Section 5.1 Study description

Paragraph 1, first sentence:

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM (400mg/day [200mg bid]) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects ≥12 years of age with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8).

Has been changed to:

SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM (see Table 7-3) vs placebo as adjunctive therapy for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs (see Section 7.8).

Paragraphs 2 through 4:

Approximately 200 subjects across approximately 150 sites in the US, Canada, Europe, Asia, and Australia with possible extension to other countries and regions, will be randomized in this study.

The study will last a maximum of 32 weeks per subject. The study consists of a 4-week Prospective Baseline Period, a 5-week (minimum) to 24-week (maximum) Treatment Period (including a 3-week titration), and a 3- to 4-week End of Study Period.

Subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 9 (Week 24) or the ET Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete a 1-week blinded taper followed by a 2-week Safety Follow-up Period.

Have been changed to:

Approximately 200 subjects across approximately 150 sites in the US, Canada, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

The study will last a maximum of 36 weeks per subject. The study is comprised of the following: a 4-week Prospective Baseline Period and a 6-week (minimum) to 24-week (maximum) Treatment Period, which includes a 6-week Titration Period and an 18-week (maximum) Maintenance Period. Eligible subjects who choose to enter the open-label extension study (EP0012) after the completion of Visit 10 (Week 24) or the Early Termination (ET) Visit will complete a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period.

Paragraph 5 sentence 4:

Thus, a total of ≥3 PGTC seizures in the 16-week Combined Baseline Period (12-week Historical and 4-week Prospective Baseline) are required for study randomization to treatment (see Section 6.1, Inclusion Criterion 6).

Has been changed to:

Thus, a total of ≥3 PGTC seizures in the 16-week Combined Baseline Period (12-week Historical and 4-week Prospective Baseline) are required for study randomization to treatment (see Section 6.1, Inclusion Criterion 5)

Paragraph 6, sentence 1 through 5:

At Visit 1, subjects will be given a seizure diary to document all types of seizures, concomitant AEDs, and any other pertinent health status information. Seizure frequency and type eligibility will be verified by reliably documented seizure history collected (eg, in a seizure diary) over the 12 weeks prior to Visit 1. In addition, prior to Visit 1, subjects are required to have had an EEG showing discharges consistent with IGE (generalized >3Hz epileptiform discharges and a normal EEG background). A confirmatory EEG may be performed during the Prospective Baseline, if approved by the Central Reviewer. Investigators will send a copy of the EEG tracing and report to the Central Reviewer.

Has been changed to:

At Visit 1, subjects and/or caregivers will be given a seizure diary to document all types of seizures, concomitant AEDs, and any other pertinent health status information. Seizure frequency and type eligibility will be verified by reliably documented seizure history collected (eg, in a seizure diary) 12 weeks prior to Visit 1. In addition, prior to Visit 1, subjects are required to have had an EEG showing discharges consistent with IGE (eg, generalized ≥3Hz epileptiform discharges and a normal EEG background). A confirmatory EEG may be performed during the Prospective Baseline, if approved by the Central Reviewer. Investigators will send a copy of the EEG report to the Central Reviewer.

Paragraph 7, sentence 5:

Subjects will be contacted via telephone 2 weeks following Visit 1 to assess continued eligibility and will be reminded of the importance of accurate seizure diary completion.

Has been changed to:

Subjects and/or caregivers will be contacted via telephone 2 weeks following Visit 1 to assess continued eligibility and will be reminded of the importance of accurate seizure diary completion.

Paragraph 8 through the end of the section:

At the end of the Prospective Baseline (Visit 2), eligible subjects will be randomized to receive LCM (400mg/day [200mg bid]) or placebo in a 1:1 fashion (active:placebo) and stratified by Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) and by age at informed consent (≥12 to <18 years of age vs ≥18 years of age). The Treatment Period starts at the time of the Randomization Visit (Visit 2).

At the Randomization Visit (Visit 2) subjects will complete the Visit 2 assessments and take the first dose of study drug at the clinic. Subjects will begin with a dose titration at LCM 100mg/day

(50mg bid) or placebo for 1 week. Subjects will receive a telephone call at the end of the first week of dose titration reminding them to increase their dose to LCM 200mg/day (100mg bid) or placebo. Subjects will return to the clinic at Visit 3 (end of Week 2) and will receive LCM 300mg/day (150mg bid) or placebo. At the end of Week 3, subjects will receive a telephone call reminding them to increase their dose to LCM 400mg/day (200mg bid) or placebo for the remaining duration of the Treatment Period. Five additional clinic visits will occur during the Treatment Period: Visit 5 (Week 8), Visit 6 (Week 12), Visit 7 (Week 16), Visit 8 (Week 20), and ET Visit/Visit 9 (Week 24).

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥5 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures

Subjects must complete the first 5 weeks of the Treatment Period after randomization. Upon experiencing 2 PGTC seizures and completion of the first 5 weeks, the subject will complete the ET Visit. The seizures may occur on the same day, but the initiation and completion of each individual seizure must be distinguishable allowing reliable counting of individual seizures.

If a subject has <2 PGTC seizures during the first 5 weeks of the Treatment Period, the subject will continue until a total of 2 PGTC seizures have occurred or the 24-week Treatment Period has been completed. Subjects experiencing ≥2 PGTC seizures before the end of the 24-week Treatment Period will complete an ET Visit. Subjects who complete the 24-week Treatment Period will complete Visit 9 (Week 24). Eligible subjects who choose to enter EP0012 will complete a 4-week blinded transition followed by completion of the Final Clinic Visit. During the 4-week blinded transition, subjects receiving placebo during SP0982 will be titrated to LCM 400mg/day. For those subjects continuing participation in EP0012, the Final Clinic Visit will be the same as Visit 1 of EP0012 (see Section 7.2).

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 9 (Week 24), and a 1-week blinded taper followed by an End of Taper Visit. Following the End of Taper Visit, the subject will return 2 weeks after the last dose of study drug for a Final Clinic Visit (see Section 7.2).

Unscheduled visits may be performed at any time after Visit 1 at the discretion of the investigator.

No dose reduction is allowed until the subject reaches the randomized target dose. If the subject is unable to tolerate the target dose, a single dose reduction of study drug to LCM 300mg/day or placebo is permitted. No other dose reductions are allowed. In the case of intolerable AEs during the titration, the subject must be withdrawn from the study. If a dose reduction is required, the subject must come in for a visit (scheduled or unscheduled). If the subject is not able to tolerate the study drug after 1 dose reduction, the subject must be withdrawn from the study. All dose reductions should be discussed with the Medical Monitor. Once the dose has been reduced, it cannot be increased.

A schematic diagram of the study is provided in Section 5.3.

Has been changed to:

At the end of the Prospective Baseline (Visit 2), eligible subjects will be randomized to receive LCM or placebo (see Table7-1) in a 1:1 fashion (active:placebo) and stratified by Baseline PGTC

seizure frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) and by age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age, and ≥18 years of age). The Treatment Period starts at the time of the Randomization Visit (Visit 2).

At the Randomization Visit (Visit 2) eligible subjects will complete the Visit 2 assessments and take the first dose of study drug at the clinic and enter a 6-week Titration Period. The recommended LCM (or matching placebo) dosing during the Titration Period to achieve the target Maintenance Period doses is provided in Table7-1. All subjects should follow the recommended dosing schedule, unless dose adjustments based on tolerability are needed. Table7-2 provides LCM (or matching placebo) dosing with flexibility based on tolerability during the Titration Period. During the Titration Period, subjects must achieve a target Maintenance Period dose range (see Table7-3).

During the Maintenance Period, a single dose reduction of study drug or placebo is permitted as long as the minimum target dose is maintained (Table7-3). No other dose reductions are allowed. If a dose reduction is required, a (un)scheduled visit, either telephone or clinic visit, is required. If the subject is not able to tolerate the study drug after 1 dose reduction, the subject must enter the Taper Period and be withdrawn from the study. All dose reductions should be discussed with the Medical Monitor. Once the dose has been reduced, it cannot be increased.

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures

Subjects who experience >2 PGTC seizures and who also complete ≥6 weeks (ie, ≥42 days) of the treatment period after randomization will be required to exit and complete the ET Visit (Section 6.3). The seizures may occur on the same day, but the initiation and completion of each individual seizure must be distinguishable allowing reliable counting of individual seizures.

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24), respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. The Final Clinic Visit is the same as Visit 1 of EP0012 (see Section 7.2.3). During the 4-week blinded transition, subjects receiving placebo during SP0982 will have their dose titrated to LCM (see Table7-4).

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. Following the End of Taper Visit, there will be a 30-day Safety Follow-up Period (see Section 7.2.4).

Unscheduled visits may be performed at any time after Visit 1 at the discretion of the investigator.

Schematic diagrams of the study are provided in Section 5.3.

Change #12

Section 5.1.1 Study duration per subject

The maximum duration of study drug administration is 28 weeks. The study will last a maximum of 32 weeks per subject, consisting of the following study periods:

- 4-week Prospective Baseline Period
- 5-week (minimum) to 24-week (maximum) Treatment Period (including a 3-week titration)
- 3- to 4-week End of Study Period consisting of either:
  - 4-week blinded transition (required for subjects participating in EP0012)
  - 1-week blinded taper followed by a 2-week Safety Follow-up Period (required for subjects not participating in EP0012)

Subjects can enter EP0012 after the completion of Visit 9 (Week 24) or ET Visit and a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete a 1-week blinded taper followed by a 2-week Safety Follow-up Period (see Section 7.2).

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

Has been changed to:

The maximum duration of study drug administration is 28 weeks. The study will last a maximum of 36 weeks per subject, consisting of the following study periods:

- 4-week Prospective Baseline Period
- 6-week (minimum) to 24-week (maximum) Treatment Period (including a 6-week titration)
- 4-week End of Study Period consisting of either:
  - 4-week blinded transition (required for subjects participating in EP0012)
  - Up to 4-week blinded taper followed by a 30-day Safety Follow-up Period (required for subjects not participating in EP0012)

Subjects can enter EP0012 after the completion of Visit 10 (Week 24) or ET Visit and a 4-week blinded transition. Subjects who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by a 30-day Safety Follow-up Period (see Section 7.2.4).

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

Change #13

Section 5.1.2 Subject completers

The following subjects will be considered study completers:

- Subjects who meet any of the predetermined exit criteria (Section 6.3)

Subjects who do not experience 2 PGTC seizures within the 24-week Treatment Period

Has been changed to:

The following subjects will be considered study completers:

- Subjects who meet any of the predetermined exit criteria (Section 6.3)
- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period

Change #14

Section 5.1.3 Planned number of subjects

The number of screened subjects may vary according to the observed screen failure rate. Approximately 200 subjects (100 per treatment arm) will be randomized to achieve a total of 125 events, where an event is defined as the occurrence of the second PGTC seizure. There will be approximately 150 sites.

Has been changed to:

The number of screened subjects may vary according to the observed screen failure rate. Approximately 200 subjects (100 per treatment arm) will be randomized to achieve a total of 125 events, where an event is defined as the occurrence of the second PGTC seizure.

Subjects will be enrolled in the following age categories:

- ≥4 years of age to <12 years of age (approximately 50 subjects)
- ≥12 years of age to <18 years of age (approximately 50 subjects)
- ≥18 years of age (approximately 100 subjects)

There will be approximately 150 sites in order to recruit the required subjects; additional sites will be added if deemed necessary. A target of approximately 50% of the randomized subjects should consist of subjects <18 years of age. Of these 100 subjects, 50% will be enrolled in each of the 2 age categories <18 years of age.

Change #15

Section 5.1.4 Anticipated regions and countries

The study will be conducted in the US, Canada, Europe, Asia, and Australia, with possible extension to other countries and regions.

Has been changed to:

The study is planned to be conducted in the US, Canada, Europe, Asia, and Australia, with possible extension to other countries and regions.

Change #16

Section 5.2 Schedule of study assessments

Paragraph 1 and Table 5–1:

The schedule of study assessments is provided in Table 5–1.

Table 5–1: Schedule of study assessments for SP0982

	Prospective Baseline		Treatment Period										End of Study Period			Unscheduled[a]
Duration	**4 weeks**		**5 to 24 weeks (maximum)[b]**										**Taper**		**Transition**	**NA**
													1-week taper	**2-week safety follow-up**	**4-week transition**	
Visit[c]	**V1**	**TC**	**V2[d]**	**TC[e]**	**V3**	**TC[f]**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9/ ET[g]**	**End of Taper[h]**	**Final Clinic Visit[i]**	**Final Clinic Visit**	**Visit**
Study week	**-4**	**-2**		**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**27**	**28**	**NA**
Informed Consent/Assent	X															
Inclusion/Exclusion criteria	X	X	X													
Subject ID card dispensing	X															
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/Epilepsy history	X															
Physical exam (complete)[j]	X		X									X		X	X	
Physical exam (brief)[k]					X		X	X	X	X	X					
Neurological exam (complete)[l]	X		X									X		X	X	
Neurological exam (brief)[m]					X		X	X	X	X	X					
12-lead ECG[n]	X		X				X	X		X		X	X	X	X	
Vital signs (BP and pulse) including orthostatic assessments[z]	X		X		X		X	X	X	X	X	X	X	X	X	X
Body weight and height[o]	X								X			X	X	X	X	
EEG[p]	X															
Tanner Stage[q]	X											X				
Laboratory tests:																
Chemistry/hematology	X		X				X	X		X		X	X	X	X	
Urinalysis	X		X				X	X		X		X	X	X	X	
Pregnancy test[r]	X		X		X		X	X	X	X	X	X	X	X	X	
LCM plasma concentration[s]							X	X				X				
Contact IVRS/IWRS[t]	X		X		X		X	X	X	X	X	X	X	X	X	X
Randomization			X													
Dispense subject diary	X		X		X		X	X	X	X	X	X	X			
Subject diary return/review			X		X		X	X	X	X	X	X	X	X	X	
Dispense study drug[u]			X[v]		X		X	X	X	X	X	X				
Study drug review/return					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
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Achenbach CBCL[w]			X				X					X				

Table 5–1: Schedule of study assessments for SP0982

	Prospective Baseline		Treatment Period										End of Study Period			Unscheduled[a]
Duration	**4 weeks**		**5 to 24 weeks (maximum)[b]**										**Taper**		**Transition**	**NA**
													1-week taper	**2-week safety follow-up**	**4-week transition**	
Visit[c]	**V1**	**TC**	**V2[d]**	**TC[e]**	**V3**	**TC[f]**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9/ ET[g]**	**End of Taper[h]**	**Final Clinic Visit[i]**	**Final Clinic Visit**	**Visit**
Study week	**-4**	**-2**		**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**27**	**28**	**NA**
BRIEF[x]			X				X					X				
EQ-5D-3L			X									X				
QOLIE-31-P/PedsQL[y]			X									X				
C-SSRS	X		X		X		X	X	X	X	X	X	X	X	X	
Healthcare resource use	X		X		X		X	X	X	X	X	X	X	X	X	
Work/school days lost	X		X		X		X	X	X	X	X	X	X	X	X	
Days with help from a caregiver	X		X		X		X	X	X	X	X	X	X	X	X	
Socio-professional data			X													

AE=adverse event; AED=antiepileptic drug; bid=twice daily; BP=blood pressure; exam=examination; BRIEF= Behavior Rating Inventory of Executive Function®; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EEG=electroencephalogram; EQ-5D-3L= EuroQol-5D; ET=Early Termination; ID=identification; IGE=idiopathic generalized epilepsy; IVRS/IWRS=interactive voice/web response system; LCM=lacosamide; NA=not applicable; PEDsQL=Pediatric Quality of Life Inventory; PGTC=primary generalized tonic-clonic; QOLIE-31-P= Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31; TC=telephone contact; V=Visit

[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 above, further assessments can be completed as needed and may include ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed if the unscheduled visit is due to an AE.

[b] The Treatment Period starts at the time of the Randomization Visit (Visit 2). The Treatment Period continues until 1 of the following occurs (whichever occurs first): completion of ≥5 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures, or completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures.

[c] A window of ±2 days relative to Visit 1 is applicable for all visits and Telephone Contacts.

[d] All assessments at Visit 2 should be conducted prior to the first dose of study drug. At the end of the Prospective Baseline, subjects will be randomized at Visit 2 to receive LCM (400mg/day [200mg bid]) or placebo in a 1:1 fashion (active:placebo) and commence the Treatment Period with a double-blind 3-week titration. Randomization will be stratified based on the PGTC seizure frequency during the Combined Baseline Period (ie, ≤2 per 28 days vs >2 per 28 days) and age at informed consent (≥12 to <18 years of age vs ≥18 years of age).

[e] At the Randomization Visit (Visit 2), subjects will begin with a dose titration at LCM 100mg/day (50mg bid) or placebo for 1 week followed by LCM 200mg/day (100mg bid) or placebo for 1 week. Subjects will receive a telephone call at the end of the first week of titration reminding them to increase their dose to LCM 200mg/day (100mg bid) or placebo.

[f] Subjects will return to the clinic at Visit 3 (end of Week 2) and will receive LCM 300mg/day (150mg bid) or placebo. At the end of Week 3, subjects will receive a telephone call reminding them to increase their dose to LCM 400mg/day (200mg bid) or placebo for the remaining duration of the Treatment Period.

[g] Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure (Section 6.3).

[h] After the second PGTC seizure and completion of at least 5 weeks of the Treatment Period, or after completion of the 24-week Treatment Period; the subject may, at the ET Visit or Visit 9, respectively, enter EP0012. Subjects not entering EP0012 will taper study drug during a 1-week blinded taper at LCM 200mg/day/week or matching placebo before entering a 2-week Safety Follow-up Period.

[i] For subjects completing the End of Taper Visit, a Final Clinic Visit will be completed 2 weeks after the last dose of study drug.

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

[k] The brief physical examination will include review of the following body systems: cardiovascular, pulmonary, abdominal (hepato-gastrointestinal), and dermatologic.

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

[m] The brief neurological examination will include selected assessments of mental status, cranial nerves, and coordination/cerebellar function.

[n] The ECG recordings should be performed at approximately the same time of day and prior to blood sample collection. 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.

[o] Height will be recorded at Visit 1, at Visit 9/ET Visit, and at the Final Clinic Visit (after the 4-week blinded transition).

[p] Subjects are required to have had an EEG showing discharges consistent with IGE prior to Visit 1. A confirmatory EEG may be performed during the Prospective Baseline, if approved by the Central Reviewer. Investigators will send a copy of the EEG tracing and report to the Central Reviewer. The information provided will be reviewed and any questions regarding the subject's eligibility will be discussed with the investigator prior to the subject being randomized.

[q] The Tanner Stage will be performed for subjects who are <18 years of age at Visit 1. At Visit 9/ET Visit, if subject is >18years of age, a repeat assessment is not necessary.

[r] Serum pregnancy tests will be conducted at the following visits: Visit 1, Visit 9/ET Visit, and the Final Clinic Visit. At Visit 2, a urine dipstick pregnancy test should be performed prior to IVRS/IWRS contact. The result of the urine dipstick test must be negative prior to administration of the first dose of study drug. All other pregnancy tests (ie, Visits 3 through Visit 8 and the End of Taper Visit) will be urine dipstick.

[s] Blood samples for analysis of LCM plasma concentrations will be collected at any time between 2 successive bid doses.

[t] An IVRS/IWRS will be used to control all drug distribution and inventory for this study.

[u] No dose reduction is allowed until the subject reaches the randomized target dose. If the subject is unable to tolerate the target dose, a single dose reduction of study drug to LCM 300mg/day or placebo is permitted. No other dose reductions are allowed. In the case of intolerable AEs during the titration, the subject must be withdrawn from the study. If a dose reduction is required, the subject must come in for a visit (scheduled or unscheduled). If the subject is not able to tolerate the study drug after 1 dose reduction, the subject must be withdrawn from the study. All dose reductions should be discussed with the Medical Monitor. Once the dose has been reduced, it cannot be increased.

[v] At Visit 2, subjects should take the first dose of study drug in the clinic.

[w] The Achenbach CBCL to be used is the CBCL/6 to 18 for children ≥12 years to <18 years of age; 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 extension study EP0012.

[x] The BRIEF should be used for subjects ≥12 to <18.

[y] The QOLIE-31-P will be performed for subjects who are ≥18 and the PedsQL will be performed for subjects <18. The version of the PedsQL used should be consistent with the subject's age at each visit when it is administered.

[z] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

Has been changed to:

The schedule of study assessments is provided in Table 5–1 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits), Table 5–2 (Transition Period), and Table 5–3 (Taper Period and Safety Follow-up Period).

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Assessments	Prospective Baseline 4 weeks			Treatment Period[a]											Unscheduled[b]
				6 to 24 weeks (maximum)											NA
				Titration Period (6 weeks)[e]						Maintenance Period (18 weeks)					
Visit[c]	V1	TC	V2[d]	TC[e]	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ET[f]	Visit
Study week	-4	-2		1	2	3	4	5	6	8	12	16	20	24	NA
Informed Consent/Assent	X														
Inclusion/Exclusion criteria	X	X	X												
Subject ID card dispensing	X														
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/Epilepsy history	X														
Physical exam (complete)[g]	X		X											X	
Physical exam (brief)[h]					X		X		X	X	X	X	X		
Neurological exam (complete)[i]	X		X											X	
Neurological exam (brief)[j]					X		X		X	X	X	X	X		
12-lead ECG[k]	X		X		X		X		X		X		X	X	
Vital signs (BP and pulse) including orthostatic assessments[l]	X		X		X		X		X	X	X	X	X	X	
Body weight	X		X		X		X		X	X	X	X	X	X	
Height	X													X	
EEG[m]	X														
Tanner Stage[n]			X											X	
Laboratory tests:															
Chemistry/hematology	X		X		X				X		X		X	X	
Endocrinology			X											X	
Urinalysis[o]	X		X		X				X		X		X	X	
Pregnancy test[p]	X		X		X		X		X	X	X	X	X	X	
LCM plasma concentration[q]									X					X	
Contact IVRS/IWRS[r]	X		X		X		X		X	X	X	X	X	X	X
Randomization			X												
Dispense subject diary[s]	X		X		X		X		X	X	X	X	X	X	
Subject diary return/review[s]			X		X		X		X	X	X	X	X	X	
Dispense study drug[t]			X[u]		X		X		X	X	X	X	X	X	

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Assessments	Prospective Baseline 4 weeks			Treatment Period[a]											Unscheduled[b]
				6 to 24 weeks (maximum)											NA
				Titration Period (6 weeks)[e]					Maintenance Period (18 weeks)						
Visit[c]	V1	TC	V2[d]	TC[e]	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ET[f]	Visit
Study drug review/return					X		X		X	X	X	X	X	X	
Withdrawal criteria		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
Achenbach CBCL[v]			X											X	
BRIEF-P/BRIEF[w]			X											X	
EQ-5D-3L[x]			X											X	
QOLIE-31-P/PedsQL[y]			X											X	
C-SSRS[z]	X		X		X		X		X	X	X	X	X	X	
Healthcare resource use			X		X		X		X	X	X	X	X	X	
Work/school days lost			X		X		X		X	X	X	X	X	X	
Days with help from a caregiver			X		X		X		X	X	X	X	X	X	
Socio-professional data			X		X		X		X	X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; bid=twice daily; BP=blood pressure; exam=examination; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EEG=electroencephalogram; EQ-5D-3L=EuroQol-5D; ET=Early Termination; ID=identification; IGE=idiopathic generalized epilepsy; IVRS/IWRS=interactive voice/web response system; LCM=lacosamide; NA=not applicable; PEDsQL=Pediatric Quality of Life Inventory; PGTC=primary generalized tonic-clonic; QOLIE-31-P=Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31; TC=telephone contact; V=Visit

[a] The Treatment Period starts at the time of the Randomization Visit (Visit 2). The Treatment Period continues until 1 of the following occurs (whichever occurs first): completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures, or completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or TCs, at the discretion of the investigator. In addition to the required assessments indicated above, depending on the type of visit (clinic or telephone), further assessments can be completed as needed and may include ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed (for subjects ≥6 years of age) if the unscheduled visit is due to an AE.

[c] A window of ±2 days relative to Visit 1 is applicable for all protocol specified visits and TCs. During the Treatment Period, each visit should occur at the end of the week indicated in accordance with this time window.

[d] All assessments at Visit 2 should be conducted prior to the first dose of study drug. At the end of the Prospective Baseline, subjects will be randomized at Visit 2 to receive LCM or placebo in a 1:1 fashion (active:placebo) and commence the Treatment Period with a 6-week, double-blind, flexible dose titration (see Section 7.2.1).

[e] Subjects and/or caregivers will receive TCs throughout titration (Study Weeks 1, 3, and 5) to discuss titration dosing options.

[f] Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure (Section 6.3).

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

[h] The brief physical examination will include review of the following body systems: cardiovascular, pulmonary, abdominal (hepato-gastrointestinal), and dermatologic.

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

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

[k] The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

[l] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

[m] Subjects are required to have had an EEG showing discharges consistent with IGE prior to Visit 1. A confirmatory EEG may be performed during the Prospective Baseline, if approved by the Central Reviewer. Investigators will send a copy of the EEG report to the Central Reviewer. The information provided will be reviewed and any questions regarding the subject's eligibility will be discussed with the investigator prior to the subject being randomized.

[n] The Tanner Stage will be performed only for subjects who are pubescent at Visit 2 or who enter puberty during the course of the study.

[o] Urinalysis will be required for subjects ≥5 years of age only.

[p] Serum pregnancy tests will be conducted at the following visits: Visit 1, Visit 10/ET Visit. At Visit 2, a urine dipstick pregnancy test should be performed prior to IVRS/IWRS contact. The result of the urine dipstick test must be negative prior to administration of the first dose of study drug. All other pregnancy tests (ie, Visits 3 through Visit 9) will be urine dipstick. Pregnancy tests will be performed for female subjects of childbearing potential only.

[q] Blood samples for analysis of LCM plasma concentrations will be collected at any time between 2 successive bid doses.

[r] An IVRS/IWRS will be used to control all drug distribution and inventory for this study.

[s] At all visits, subjects and/or caregivers will be reminded to report the occurrence of all seizure types, including days without seizures.

[t] During the Maintenance Period, a single dose reduction is allowed as long as the minimum target dose is maintained (see Table 7–3). Once the dose has been reduced, it cannot be increased. Subjects who are not able to tolerate the minimum target dose during the Maintenance Period will be withdrawn from the study. All dose reductions should be discussed with the Medical Monitor.

[u] At Visit 2, subjects should take the first dose of study drug in the clinic.

[v] The Achenbach CBCL/1½-5 is for children <5 years and 11 months of age and the CBCL/6-18 is for children ≥6 years to <18 years of age; the questionnaire is 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.

[w] The BRIEF-P should be used for subjects who are <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.

[x] The EQ-5D-3L will be performed in subjects who are ≥12 years of age.

[y] The QOLIE-31-P will be performed for subjects who are ≥18 years of age and the PedsQL will be performed for subjects <18 years of age. The version of the PedsQL used should be consistent with the subject's age at Visit 2 and should be maintained for each subject for the duration of the study.

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

[aa] Thyroid function will be required in subjects <18 years of age only.

Table 5–2: Schedule of study assessments for SP0982 (Transition Period)

Assessment	Transition Period (4 weeks)[a]	
	Transition TC or Visit[b]	Final Clinic Visit (EP0012 Visit 1)
	2 weeks after Visit 10/ET	
Concomitant medications and AED(s)	X	X
Body weight		X
Height		X
Physical exam (complete)[d]		X
Neurological exam (complete)[e]		X
12-lead ECG[f]		X
Vital signs (BP and pulse) including orthostatic assessments[c]		X
Laboratory tests:		
Chemistry/hematology		X
Urinalysis[i]		X
Endocrinology		X
Pregnancy test[j]		X
Contact IVRS/IWRS		X
Subject diary return/review[g]		X
Study drug review/return		X
Withdrawal criteria	X	X
AE reporting	X	X
C-SSRS[h]		X
Healthcare resource use		X
Work/school days lost		X
Days with help from a caregiver		X
Socio-professional data		X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Early Termination; IVRS/IWRS=interactive voice/web response system; TC=telephone contact

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

[a] At the end of Visit 10/ET, subjects who complete the study may be eligible to participate in an open-label extension study (EP0012). Subjects who choose to enroll in the open-label extension study will proceed to a blinded 4-week Transition Period.

[b] A Transition TC is required. A Transition Clinic Visit is optional, at the discretion of the investigator. Subjects requiring a clinic visit will have the same assessments conducted as an Unscheduled Visit.

[c] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

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

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

[f] The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

[g] The subject diary will be dispensed at Visit 1. At all subsequent visits, subjects and or caregivers will be reminded to report the occurrence of all seizure types, including days without seizures.

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

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

[j] Urine pregnancy tests will be performed for female subjects of childbearing potential only.

[k] Thyroid function will be required in subjects <18 years of age only.

Table 5–3: Schedule of study assessments for SP0982 (Taper Period and Safety Follow-up Period)

Assessment	Taper Period[a] (up to 4 weeks)	Safety Follow-up Period[c]	
		Safety Follow-up Visit	Safety Follow-up TC
	End of Taper Visit[b]	2 weeks (±2 days) after last dose of study drug	30 days (-1/+3 days) after last dose of study drug
Concomitant medications and AED(s)	X	X	X
Physical exam (complete)[k]	X	X	
Neurological exam (complete)[l]	X	X	
12-lead ECG[h]	X	X[i]	
Vital signs (BP and pulse) including orthostatic assessments[j]	X	X	
Body weight	X	X	
Laboratory tests:			
Chemistry/hematology	X	X[i]	
Endocrinology[m]		X[i]	
Urinalysis[f]	X	X	
Pregnancy test[g]	X	X	
Contact IVRS/IWRS	X		
Subject diary return/review[d]	X		
Study drug review/return	X		
Withdrawal criteria	X		
AE reporting	X	X	X
C-SSRS[e]	X	X	
Healthcare resource use	X	X	
Work/school days lost	X	X	
Days with help from a caregiver	X	X	
Socio-professional data	X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IVRS/IWRS=interactive voice/web response system; TC=telephone contact.

[a] Subjects completing Visit 10 (Week 24) or the ET Visit who choose not to continue in EP0012 must complete a blinded taper followed by the End of Taper Visit.

[b] An End of Taper Visit will be scheduled at the end of the Taper Period (up to 4 weeks) depending on dose level achieved; see Table 7-5. Of note, for subjects who enter the Taper Period at ≤2mg/kg/day (oral solution) or 100mg/day (tablets), the End of Taper Visit will take the place of the ET Visit.

[c] There will be a 30-day (-1/+3 days) Safety Follow-up Period for subjects who complete the End of Taper Visit. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed 2 weeks later by a TC.

[d] The last subject diary will be returned at the End of Taper Visit.

[e] The C-SSRS will be completed for all subjects ≥6 years of age.
[f] Urinalysis will be required for subjects ≥5 years of age only.
[g] Urine pregnancy tests will be performed for female subjects of childbearing potential only.
[h] The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.
[i] The assessment will be required only for subjects with an abnormal value (clinical chemistry, hematology, or endocrinology) or reading (ECG) at the previous clinic visit.
[j] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.
[k] The complete physical examination will include cardiac and respiratory function via auscultation, and review of all body systems.
[l] The complete neurological examination will include selected assessments of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.
[m] Thyroid function will be required in subjects <18 years of age only.

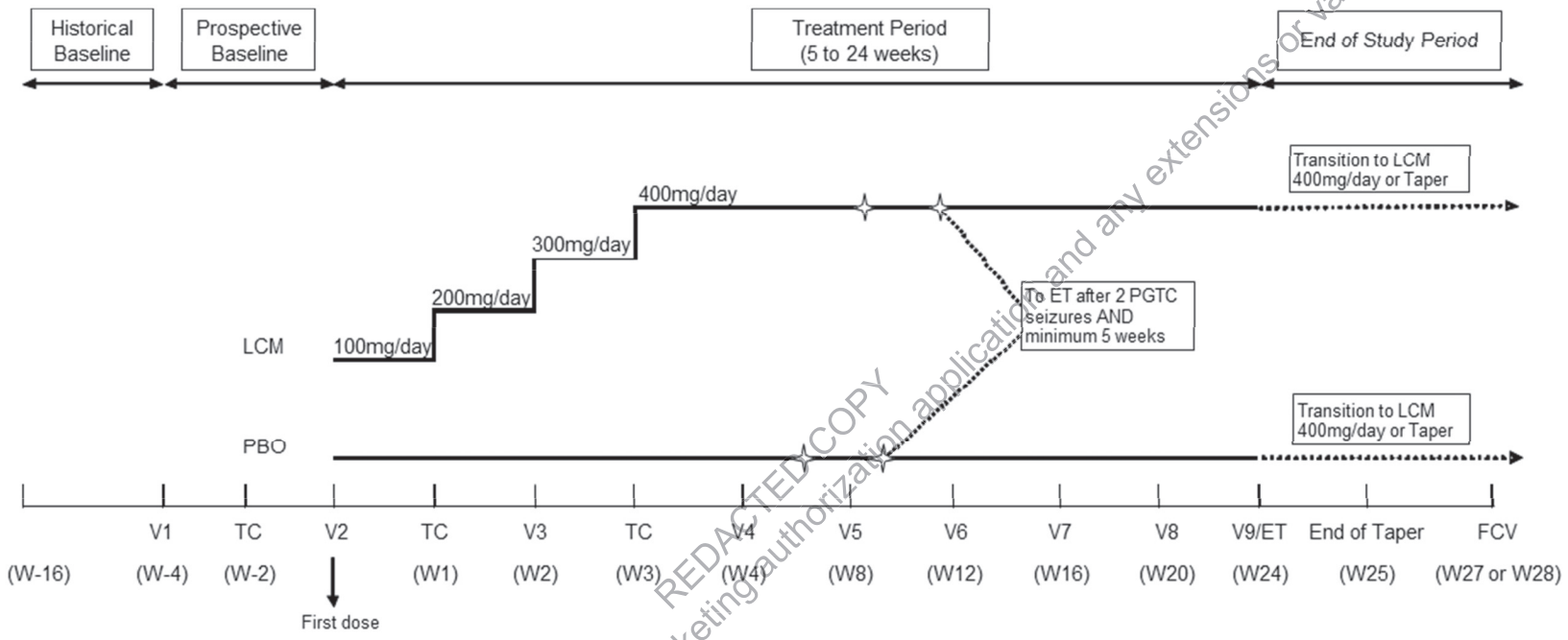
Change #17

Section 5.3 Schematic diagrams for SP0982

Paragraph 1 and Figure 5-2:

The schematic diagrams are provided in Figure 5-1 and Figure 5-2.

Figure 5-2: SP0982 overall schematic diagram



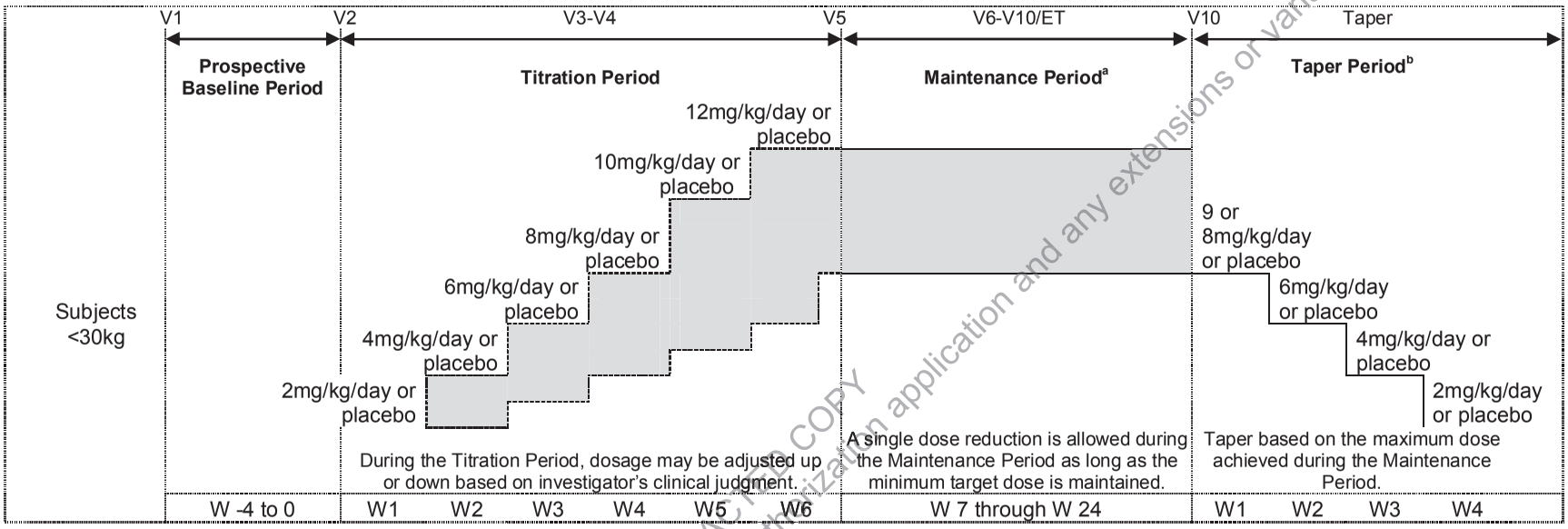
ET=Early Termination Visit; FCV=Final Clinic Visit; LCM=lacosamide; PBO=placebo; PGTC=primary generalized tonic-clonic; TC=telephone contact; V=Visit; W=Week
✧ = PGTC seizure

Have been changed to:

The schematic diagram for the Combined Baseline Period eligibility is provided in Figure 5-1.

A schematic diagram for the Prospective Baseline Period through the Taper Period with successive panels for pediatric subjects weighing <30kg, pediatric subjects weighing ≥30kg to <50kg, and adult subjects and pediatric subjects weighing ≥50kg is provided in Figure 5-2. The schematic diagram for the Transition Period is provided in Figure 5-3.

Figure 5–2: SP0982 Prospective Baseline Period through the Taper Period schematic diagram



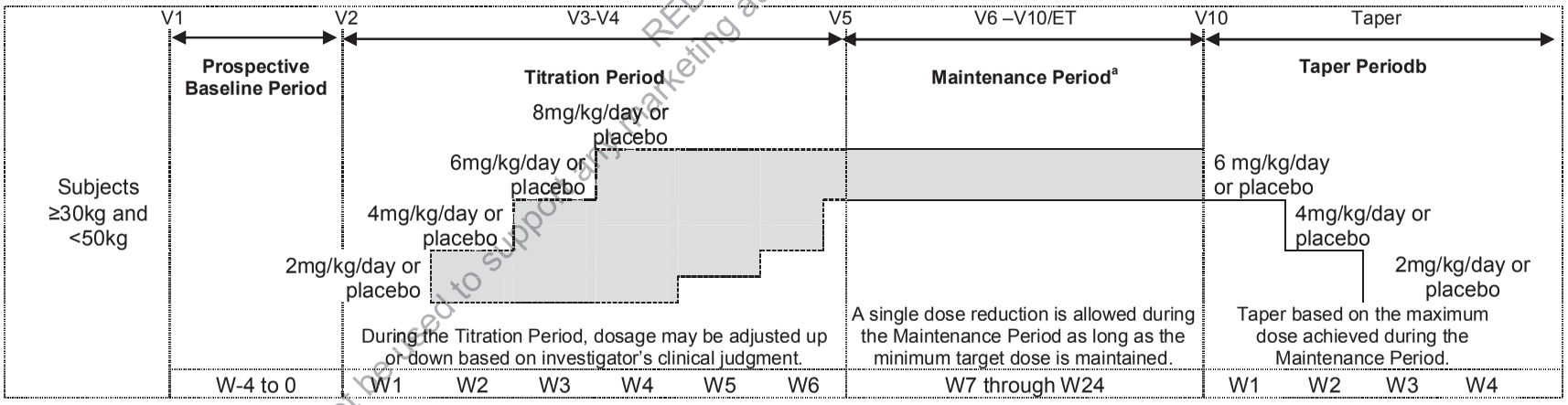
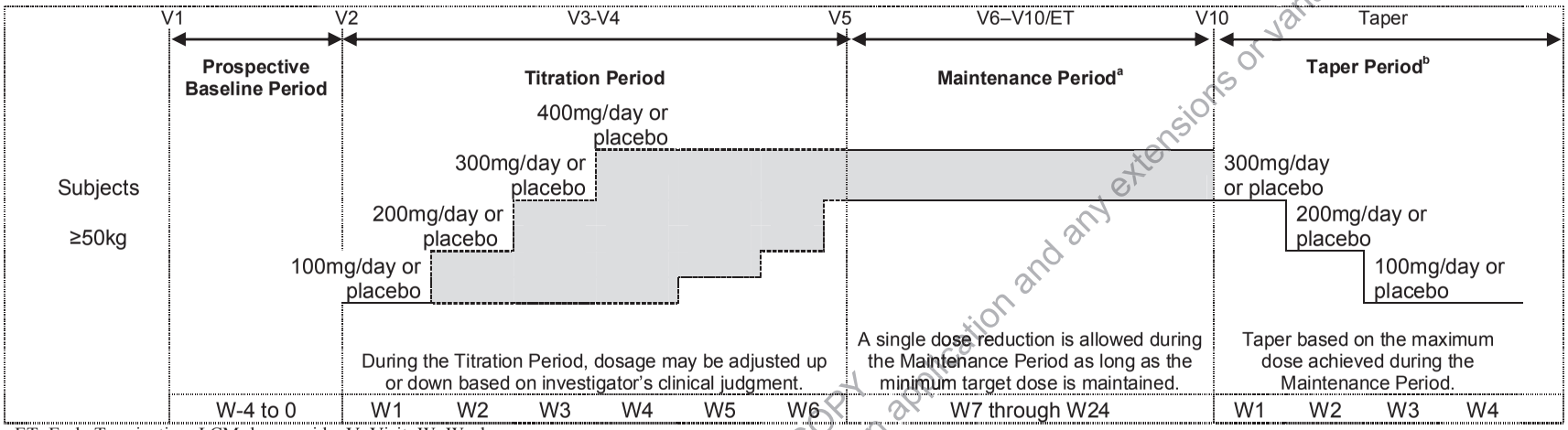


Figure 5-2: SP0982 overall schematic diagram



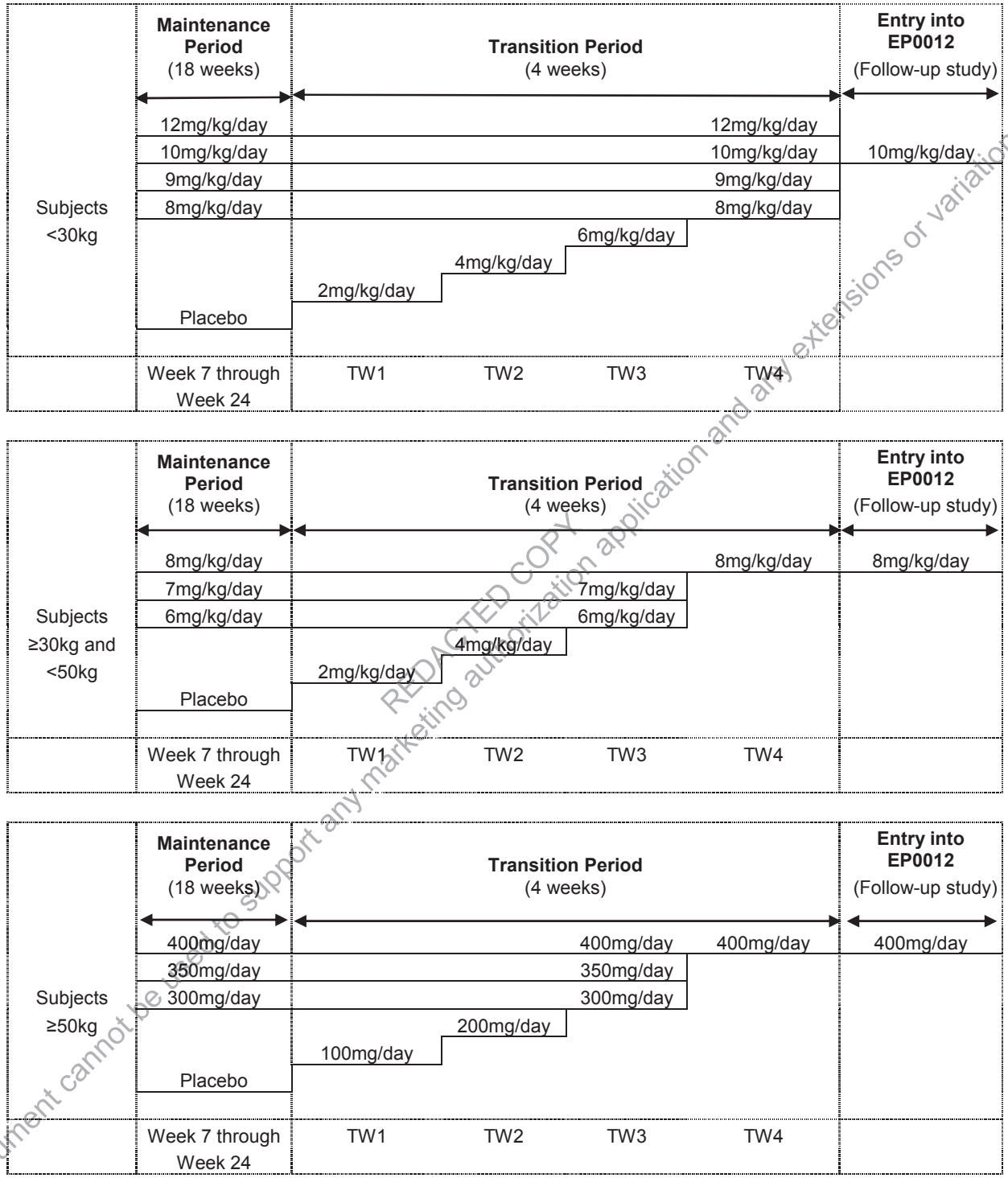
ET=Early Termination; LCM=lacosamide; V=Visit; W=Week

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

[a] Subjects will be required to achieve and maintain a minimum LCM (or matching placebo) dose for at least the final 3 days of Week 6 to be eligible for entry into the Maintenance Period.

[b] If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit. There will be a 30-day Safety Follow-up Period for subjects who complete the End of Taper Visit.

Figure 5–3: SP0982 Transition Period schematic diagram



TW=transition week
Note: Lacosamide dosing is designated as "mg/kg/day" (oral solution) and "mg/day" (tablets) and matching placebo is shown as "placebo."

Change #18

Section 5.4.1 Rationale for dose

The LCM 100mg/day dose was selected to be the starting dose for this study to ensure a safe and well-tolerated up-titration scheme. The LCM 400mg/day maintenance dose was well tolerated and demonstrated efficacy in 3 primary efficacy studies as adjunctive therapy in subjects with partial-onset seizures. In SP0961, the Phase 2 pilot study in subjects with uncontrolled PGTC seizures with IGE, the 400mg/day dose was also well tolerated. Generally, the doses of AEDs used for the treatment of partial-onset seizures are similar to those used to treat generalized seizures. Thus, the 400mg/day target dose is considered the optimal maintenance dose for the population with uncontrolled PGTC seizures with IGE.

Has been changed to:

For adult subjects, the LCM 100mg/day dose was selected to be the starting dose for this study to ensure a safe and well-tolerated up-titration scheme. The LCM 400mg/day maintenance dose was well tolerated and demonstrated efficacy in 3 primary efficacy studies as adjunctive therapy in subjects with partial-onset seizures. In SP0961 (the Phase 2 pilot study) and SP0962 (the open-label extension study) in subjects with uncontrolled PGTC seizures with IGE, the 400mg/day dose was also well tolerated. Generally, the doses of AEDs used for the treatment of partial-onset seizures are similar to those used to treat generalized seizures. Thus, the 300mg/day to 400mg/day target dose range is considered the optimal maintenance dose for the population with uncontrolled PGTC seizures with IGE.

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 pediatric dosing recommendations for SP0982 are to achieve LCM plasma concentrations similar to the average steady-state LCM plasma concentration reached after a LCM 400mg/day dose administration in adult studies, which is approximately 8µg/mL.

Change #19

Section 5.4.2 Rationale for second PGTC seizure

Paragraph 1, last 2 sentences:

In the time to n^{th} seizure design, subjects are required to remain in the study for a minimum of 5 weeks. If a subject experiences ≥2 seizures while on treatment, then after 5 weeks the subject exits the study, rather than continuing to have PGTC seizures, while remaining eligible to receive LCM in the open-label extension study (EP0012).

Have been changed to:

In the time to n^{th} seizure design, subjects are required to remain in the study for a minimum of 6 weeks. If a subject experiences ≥2 seizures while on treatment, then after 6 weeks the subject exits the study, rather than continuing to have PGTC seizures, while remaining eligible to receive LCM in the open-label extension study (EP0012).

Paragraph 2, fourth sentence:

Lacosamide, by comparison, reaches a minimally effective dose in the second week (200mg/day).

Has been changed to:

Lacosamide, by comparison, reaches a minimally effective dose in the second week (200mg/day) for a majority of trial subjects

Change #20

Section 5.4.3 Rationale for minimum duration of treatment

Paragraph 1:

The minimum duration of the Treatment Period for each subject will be 5 weeks. There are 2 reasons for the requirement of a minimum Treatment Period duration:

Has been changed to:

The minimum duration of the Treatment Period for each subject will be 6 weeks. There are 3 reasons for the requirement of a minimum Treatment Period duration:

The following third bullet was added:

- To allow for increased flexible dosing during titration

Last paragraph, third sentence:

By allowing subjects to exit the study after completing 5 weeks of the Treatment Period, sufficient double-blind safety data can be collected from a high proportion of subjects to be meaningful.

Has been changed to:

By allowing subjects to exit the study after completing 6 weeks of the Treatment Period, sufficient double-blind safety data can be collected from a high proportion of subjects to be meaningful.

Change #21

Section 5.4.4 Rationale for selected age range

The following paragraph was added to the end of the section:

The ≥4-year age cutoff was established based on the difficulty of establishing a clear diagnosis of IGE in younger subjects with PGTC seizures. This is further supported by epidemiology data, which indicates that the incidence and prevalence of generalized epilepsies is lower in preschoolers compared to older children (Olafsson et al, 2005).

Change #22

Section 6.1 Inclusion criteria

Inclusion criterion 4 was removed and subsequent criteria were renumbered.

Inclusion criterion 3, 5, and 9:

3. Male and female subjects 12 years of age and older with a body weight ≥50kg.
5. Subject with a confirmed diagnosis at least 24 weeks prior to Visit 1 and a disease onset at 5 to 30 years of age, consistent with IGE experiencing PGTC seizures (Type IIE) that are classifiable according to the ILAE Classification of Epileptic Seizures (ILAE, 1981)

9. Subjects are required to have had an EEG tracing and report showing discharges consistent with IGE (generalized >3Hz epileptiform discharges and a normal EEG background) confirmed by a Central Reviewer.

Have been changed to:

3. Male and female subjects ≥4 years of age.
4. Subject with a confirmed diagnosis at least 24 weeks prior to Visit 1 and a disease onset prior to 30 years of age, consistent with IGE experiencing PGTC seizures (Type IIE) that are classifiable according to the ILAE Classification of Epileptic Seizures (ILAE, 1981).
8. Subjects are required to have had an EEG report consistent with IGE (eg, generalized ≥3Hz epileptiform discharges and a normal EEG background) confirmed by a Central Reviewer.

Change #23

Section 6.2 Exclusion criteria

Exclusion criterion 5 was removed and subsequent criteria were renumbered.

Exclusion criterion 1, 4, 6, 17, and 22:

1. Subject has previously participated in this study or subject has previously received LCM, with the exception of subjects whose exposure was limited to a single iv dose.
4. Subject has a diagnosis of developmental delay or mental retardation including mild forms.
6. Subject has a history of status epilepticus.
17. Subject has impaired renal function, ie, creatinine clearance (CL_{cr}) is lower than 50mL/min.
22. Female subject who is pregnant or nursing, and/or a woman of childbearing potential who is not surgically sterile, 2 years postmenopausal or 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.

Have been changed to:

1. Subject has previously participated in this study or subject has previously been assigned to treatment in a study of LCM.
4. Subject has symptomatic generalized epilepsy ([ILAE, 1989] eg, Lennox-Gastaut Syndrome) or evidence of both focal and generalized epilepsy.
5. Subject has a history of convulsive status epilepticus 1 year prior to Screening.
16. Subject has impaired renal function (ie, creatinine clearance [CLcr] is <30mL/min) at Screening (see Section 10.6).
21. Female subject who is pregnant or nursing and/or a woman of childbearing potential who is not surgically sterile, 2 years postmenopausal, 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 <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, 2 years postmenopausal, 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 #24

Section 6.3 Exit criteria

Subjects must complete the first 5 weeks of the Treatment Period after randomization and will be required to exit the study if either of the following events occur:

- Subject completes the first 5 weeks of the Treatment Period (after randomization) and experiences ≥2 PGTC seizures during that time
- Subject experiences a second PGTC seizure after the first 5 weeks of the Treatment Period

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure.

Has changed to:

Subjects will be required to exit the study if either of the following events occur:

- Subject completes the first 6 weeks of the Treatment Period (after randomization) and experiences ≥2 PGTC seizures during that time
- Subject experiences a second PGTC seizure after the first 6 weeks of the Treatment Period

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure.

Change #25

Section 6.4 Withdrawal criteria

Bullet 1, 2, and 8:

- In the case of intolerable AEs during the titration, the subject must be withdrawn from the study. No dose reduction is allowed during titration.
- The subject requires a subsequent dose increase after dose reduction to LCM 300mg/day during the Treatment Period or the subject requires more than 1 dose reduction during the Treatment Period.
- 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.

Have been changed to:

- The subject is unable to attain at least the minimum Maintenance Period target dose (Table 7–3).
- The subject requires a subsequent dose increase after dose reduction during the Maintenance Period or the subject requires more than 1 dose reduction during the Maintenance Period.
- Subject ≥6 years of age 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.

The following bullet was added after Bullet 13:

- Subject develops an intolerable AE during the course of the study.

Change #26

Section 7.1 Description of investigational medicinal product

Lacosamide and matching placebo will be provided as white, film-coated tablets. Oral tablets of LCM 100mg and LCM 50mg and matching placebo will be packaged in wallet cards and administered during the Treatment Period.

Has been changed to:

Investigational medicinal product will be provided as LCM oral solution (syrup) (LCM 10mg/mL), LCM tablets (LCM 50mg), and matching placebos.

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

The LCM 50mg tablets and matching placebo are white, oval tablets debossed with "SP" on one side. Tablets will be packaged in high-density polyethylene (HDPE) bottles.

Change #27

Section 7.2 Treatments to be administered

At Visit 2, the subject will be randomized to receive either LCM or matching placebo. Subjects will then begin a dose titration at LCM 100mg/day (50mg bid) or placebo for 1 week. Subjects will receive a telephone call at the end of the first week of titration reminding them to increase their dose to LCM 200mg/day (100mg bid) or placebo. Subjects will return to the clinic at Visit 3 (end of Week 2) and will receive LCM 300mg/day (150mg bid) or placebo. At the end of Week 3, subjects will receive a telephone call reminding them to increase their dose to LCM 400mg/day (200mg bid) or placebo for the remaining duration of the Treatment Period. Five additional clinic visits will occur during the Treatment Period: Visit 5 (Week 8), Visit 6 (Week 12), Visit 7 (Week 16), Visit 8 (Week 20), and ET Visit/Visit 9 (Week 24).

After completing ≥5 weeks and experiencing the second PGTC seizure during the Treatment Period, or after completing the 24-week Treatment Period (whichever comes first), the subject may, at the ET Visit or Visit 9 (Week 24), respectively, choose to continue in EP0012. Subjects completing Visit 9 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. The Final Clinic Visit is the same as Visit 1 of EP0012. All subjects' first dose in EP0012 will be LCM 400mg/day (200mg bid) (see Table 7-1).

The following schematic displays the scenario for subject dispensation: subject completes the Visit 9 (Week 24) or the ET Visit on LCM 300mg/day (150mg bid), or LCM 400mg/day (200mg bid), or placebo and continues into EP0012.

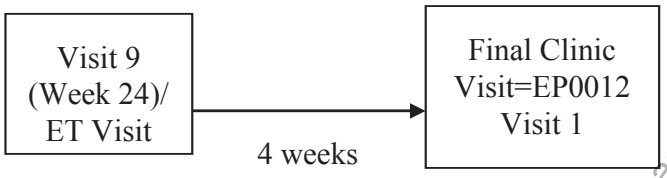


Table 7-1 summarizes the transition steps for each treatment dose for subjects entering EP0012.

Table 7-1: Dose transition steps for subjects entering EP0012

Treatment dose	**Transition (4 weeks)**			
	Week 1	Week 2	Week 3	Week 4
LCM 300mg/day	300mg/day	300mg/day	300mg/day	400mg/day
LCM 400mg/day	400mg/day	400mg/day	400mg/day	400mg/day
Placebo	100mg/day	200mg/day	300mg/day	400mg/day

LCM=lacosamide

Subjects completing Visit 9 (Week 24) or the ET Visit who choose not to continue in EP0012 must complete a 1-week blinded taper followed by the End of Taper Visit. Subjects completing Visit 9 (Week 24) or the ET Visit on LCM 400mg/day (200mg bid), LCM 300mg/day (150mg bid), or placebo will have their doses tapered over 1 week. Two weeks after the last dose of study drug following the End of Taper Visit, subjects will complete a Final Clinic Visit (see Table 7-2).

The following schematic displays the scenario for subject dispensation: subject completes Visit 9 (Week 24) or ET Visit on LCM 300mg/day (150mg bid), LCM 400mg/day (200mg bid), or placebo and does not continue into EP0012.

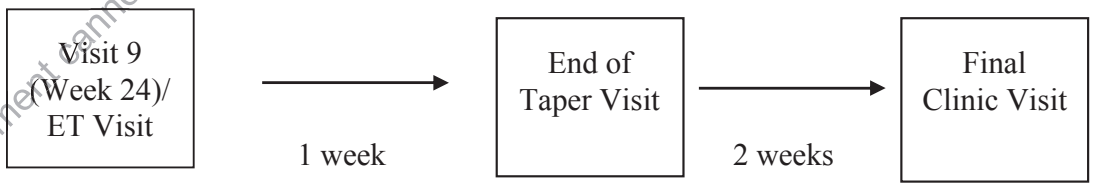


Table 7-2 summarizes the transition steps for each treatment dose for subjects not entering EP0012.

Table 7-2: Taper steps for subjects not entering EP0012

Treatment dose	Taper (1 week)	Safety Follow-up (2 weeks)	
	Week 1	Week 1	Week 2
LCM 300mg/day	100mg/day	-	-
LCM 400mg/day	200mg/day	-	-
Placebo	Placebo	-	-

LCM=lacosamide

Has been changed to:

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

At Visit 2, subjects will be randomized to receive either LCM (oral solution for pediatric subjects [≥4 to <18 years of age] weighing <50kg or tablets for adult subjects [≥18 years of age] and pediatric subjects weighing ≥50kg) or matching placebo. At the end of Visit 2, subjects should take the first dose of study drug while in the clinic.

SP0982 will target Maintenance Period doses of LCM or matching placebo as presented in Table 7–3.

7.2.1 Titration Period

Table 7–1 provides the recommended LCM (or matching placebo) dosing during the Titration Period for subjects to reach the target doses for the Maintenance Period. All subjects should follow this recommended dosing schedule, unless dose adjustments based on tolerability are needed.

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

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

LCM=lacosamide
[a] The oral solution formulation is for pediatric subjects weighing <50 kg.
[b] The tablet formulation is for adult subjects (≥18 years of age) and pediatric subjects weighing ≥50kg.

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

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

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

LCM=lacosamide; Max=maximum; Min=minimum
Note: Asymmetrical dosing with no more than 50mg difference between morning and evening doses will be allowed for subjects who require back titration in a 50mg increment.
[a] Titration step to achieve a dose not previously administered

All subjects are required to complete Week 1 dosing before study drug dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further study drug dose increase or whether a subject should hold the dose for a longer duration. There is no limit to the number of back-titration steps or dose holds allowed and all are at the investigator's discretion; however, subjects must achieve the minimum LCM (or matching placebo) target dose by the end of the Titration Period (Table 7–3). If it becomes apparent that a subject is unable to attain at least the minimum Maintenance Period target dose, then the subject must enter the Taper Period and be withdrawn from the study.

Subjects who titrate to a next higher dose level should remain at that dose prior to a dose increase for ≥7 days unless a back-titration step is required based on tolerability. Subjects who have their study drug back titrated must remain on the lower dose for ≥3 days (in order to reach steady state) before a subsequent dose increase.

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

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

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

LCM=lacosamide; Max=maximum; Min=minimum

7.2.2 Maintenance Period

Subjects will enter a 18-week Maintenance Period at the dose they received on the last day of the Titration Period in accordance with targeted Maintenance Period dosing (Table 7-3).

During the Maintenance Period, a single dose reduction is allowed as long as the minimum dose requirement is maintained. Once the dose has been reduced, it cannot be increased. Subjects who are not able to tolerate the minimum target dose during the Maintenance Period (Table7-3) will be withdrawn from the study and enter an up to 4-week blinded Taper Period. All dose reductions should be discussed with the Medical Monitor.

7.2.3 Transition Period (for subjects who enter EP0012)

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period, or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24), respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. Two weeks after Visit 10 (Week 24) or the ET Visit, a Transition telephone contact is required; a subsequent Clinic Visit is at the discretion of the investigator (Table 5–2). The Final Clinic Visit is the same as Visit 1 of EP0012.

The following schematic displays the scenario for subject dispensation:

ET=Early Termination; TC=telephone contact

[a] A Transition telephone contact is required. A Transition Clinic Visit is optional, at the discretion of the investigator.

Subjects will transition in a double-blind fashion to LCM dosing as described Table 7–4. At the completion of the Transition Period, subjects eligible to enter EP0012 will be placed on a common dose (see Figure 5–3).

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

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

LCM=lacosamide

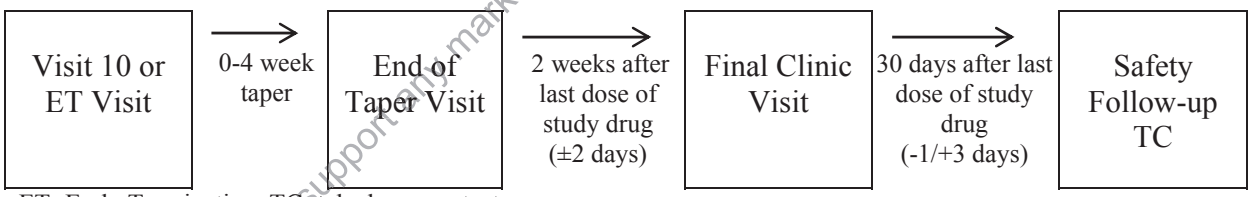
7.2.4 Taper Period

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit (Table 7-5).

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.

Following the End of Taper Visit, there will be a 30-day Safety Follow-up Period. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-up telephone contact 30 days after the last dose of study drug.

The following schematic displays the scenario for subject dispensation



ET=Early Termination; TC=telephone contact
Note: An End of Taper Visit will be scheduled at the end of the Taper Period (up to 4 weeks) depending on the dose level achieved; see Table 7-5. Of note, for subjects who enter the Taper Period at ≤2mg/kg/day (oral solution) or 100mg/day (tablets), the End of Taper Visit will take the place of the ET Visit.

Table 7-5 summarizes the Taper Period dosing for each treatment dose for subjects not entering EP0012.

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

LCM (or matching placebo) dose achieved	LCM (or matching placebo) doses for the Taper Period			
	Week 1	Week 2	Week 3	Week 4
11 or 12mg/kg/day	9mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
9 or 10mg/kg/day	8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day
7 or 8mg/kg/day	6mg/kg/day	4mg/kg/day	2mg/kg/day	NA
5 or 6mg/kg/day	4mg/kg/day	2mg/kg/day	NA	NA
3 or 4mg/kg/day	2mg/kg/day	NA	NA	NA
2mg/kg/day	NA	NA	NA	NA
350 or 400mg/day	300mg/day	200mg/day	100mg/day	NA
250 or 300mg/day	200mg/day	100mg/day	NA	NA
150 or 200mg/day	100mg/day	NA	NA	NA
100mg/day	NA	NA	NA	NA

LCM=lacosamide; NA=not applicable (taper not required)
Note: The oral solution is dosed as "mg/kg/day" and tablets are dosed as "mg/day."

Change #28

Section 7.3 Packaging

Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage. Lacosamide and matching placebo will be packaged in treatment kits including wallet cards. Each wallet card will contain IMP for 7 days plus 3 reserve days.

Has been changed to:

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

Lacosamide tablets and matching placebos will be packaged in HDPE bottles.

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

Change #29

Section 7.5 Handling and storage requirements

Paragraphs 2, 3, and 4:

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 (eg, once a week), 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.

Have been changed to:

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

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) before further use of the IMP and communicated to the sponsor's designee in accordance with the pharmacy manual.

Change #30

Section 7.6 Drug accountability

Paragraph 1, sentence 2:

Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms.

Has been changed to:

Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the sponsor's designee must also be recorded on the appropriate forms.

Paragraph 5, sentence 1:

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original package.

Has been changed to:

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB's designee, preferably in their original package.

Change #31

Section 7.7 Procedures for monitoring subject compliance

Paragraph 3:

Timely completion of the subject diary is essential for evaluation of safety and efficacy. Subject diary completion, including AED usage, will be evaluated at each visit. Sites are encouraged to call subjects to inquire about their diary completion.

Has been changed to:

Timely completion of the subject diary is essential for evaluation of safety and efficacy. Subject diary completion, including AED usage, will be evaluated at each clinic visit and telephone contact. Sites are encouraged to call subjects to inquire about their diary completion. Investigators should advise subjects and/or caregivers about the importance of reporting non-PGTC seizures. Subjects should be reminded that diaries must include daily entries even if no seizures have occurred.

Change #32

Section 7.8.1 Permitted concomitant treatments (medications and therapies)

The following 2 sentences were added to the end of the section:

Contraceptive treatment is allowed as described in Section 6.2 (Exclusion Criteria 21).

Stable use of amphetamines and sedative antihistamines is allowed during the study.

Change #33

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

Last bullet:

- Only stable, low doses of non-benzodiazepine anxiolytics or once-daily hypnotics are allowed for nonepilepsy indications.

Has been changed to:

- Only stable, low doses (<50% of the maximum daily dose recommended by the country-specific product label) of non-benzodiazepine anxiolytics or once-daily hypnotics are allowed for nonepilepsy indications.

Change #34

Section 8 STUDY PROCEDURES BY VISIT

Sentence 2:

A detailed schedule of study assessments is provided in Table 5–1.

Has been changed to:

A detailed schedule of study assessments is provided in Table 5–1, Table 5–2, and Table 5–3.

Change #35

Section 8.1.1 Visit 1 (Week -4)

The following Bullets 12, 13, 14, and 15 were deleted:

- Healthcare resource use
- Work/school days lost

- Days with help from a caregiver
- Tanner Stage (for subjects under 18 years of age at Visit 1)

Bullets 3, 7, and 9:

- EEG (Subjects are required to have had an EEG showing discharges consistent with IGE prior to Visit 1.)
- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- C-SSRS assessment

Have been changed to:

- EEG report
- ECG 12-lead assessment (see Section 10.7.1)
- C-SSRS assessment (for subjects ≥6 years of age)

Change #36

Section 8.1.2 Telephone Contact (Week -2)

Paragraph 1, first sentence:

The investigator (or designee) should contact the subject by telephone 2 weeks following Visit 1.

Has been changed to:

The investigator (or designee) should contact the subject by telephone 2 weeks following Visit 1 to assess continued eligibility and will remind the subject of the importance of accurate seizure diary completion.

Change #37

Section 8.2 Treatment Period

The following text was added:

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures

Change #38

Section 8.2.1 Visit 2 (Day 0)

Has been changed to:

8.2.1 Visit 2 (Day 0) Randomization

The following bullet was added:

- Body weight

Bullets 5, 7, 8, 11, and 13:

- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- C-SSRS assessment
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Dispense study drug (At Visit 2, subjects should take the first dose of study drug [LCM 50mg or placebo] in the clinic)
- BRIEF

Have been changed to:

- ECG 12-lead assessment (see Section 10.7.1)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Dispense study drug
- BRIEF-P/BRIEF
- Tanner Stage (will be performed only for subjects who are pubescent at Visit 2 or who enter puberty during the course of the study)
- *The following text was added to the end of the section:*

The subject will take the first dose of study drug in the clinic.

Change #39

Section 8.2.2 Telephone Contact (end of Week 1)

The investigator (or designee) should contact the subject by telephone at the end of Week 1. Subject will be reminded to increase their dose to LCM 200mg/day (100mg bid) or placebo. During the telephone contact, the following assessments will be performed:

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

Has been changed to:

8.2.2 Titration Period

8.2.2.1 Week 1 to Week 6

Both clinic visits and telephone contacts will be conducted during the Titration Period, beginning with a telephone contact at the end of Week 1 and continuing through clinic Visit 5 at the end of Week 6.

At each clinic visit and telephone contact, the investigator, in conjunction with the subject and/or parent(s)/legal representative(s), will decide how to proceed with study drug dosing based on tolerability (including vital signs, body weight, 12-lead ECG, and AE reporting, as applicable to the type of visit contact). If the withdrawal of study drug is required during the Titration Period, the subject will enter the blinded Taper Period (Table 7-5).

8.2.2.1.1 Telephone contact (Week 1, Week 3, Week 5, and unscheduled)

The following assessments will be performed during telephone contacts (both scheduled [Week 1, Week 3, and Week 5] and unscheduled) during the Titration Period:

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

Change #40

Section 8.2.3 Visit 3 (end of Week 2)

Has been changed to:

8.2.2.1.2 Visit 3 (end of Week 2)

The following bullet was removed:

- Urine pregnancy test (for women of childbearing potential)

The following bullets were added:

- Body weight
- ECG 12-lead assessment (see Section 10.7.1)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Socioprofessional data

Bullet 4:

- C-SSRS assessment

Has been changed to:

- C-SSRS assessment (for subjects ≥6 years of age)

Change #41

Section 8.2.4 Telephone Contact (end of Week 3)

The investigator (or designee) should contact the subject by telephone at the end of Week 3. Subjects will be reminded to increase their dose to LCM 400mg/day (200mg bid) or placebo for the remaining duration of the Treatment Period. During the telephone contact, the following assessments will be performed:

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

8.2.5 Visit 4 (end of Week 4)

During Visit 4 (end of Week 4), the following assessments will be performed:

- Physical examination (brief)
- Neurological examination (brief)
- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, a urine pregnancy test [for women of childbearing potential], and LCM plasma concentration)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Achenbach CBCL
- BRIEF
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

- Contact IVRS/IWRS

Have been changed to:

8.2.2.1.3 Visit 4 (end of Week 4)

During Visit 4 (end of Week 4), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- ECG 12-lead assessment (see Section 10.7.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Urine pregnancy test (for women of childbearing potential)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IVRS/IWRS

Change #42

Section 8.2.6 Visit 5 (end of Week 8)

Has been changed to:

8.2.2.1.4 Visit 5 (end of Week 6)

Sentence 1:

During Visit 5 (end of Week 8), the following assessments will be performed:

Has been changed to:

During Visit 5 (end of Week 6), the following assessments will be performed:

The following bullets have been added:

- Body weight
- Socio-professional data

Bullets 3 and 5:

- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- C-SSRS assessment

Have been changed to:

- ECG 12-lead assessment (see Section 10.7.1)
- C-SSRS assessment (for subjects ≥6 years of age)

Change #43

Section 8.2.7 Visit 6 (end of Week 12)

Has been changed to:

8.2.3 Maintenance Period

8.2.3.1 Visit 6 (end of Week 8)

Sentence 1:

During Visit 6 (end of Week 12), the following assessments will be performed:

Have been changed to:

During Visit 6 (end of Week 8), the following assessments will be performed:

The following bullet has been added:

- Socio-professional data

Bullet 5:

- C-SSRS assessment

Has been changed to:

- C-SSRS assessment (for subjects ≥6 years of age)

Change #44

Section 8.2.8 Visit 7 (end of Week 16)

Sentence 1:

During Visit 7 (end of Week 16), the following assessments will be performed:

Have been changed to:

8.2.3.2 Visit 7 (end of Week 12)

During Visit 7 (end of Week 12), the following assessments will be performed:

The following bullets have been added:

- Body weight
- Socio-professional data

Bullets 3 and 5:

- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- C-SSRS assessment

Have been changed to:

- ECG 12-lead assessment (see Section 10.7.1)
- C-SSRS assessment (for subjects ≥6 years of age)

Change #45

Section 8.2.9 Visit 8 (end of Week 20)

Sentence 1:

During Visit 8 (end of Week 20), the following assessments will be performed:

Have been changed to:

8.2.3.3 Visit 8 (end of Week 16)

During Visit 8 (end of Week 16), the following assessments will be performed:

The following bullets have been added:

- Socio-professional data
- Body weight

Bullet 4:

- C-SSRS assessment

Has been changed to:

- C-SSRS assessment (for subjects ≥6 years of age)

Change #46

Section 8.2.10 ET Visit/Visit 9 (end of Week 24)

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be

advised to have subjects return for their ET Visit within 1 week of the subject's second seizure (see Section 6.3).

During the ET Visit/Visit 9 (end of Week 24), the following assessments will be performed:

- Body weight and height
- Physical examination (complete)
- Neurological examination (complete)
- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, a serum pregnancy test [for women of childbearing potential], and LCM plasma concentration)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Achenbach CBCL
- BRIEF
- EQ-5D-3L
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age)
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver
- Tanner Stage (for subjects under 18 years of age)
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IVRS/IWRS

Has been changed to:

8.2.3.4 Visit 9 (end of Week 20)

During Visit 9 (end of Week 20), the following assessments will be performed:

- Body weight
- Physical examination (brief)
- Neurological examination (brief)
- ECG 12-lead assessment (see Section 10.7.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a urine pregnancy test [for women of childbearing potential])
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IVRS/IWRS

8.2.3.5 Visit 10/ET Visit (end of Week 24)

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure (see Section 6.3).

During the Visit 10/ET Visit (end of Week 24), the following assessments will be performed:

- Body weight
- Height
- Physical examination (complete)
- Neurological examination (complete)

- ECG 12-lead assessment (see Section 10.7.1)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, urinalysis, a serum pregnancy test [for women of childbearing potential], and LCM plasma concentration)
- Subject diary return/review
- Dispense subject diary
- Dispense study drug
- Study drug review/return
- Achenbach CBCL (same version used at Visit 2)
- BRIEF/ BRIEF-P (same version used at Visit 2)
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age, same version used at Visit 2)
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver
- Tanner Stage (will be performed only for subjects who are pubescent at Visit 2 or who enter puberty during the course of the study)
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria
- Contact IVRS/IWRS

Change #47

Section 8.3.1 Transition and Final Clinic Visit

Has been changed to:

8.3.1 Transition Period

8.3.1.1 Transition Clinic Visit/telephone contact

Paragraph 1:

Subjects who experience their second PGTC seizure and have completed at least 5 weeks of the Treatment Period, or who complete the 24-week Treatment Period without experiencing their

second PGTC seizure will be eligible to enroll in EP0012. Eligible subjects who choose to continue in EP0012 must complete a 4-week blinded transition followed by a Final Clinic Visit. For subjects participating in EP0012, the Final Clinic Visit will serve as Visit 1 of EP0012. Subjects choosing to enter EP0012 must sign and date the EP0012 extension IEC/IRB-approved informed consent prior to receiving EP0012 study drug.

Has been changed to:

A Transition telephone contact is required. The following assessments will be performed during the Transition telephone contact:

- AE reporting
- Concomitant medications and AEDs
- Withdrawal criteria

A Transition Clinic Visit is optional, at the discretion of the investigator. Subjects requiring a clinic visit will have the same assessments conducted as an Unscheduled Visit (see Section 8.4).

8.3.1.2 Final Clinic Visit

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24), respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. The Final Clinic Visit is the same as Visit 1 of EP0012. Subjects choosing to enter EP0012 must sign and date the EP0012 extension IEC/IRB-approved informed consent prior to receiving EP0012 study drug.

Bullets 4 and 6:

- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- C-SSRS assessment
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a serum pregnancy test [for women of childbearing potential])

Have been changed to:

- ECG 12-lead assessment (see Section 10.7.1)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, urinalysis, and a urine pregnancy test [for women of childbearing potential])

Change #48

Section 8.3.2 Taper

Has been changed to:

8.3.2 Taper and Safety Follow-up Period

8.3.2.1 End of Taper Visit

Paragraph 1:

Subjects completing Visit 9 (Week 24) or the ET Visit who choose not to continue in EP0012 must complete a 1-week blinded taper followed by the End of Taper Visit. At the End of Taper Visit, the following assessments will be performed:

Has been changed to:

Subjects completing Visit 10 (Week 24) or the ET Visit who choose not to continue in EP0012 must complete an up to 4-week blinded taper followed by the End of Taper Visit. At the End of Taper Visit, the following assessments will be performed:

The following Bullets have been added:

- Physical examination (complete)
- Neurological examination (complete)
- Socio-professional data

Bullets 2 and 4:

- ECG (12-lead) assessment (1 recording to be performed prior to any blood draws and, if possible, with the subject in the supine position for at least 5 minutes preceding ECG recording)
- C-SSRS assessment

Have been changed to:

- ECG 12-lead assessment (see Section 10.7.1)
- C-SSRS assessment (for subjects ≥6 years of age)

The following section has been added:

8.3.2.2 Safety Follow-up Visit

Following the End of Taper Visit, the subject will return 2 weeks (±2 days) after the last dose of study drug for a Safety Follow-up Visit. During the Safety Follow-up Visit, the following assessments will be performed:

- Body weight
- Physical examination (complete)
- Neurological examination (complete)

- ECG 12-lead assessment (see Section 10.7.1) (required only for subjects with an abnormal reading at the previous clinic visit)
- Vital signs (pulse rate, systolic BP, and diastolic BP, including orthostatic assessments)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology [required only for subjects with an abnormal value at the previous clinic visit], urinalysis, and a urine pregnancy test [for women of childbearing potential]).
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver
- Socio-professional data
- AE reporting
- Concomitant medications and AEDs

8.3.2.2. Safety Follow-up telephone contact

Thirty days (-1/+3 days) after the last dose of study drug, the subject will receive a Safety Follow-up telephone contact. During the Safety Follow-up telephone contact, the following assessments will be performed:

- AE reporting
- Concomitant medications and AEDs

Change #49

Section 8.4 Unscheduled Visit

Paragraphs 1 and 2:

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:

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

Has been changed to:

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

If an unscheduled visit is due to an AE, then the C-SSRS (for subjects ≥6 years of age) is required.

Last paragraph:

In addition to the required assessments listed above, further assessments can be completed as needed and may include ECG, laboratory tests, dispense study drug, diary review, etc.

Has been changed to:

In addition to the required assessments listed above, depending on the type of visit (clinic or telephone), further assessments can be completed as needed and may include ECG, vital signs, laboratory tests, dispense study drug, diary review, etc.

Change #50

Section 9.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Time to the first PGTC seizure during the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 5 weeks of the Treatment Period
- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period

Has been changed to:

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures for the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 6 weeks of the Treatment Period
- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Time to the first PGTC seizure during the 24-week Treatment Period

Change #51

Section 9.3 Other efficacy variables

Bullets 1, 3, 9 and 15:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 5 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 5 weeks of the Treatment Period

- EuroQol-5 Dimension (EQ-5D-3L) items

Have been changed to:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 6 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- EuroQol-5 Dimension (EQ-5D-3L) items (for subjects ≥12 years of age)

Change #52

Section 9.3.1 Seizure frequency

The following paragraph was added to the end of the section:

Investigators should advise subjects and/or caregivers about the importance of reporting non-PGTC seizures. Subjects should be reminded that diaries must include daily entries even if no seizures have occurred.

Change #53

Section 9.3.2 Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P)

First sentence:

The QOLIE-31-P Version 2 will be used to evaluate the health-related quality of life (HRQoL) of study subjects (Cramer and Van Hammée, 2003).

Has been changed to:

The QOLIE-31-P Version 2 will be used to evaluate the health-related quality of life (HRQoL) of study subjects ≥18 years of age (Cramer and Van Hammée, 2003).

Change #54

Section 9.3.3 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).

The PedsQL Measurement Model consists of developmentally appropriate forms for pediatric subjects 12 years of age 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 HRQoL is measured for pediatric subjects ≥2 years to ≤18 years of age.

The multidimensional 23-item PedsQL generic core scales encompass the essential core domains for pediatric HRQoL measurement: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). 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 23 items, with higher scores indicating higher HRQoL.

Has been changed to:

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001). The version of the PedsQL used at Visit 2 should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Section 5.2).

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

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

Change #55

Section 9.3.4 ED-5D-3L Quality of Life Assessment

Has been changed to:

9.3.4 EQ-5D-3L Quality of Life Assessment

First sentence:

The EQ-5D-3L (EuroQol Group, 2011) is a self-administered questionnaire designed to measure health status.

Has been changed to:

The EQ-5D-3L (EuroQol Group, 2011) is a self-administered questionnaire designed to measure health status in subjects ≥12 years of age.

Change #56

Section 9.3.6 Number of working days or school days lost

The number of working or school days lost by the subject will be recorded.

Has been changed to:

The number of working or school days lost by the subject will be recorded, as applicable.

Change #57

Section 9.3.7 Number of days with help from a caregiver

The number of days with help from a caregiver will be recorded.

Has been changed to:

The number of days with help from a caregiver will be recorded, as applicable.

Change #58

Section 9.3.8 Socio-professional data

Socio-professional data, such as highest level of education, current professional status, housing status, and regular assistance will be collected only at Visit 2.

Has been changed to:

Socio-professional data, such as highest level of education, current professional status, housing status, and regular assistance will be collected throughout the study, as applicable.

Change #59

Section 10.1.6 Pregnancy

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

- The subject should return for an ET Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the ET Visit.
- A Safety Follow-up Visit (Final Clinic Visit) should be scheduled 2 weeks after the subject has discontinued their 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 an 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.

Has been changed to:

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's Drug Safety department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an ET Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the ET Visit.
- A Safety Follow-up Visit (Final Clinic Visit) should be scheduled 2 weeks after the subject has discontinued her IMP.

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

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. Every reasonable attempt should be made to follow the health of the child 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. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's Drug Safety department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/CRO contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's Drug Safety department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's Drug Safety department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital

anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

Change #60

Section 10.3 Adverse events of special interest

The following adverse event of special interest was added.

- Emergence of non-preexisting or worsening of any existing epileptic seizure types.

Change #61

Section 10.6 Laboratory measurements

First sentence:

Blood and urine specimens for routine assay of hematology, clinical chemistry, and urinalysis parameters will be collected according to the schedule of study assessments in Table 5–1.

Has been changed to:

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis parameters will be collected according to the schedule of study assessments in Section 5.2. A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.6.2). The procedures for handling and shipping these specimens will be provided to the sites.

The laboratory tests to be performed are presented in Table 10-2*:*

Table 10-2: Laboratory tests

Hematology	Clinical chemistry	Urinalysis
Hematocrit Hemoglobin Platelet count RBC count WBC count Differential count	Calcium Phosphorus Serum electrolytes (sodium, potassium, chloride, bicarbonate) Creatinine BUN AST ALT Total bilirubin Alkaline phosphatase GGT Glucose Albumin Total serum protein Uric acid	pH Ketones Glucose Albumin Specific gravity Microscopic exam for blood cells or casts/hpf Urine pregnancy test

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyl transferase; hpf=high power field; RBC=red blood cell; WBC=white blood cell

Has been changed to:

Table 10-2: Laboratory tests

Hematology	Clinical chemistry	Endocrinology[a]	Urinalysis[b]
Hematocrit Hemoglobin Platelet count RBC count WBC count Differential count	Calcium Phosphorus Serum electrolytes (sodium, potassium, chloride, bicarbonate) Creatinine BUN AST ALT Total bilirubin Alkaline phosphatase GGT Glucose Albumin Total serum protein Uric acid	TSH T_3 (total and serum-free) T_4 (total and serum-free)	pH Ketones Glucose Albumin Specific gravity Microscopic exam for blood cells or casts/hpf

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

[a] Thyroid function will be required in subjects <18 years of age only.
[b] Urinalysis will be required for subjects ≥5 years of age only.

Creatinine clearance will be estimated using 2 different formulas. In subjects ≥12 years of age, creatinine clearance will be estimated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976). In subjects <12 years of age, creatinine clearance will be estimated using the updated Schwartz bedside formula (Schwartz and Work, 2009).

Change #62

Section 10.6.2 Pregnancy testing

Females of childbearing potential (who have not been surgically sterilized or who are not at least 2-years postmenopausal) will have serum and urine dipstick pregnancy testing performed according to the schedule of study assessments in Table 5–1.

Has been changed to:

Females of childbearing potential (who have not been surgically sterilized or who are not at least 2 years postmenopausal) will have serum and urine dipstick pregnancy testing performed according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

Change #63

Section 10.7.1 12-lead ECG

Standard 12-lead ECGs will be performed according to the schedule of study assessments in Table 5–1.

The 12-lead ECG recording should be performed at approximately the same time of day and prior to blood sample collection. 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:

Standard 12-lead ECGs will be performed according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

The ECG recordings should be performed at the same time of day (when possible) and prior to blood sample collection and vital sign assessments. Care should be taken to assure proper lead placement and quality ECG recordings. If possible, subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording. In pediatric subjects (<18 years of age), 12-lead ECGs (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

Change #64

Section 10.7.2 Vital signs and body weight

Noninvasive BP (systolic and diastolic) and pulse rate will be measured at clinic visits in a supine position after at least 3 minutes at rest, according to the schedule of study assessments in Table 5–1. Assessment of orthostatic changes will be as follows: after the 3-minute measurement in a supine position, the subject is asked to stand and BP and pulse rate are taken 1 minute and 3 minutes after standing up as feasible. Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

Body weight will be determined without shoes and wearing light clothing and height will be measured without shoes. Body weight and height will be measured using equipment that is age appropriate and assessed according to the tabular schedule of study assessments (Table 5–1).

Has been changed to:

10.7.2 Vital signs, body weight, and height

Noninvasive BP (systolic and diastolic) and pulse rate will be measured at clinic visits in a supine position after at least 3 minutes at rest, according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3. Assessment of orthostatic changes will be as follows: after the 3-minute measurement in a supine position, the subject is asked to stand and BP and pulse rate are taken approximately 1 minute and approximately 3 minutes after the subject stands up, as feasible. Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

Body weight will be determined without shoes and wearing light clothing and height will be measured without shoes. Body weight and height will be measured using equipment that is age appropriate and assessed according to the tabular schedule of study assessments (Table 5–1, Table 5–2, and Table 5–3).

Change #65

Section 10.7.3 Physical examination

Sentence 1:

Physical examinations will be performed by a medically qualified clinician licensed to perform the examination, according to the schedule of study assessments in Table 5–1.

Has been changed to:

Physical examinations will be performed by a medically qualified clinician licensed to perform the examination, according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

Change #66

Section 10.7.3.1 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 and review of all body systems.

Change #67

Section 10.7.4 Tanner Stage

At Visit 1 and Visit 9/ET Visit, the investigator or qualified designee will evaluate the subject's sexual development using a 3-item scale. The Tanner Stage will be performed for subjects who are <18 years of age at Visit 1. At Visit 9/ET Visit, if subject is >18years of age, a repeat assessment is not necessary.

Has been changed to:

At Visit 2 and Visit 10/ET Visit, the investigator or qualified designee will evaluate the subject's sexual development using the 3-item Tanner scale, according to the tabular schedules of study procedures (Section 5.2). The investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 2 or who will enter puberty during the course of the study).

Change #68

Section 10.7.5 Neurological examination

First sentence:

Neurological examinations will be performed by a medically qualified clinician with documented training in the conduct of neurological examinations, according to the schedule of study assessments in Table 5–1.

Has been changed to:

Neurological examinations will be performed by a medically qualified clinician with documented training in the conduct of neurological examinations, according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5–3.

Change #69

Section 10.7.5.2 Brief neurological examination

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

Has been changed to:

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

Change #70

Section 10.7.6 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2012). 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 schedule of study assessments in Table 5–1.

Has been changed to:

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2012). 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 schedule of study assessments in in Table 5–1, Table 5–2, and Table 5–3.

All subjects who are ≥6 years of age will complete the “Baseline/Screening” version of the C-SSRS at Visit 1 and will complete the “Since Last Visit” version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age, and the “Since Last Visit” version should be used at subsequent visits.

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association. Each subject´s parent(s)/legal representative(s)/caregiver(s) (in accordance with local regulation) should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

Change #71

Section 10.7.7 Achenbach CBCL

Paragraphs 1 and 2:

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems. Behavioral problems will be scored by the parent(s)/legal representative(s). For subjects ≥12 years to <18 years of age, the CBCL/6 to 18 version will be used.

The same scale will be completed at Visit 2, Visit 4, and Visit 9/ET Visit by the parent(s)/legal representative(s). The completion of the Achenbach CBCL will require approximately 45 minutes.

Have been changed to:

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

The Achenbach CBCL/1½ -5 is for children <5 years and 11 months of age, and the CBCL/6-18is for children ≥6 years to <18 years of age; the questionnaire is to be completed by the parent(s)/legal representative(s). For each subject, the same version of the scale that is completed at Visit 2 should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Table 5–1) and should be completed by the same parent/legal representative. The completion of the Achenbach CBCL will require approximately 45 minutes.

Last paragraph:

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

Has been changed to:

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

Change #72

Section 10.7.8 BRIEF

The BRIEF is a validated tool that will be used for the evaluation of subjects ≥5 years of age. The BRIEF will be administered at Visit 2, Visit 4, and Visit 9/ET Visit.

The BRIEF includes rating forms used by parents to assess subjects' executive functioning and include validity scales to measure negativity and inconsistency of responses.

The BRIEF Rating form contains items in nonoverlapping clinical scales and validity 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. Factor analytic studies and structural equation modeling provide support for the 2 factor model of executive functioning as encompassed by the 2 Indexes.

Has been changed to:

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively. The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each subject, the same version (BRIEF-P or BRIEF) that is used at Visit 2 should be maintained for the duration of the study in accordance with the tabular schedules of study procedures (Table 5–1).

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

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

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

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

Change #73

Section 13.1.5 Per Protocol Set

First sentence:

The Per Protocol Set (PPS) is a subset of the FAS excluding subjects who completed fewer than 5 weeks of treatment or subjects with important protocol violations affecting the interpretation of the primary efficacy analysis.

Has been changed to:

The Per Protocol Set (PPS) is a subset of the FAS excluding subjects who completed fewer than 6 weeks of treatment or subjects with important protocol violations affecting the interpretation of the primary efficacy analysis.

Change #74

Section 13.1.5 Safety set

First sentence:

The Safety Set (SS) is a subset of the RS and consists of all subjects who have been treated with at least 1 tablet of study drug, either LCM or placebo.

Has been changed to:

The Safety Set (SS) is a subset of the RS and consists of all subjects who have been treated with at least 1 dose of study drug, either LCM or placebo.

Change #75

Section 13.3.1 Analysis of the primary efficacy variable

First sentence:

The primary efficacy variable, time to second PGTC seizure during the Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the 16 weeks prior to randomization) and age at informed consent (≥12 to <18 years of age vs ≥18 years of age).

Has been changed to:

The primary efficacy variable, time to second PGTC seizure during the Treatment Period, will be evaluated using a Cox proportional hazards regression model (Cox, 1972), with an effect for treatment, stratifying for the subjects' Baseline PGTC seizure frequency (≤2 per 28 days vs >2 per 28 days in the 16 weeks prior to randomization) and age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age vs ≥18 years of age).

Fourth paragraph:

The following additional sensitivity analyses on the primary efficacy endpoint will be conducted in order to assess the effect of dropouts and protocol deviations on the primary endpoint:

Has been changed to:

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

The following fourth bullet was added:

- Repeat the primary analysis using the FAS, comparing the event rates prior to vs after each interim analysis to examine possible operational bias due to unblinding.

Change #76

Section 13.3.2 Secondary efficacy analysis

Paragraphs 1, 2, and 3:

Analysis of the key secondary efficacy variable, time to first PGTC seizure during the Treatment Period, will be analyzed in the same manner as the primary endpoint using the FAS. A gatekeeping strategy will be employed to control the Type I error (Marcus et al, 1976). If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

The percent of subjects seizure-free at the end of the 24-week Treatment Period will be estimated from the Kaplan-Meier estimates of time to first seizure using 2-sided 95% confidence intervals.

Analyses of the secondary efficacy variable will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the

primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described above), will be exploratory only.

Has been changed to:

Analysis of the key secondary efficacy variable, seizure freedom for PGTC seizures for the 24-week Treatment Period, will be analyzed in the same manner as the primary endpoint using the FAS. The percentage of seizure-free subjects at the end of the 24-week Treatment Period will be estimated from the KM estimates of time to first seizure using 2-sided 95% confidence intervals. A gatekeeping strategy will be employed to control the Type I error (Marcus et al, 1976). If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

Analyses of the secondary efficacy variables will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described above) will be exploratory only.

Time to the first PGTC seizure for the 24-week Treatment Period will be analyzed in the same manner as the primary endpoint using the FAS.

Change #77

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 unblinding and locking the clinical database, a Data Review Meeting will be held. Important protocol deviations (ie, those considered to have an impact on interpretation of safety, efficacy, or study conduct) will be identified and reviewed by a panel consisting of the CPM, the study biostatistician, study physician, a representative of the monitoring team, and other appropriate team members.

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 (DCP). 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 in a blinded manner a part of the ongoing data cleaning process prior to database lock to confirm exclusion from analysis sets.

Change #78

Section 13.7 Planned interim analysis and data monitoring

Paragraph 2, added the following after sentence 1:

The IDMC will oversee the safety of the study by reviewing safety data periodically. Details will be provided in an IDMC charter.

Change #79

16 REFERENCES

The following references were added:

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol. 2005;4:627-34.

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

17.5 Protocol Amendment 3

Rationale for the amendment

In order to optimize study operations, ECGs will be evaluated locally and not centrally.

Specific changes

Change #1

Title page:

The title was updated from "Protocol SP0982 Amendment 2" to "Protocol SP0982 Amendment 3."

The information below was revised to include Protocol Amendment 3 and the type of protocol amendment:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial
Protocol Amendment 3	XX Dec 2014	Non-substantial

Change #2

The sponsor declaration page was deleted, as sponsor signatures are now captured electronically.

Change #3

Study contact information

Clinical Project Manager

Name:	[redacted], MBA, MS
Address:	8010 Arco Corporate Drive Raleigh, NC 27617 USA
Phone:	[redacted]
Fax:	

Has been changed to:

Clinical Project Manager

Name:	[redacted], MSc
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Change #4

Section 10.7.1.1 Overall ECG interpretation

Electrocardiograms will be initially reviewed locally by the investigator, subinvestigator, or qualified designated reader and also transmitted to and evaluated by a central ECG laboratory. If the reading identifies a second- or third-degree AV block or another abnormal ECG finding that is assessed by the investigator to be clinically significant, then the ECG should be repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study (see Section 6.4). 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.

Has been changed to:

Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader. If the reading identifies a second- or third-degree AV block or another abnormal ECG finding that is assessed by the investigator to be clinically significant, then the ECG should be repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study (see Section 6.4). The investigator may consult with a cardiologist 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.

17.6 Protocol Amendment 4

Rationale for the amendment

The primary purpose of this substantial amendment is to clarify elements of the study design including inclusion and exclusion criteria, exit criteria, and withdrawal criteria, as well as the duration of the Baseline Period, procedure for dividing the daily dose for the tablet formulation without breaking tablets, permitted and prohibited concomitant medication, consent for prescreening EEG, seizure count, temperature for storage of plasma samples, and determination of sample size. The protocol was also updated according to the new UCB protocol template, for example, with the addition of text regarding potential drug-induced liver injury (PDILI).

Modifications and changes

Specific changes

Change #1

Title page:

The title was updated from "Protocol SP0982 Amendment 3" to "Protocol SP0982 Amendment 4."

The information below was revised to include Protocol Amendment 4 and the type of protocol amendment:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial
Protocol Amendment 3	09 Jan 2015	Non-substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial
Protocol Amendment 3	09 Jan 2015	Non-substantial
Protocol Amendment 4	08 Jun 2016	Substantial

Change #2

STUDY CONTACT INFORMATION

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	Europe and Rest of the World: +32 2 386 2421 USA: +1 770 970 8858 or +1 800 880 6949 or +1 866 890 3175 Canada: +1 877 582 8842
Email	Global: DSICT.-@ucb.com

Has been changed to:

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 2421 **USA:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com

Change #3

LIST OF ABBREVIATIONS

ALP	alkaline phosphatase
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDC	electronic data capture
HLA	human leukocyte antigen
ICH	International ~~Conference on~~ Council for Harmonisation
IRT	interactive response technology
~~IVRS/IWRS~~	~~interactive voice/web response system~~
~~MAO~~	~~monoamine oxidase~~

MAO-A	monoamine oxidase A
PDILI	potential drug-induced liver injury
PS	Patient Safety
~~RDC~~	~~remote data capture~~

These abbreviations have also been changed wherever they occur throughout the protocol.

Change #4

Section 1, SUMMARY

Paragraph 2

Approximately 200 subjects across approximately 150 sites in the US, Canada, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 7

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs); withdrawal due to AEs; changes in hematology, chemistry, endocrinology, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; and changes in physical and neurological examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using a behavioral assessment (Achenbach Child Behavior Checklist [CBCL]) and a cognitive function assessment (Behavior Rating Inventory of Executive Function® [BRIEF®]/Behavior Rating Inventory of Executive Function Preschool Version [BRIEF-P]).

Has been changed to:

Paragraph 2

Approximately 200 subjects across approximately 150 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 7

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs); withdrawal due to AEs; changes in hematology, chemistry, endocrinology, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; incidence of new seizure types, increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period; and changes in physical and neurological examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using a behavioral assessment (Achenbach Child Behavior Checklist [CBCL]) and a cognitive function assessment (Behavior Rating Inventory of Executive Function® [BRIEF®]/Behavior Rating Inventory of Executive Function Preschool Version [BRIEF-P]).

Change #5

Section 2, INTRODUCTION

Paragraph 1

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). Epileptic seizures occur in the context of a wide range of epilepsy syndromes that may be of genetic, structural/metabolic, or of unknown origin. The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic (23%), absence (6%), and myoclonic (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

Paragraph 8

Preliminary safety and PK data suggest that exposure-response in pediatric and adult subjects treated with LCM will be similar. Lacosamide is being evaluated in pediatric subjects 1 month to 17 years of age in 3 ongoing studies: SP847 (open-label, Phase 2, PK, tolerability, and safety study), SP848 (open-label long-term safety study), and SP1047 (PK study with a 1-day evaluation period).

Has been changed to:

Paragraph 1

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated to affect almost 70 million people worldwide (Ngugi et al, 2011). Epileptic seizures occur in the context of a wide range of epilepsy syndromes that may be of genetic, structural/metabolic, or of unknown origin. The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic (23%), absence (6%), and myoclonic (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

Paragraph 8

Preliminary safety and PK data suggest that exposure-response in pediatric and adult subjects treated with LCM will be similar. Lacosamide has been evaluated in 2 completed pediatric studies, both in subjects aged 1 month to 17 years (SP847 [open-label, adjunctive therapy, pharmacokinetic study in partial-onset seizures] and SP1047 [open-label pharmacokinetic study in epilepsy]). Subjects from SP847 were also able to enroll into an ongoing open-label long-term safety study (SP848). In addition, lacosamide is being evaluated in the following ongoing pediatric efficacy and safety studies:

- SP0967 (ages ≥1 month to <4 years) as adjunctive therapy in partial-onset seizures
- SP0969 (ages ≥4 to <17 years) as adjunctive therapy in partial-onset seizures
- EP0034, open-label extension study to SP0967 and SP0969
- SP0966 (ages ≥1 month to <18 years) as adjunctive therapy, exploratory study in subjects with epilepsy syndromes associated with generalized seizures

Change #6

Sections 4.1.2 and 9.2, Secondary efficacy variables

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures for the 24-week Treatment Period

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days from the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline) to the first 6 weeks of the Treatment Period
- The percent change in PGTC seizure frequency per 28 days from Combined Baseline to the 24-week Treatment Period
- Time to the first PGTC seizure during the 24-week Treatment Period

Sections 4.1.3 and 9.3, Other efficacy variables

Other efficacy variables are:

- Percent change in days with absence seizures per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- Percent change in days with absence seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- Percent change in days with myoclonic seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period among subjects who completed the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period among subjects who completed the 24-week Treatment Period
- Seizure-free status (yes, no) for all seizure types for the first 12 weeks of the Treatment Period among subjects who completed the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all seizure types for the 24-week Treatment Period among subjects who completed the 24-week Treatment Period
- 50% response for PGTC seizures during the first 6 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 6 weeks of the Treatment Period
- 50% response for PGTC seizures during the first 12 weeks of the Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the first 12 weeks of the Treatment Period

- 50% response for PGTC seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in PGTC seizure frequency per 28 days from the Combined Baseline to the 24-week Treatment Period
- 50% response for days with absence seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in days with absence seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- 50% response for days with myoclonic seizures during the 24-week Treatment Period; a responder is a subject experiencing ≥50% reduction in days with myoclonic seizures per 28 days from the Combined Baseline to the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- Change from Baseline to end of treatment or ET in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject
- Number of days with help from a caregiver

Have been changed to:

Sections 4.1.2 and 9.2, Secondary efficacy variables

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline)
- The percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline
- Time to the first PGTC seizure during the Treatment Period

Sections 4.1.3 and 9.3, Other efficacy variables

Other efficacy variables are:

- Change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Prospective Baseline
- Change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Prospective Baseline
- Seizure-free status (yes, no) for PGTC seizures for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for PGTC seizures for the 24-week Treatment Period
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the first 12 weeks of the Treatment Period compared to Combined Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the Treatment Period compared to Combined Baseline
- Seizure-free status (yes, no) for all generalized seizure types for the first 12 weeks of the Treatment Period
- Seizure-free status (yes, no) for all generalized seizure types for the 24-week Treatment Period
- Change from Baseline in Patient-Weighted Quality of Life in Epilepsy Inventory form 31 (QOLIE-31-P) subscale (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Mental Activity/Cognitive Functioning, Overall Quality of Life and Medication Effects) and total scores in subjects ≥18 years of age or change from Baseline in the Pediatric Quality of Life Inventory (PedsQL) subscale (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and total scores in subjects <18 years of age
- Change from Baseline to end of treatment or ET in the 3-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age)

- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits
- Number of working or school days lost by subject due to epilepsy
- Number of days with help from a caregiver due to epilepsy

Change #7

Section 4.2, Safety variables

New bullet points

- Incidence of new seizure types during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

Change #8

Section 5.1, Study description

Paragraph 2

Approximately 200 subjects across approximately 150 sites in the US, Canada, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 4

Eligibility to enter SP0982 will be based on a 12-week Historical Baseline prior to screening at Visit 1. Subjects with a confirmed diagnosis of IGE with uncontrolled PGTC seizures, who had ≥2 documented PGTC seizures in the 12-week Historical Baseline, with ≥1 PGTC seizure during the first 8 weeks of the Historical Baseline will enter a 4-week Prospective Baseline. In addition, to be eligible for randomization, the subject must have ≥1 PGTC seizure during the last 4 weeks of the Historical Baseline or the 4-week Prospective Baseline. Thus, a total of ≥3 PGTC seizures in the 16-week Combined Baseline Period (12-week Historical and 4-week Prospective Baseline) are required for study randomization to treatment (see Section 6.1, Inclusion Criterion 5).
A schematic diagram for the Combined Baseline Period seizure eligibility is provided in Figure 5-1.

Have been changed to:

Paragraph 2

Approximately 200 subjects across approximately 150 sites in the US, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 4

Eligibility to enter SP0982 will be based on a 12-week Historical Baseline prior to screening at Visit 1. In rare cases where there is a gap between consenting and Visit 1 procedures, the 12-week Historical Baseline will be calculated from the date of Informed Consent/Assent.

Prior to randomization, the following 3 criteria concerning PGTC seizure frequency must be met:

- The subject must have experienced at least 3 PGTC seizures during the 16-week Combined Baseline Period,
- The subject must have experienced at least 2 PGTC seizures during the 12-week Historical Baseline Period,
- Of the above seizures, at least 1 PGTC seizure should have occurred during the first 8 weeks and at least 1 PGTC seizure should have occurred during the second 8 weeks of the 16-week Combined Baseline Period.

Examples of different scenarios and the subjects´ eligibility in terms of Baseline Period seizures are presented in a table in Inclusion Criterion 5. A schematic diagram for the Combined Baseline Period seizure eligibility is provided in Figure 5-1.

Change #9

Section 5.1.4, Anticipated sites and regions

The study is planned to be conducted in the US, Canada, Asia, and Australia, with possible extension to other countries and regions.

Has been changed to:

The study is planned to be conducted in the US, Asia, and Australia, with possible extension to other countries and regions.

Change #10

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

The following footnote has been added to Visit 1

[bb] Participation in the study starts from the time of signing the approved Informed Consent/Assent form. However, sites may conduct prescreening EEGs and prior to this, subjects will read and sign a separate Informed Consent form that has been approved by an IRB/IEC and the Sponsor, and which complies with regulatory requirements.

Change #11

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Footnote o

[o] Urinalysis will be required for subjects ≥5 years of age only.

Table 5–2: Schedule of study assessments for SP0982 (Transition Period)

Footnote i

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

Table 5–3: Schedule of study assessments for SP0982 (Taper Period and Safety Follow-up Period)

Footnote f

[f] Urinalysis will be required for subjects ≥5 years of age only.

Table 10-2: Laboratory tests

Footnote b

[b] Urinalysis will be required for subjects ≥5 years of age only.

Have been changed to:

Table 5–1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Footnote o

[o] Urinalysis will be required for all subjects.

Table 5–2: Schedule of study assessments for SP0982 (Transition Period)

Footnote i

[i] Urinalysis will be required for all subjects.

Table 5–3: Schedule of study assessments for SP0982 (Taper Period and Safety Follow-up Period)

Footnote f

[f] Urinalysis will be required for all subjects.

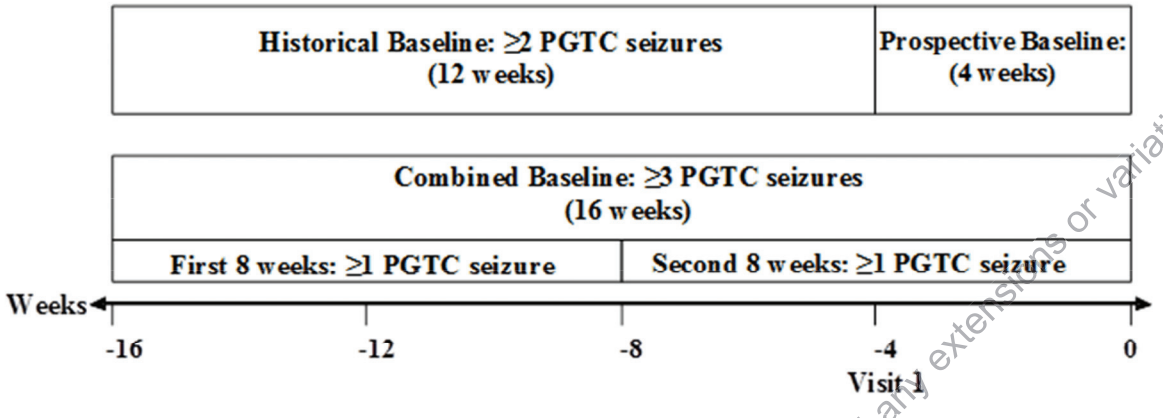
Table 10–2: Laboratory measurements

Footnote b

[b] Urinalysis will be required for all subjects.

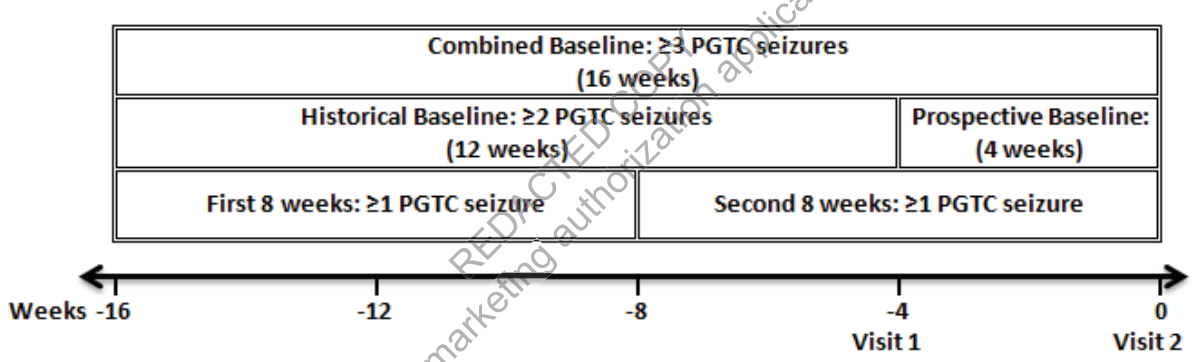
Change #12

Figure 5–1: Combined Baseline Period seizure eligibility for SP0982



Has been changed to:

Figure 5–1: Combined Baseline Period seizure eligibility for SP0982



PGTC=primary generalized tonic-clonic

Change #13

Section 5.4.1, Rationale for dose

Paragraph 2

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 pediatric dosing recommendations for SP0982 are to achieve LCM plasma concentrations similar 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:

Paragraph 2

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 pediatric dosing recommendations

for SP0982 are to achieve LCM plasma concentrations similar to the average steady-state LCM plasma concentration reached after a LCM 400mg/day dose administration in adult studies.

Paragraphs 3 and 4 have been added:

A population PK model (CL0177) was developed using plasma concentration data and demographic information from all pediatric subjects in SP847 and SP1047. The data consisted of 402 LCM plasma concentration-time records obtained in 79 children, with a balanced distribution of 14, 22, 25, and 18 subjects in the age groups 6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years, respectively. Body weights ranged from 6kg to 76kg.

Different pediatric dosing adaptation schemes were simulated with the aim of reaching the range of average steady-state plasma concentration ($C_{SS,ave}$) obtained in adults receiving LCM 400mg/day, which is approximately 8µg/mL (90% prediction interval: 5µg/mL to 12µg/mL). This was achieved with a dosing scheme of 12mg/kg/day in children weighing <30kg, 8mg/kg/day in children weighing from 30 to <50kg, and 400mg/day in children weighing ≥50kg. The proportional pediatric dose adaptation corresponding to 300mg/day in adults and in children weighing ≥50 kg, are 8mg/kg/day in children weighing <30kg, and 6mg/kg/day in children weighing from 30 to <50kg.

Change #14

Section 6.1, Inclusion criteria

5. Subject has ≥3 PGTC seizures during the 16-week Combined Baseline (12-week Historical Baseline plus 4-week Prospective Baseline) distributed as described below:

- ≥2 PGTC seizures during the 12-week Historical Baseline with ≥1 PGTC seizure during first 8 weeks of the Historical Baseline, and
- ≥1 PGTC seizure during the second 8 weeks of the Combined Baseline (ie, during the last 4 weeks of the Historical Baseline or during the 4-week Prospective Baseline)

7. Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 1 to 3 AEDs (with at least 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS (see Section 7.8).

   Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

Have been changed to:

5. Subject has ≥3 PGTC seizures during the 16-week Combined Baseline (12-week Historical Baseline plus 4-week Prospective Baseline) distributed as described below:
   - at least 3 PGTC seizures should have occurred during the 16-week Combined Baseline Period,
   - at least 2 PGTC seizures should have occurred during the 12-week Historical Baseline Period,

– of the above seizures, at least 1 PGTC seizure should have occurred during the first 8 weeks and at least 1 PGTC seizure should have occurred during the second 8 weeks of the 16-week Combined Baseline Period.

The schematic diagram for the Combined Baseline Period eligibility is provided in Figure 5–1. Examples of PGTC seizure frequency and eligibility are provided in the table below:

Number of PGTC seizures			**Is subject eligible?** (In terms of Inclusion Criterion 5)
Historical Baseline Weeks -16 to -8	**Historical Baseline Weeks -8 to -4**	**Prospective Baseline Weeks -4 to 0** (Visit 1 to Visit 2)	
2	1	0	Yes
3	0	0	No*
1	1	1	Yes
0	2	1	No
1	2	0	Yes
2	0	1	Yes
1	0	2	No
1	1	0	No*

Screening Visit

*Eligible to roll over to EP0012 if all other inclusion criteria are also met.
PGTC=primary generalized tonic-clonic

7. Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 1 to 3 AEDs (with 1 AED identified as a benzodiazepine, see examples in the table below) for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS (see Section 7.8).

   Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

Benzodiazepine AEDs	Non-Benzodiazepine AEDs	Total AEDs	Is subject eligible? (In terms of Inclusion Criterion 7)
0	1	1	Yes
0	2	2	Yes
1	1	2	Yes
1	2	3	Yes
1	0	1	**No**
0	3	3	**No**
2	1	3	**No**

AED=antiepileptic drug

Change #15

Section 6.2, Exclusion criteria

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

12. Subject has any history of alcohol or drug abuse within the previous 2 years.

15. Subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥2x the upper limit of normal (ULN) or has alkaline phosphatase levels ≥3xULN at Visit 1.

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

22. Subject has been taking 1 or more of the following medications on a regular basis within 28 days prior to Visit 1: neuroleptics, monoamine oxidase (MAO) inhibitors, barbiturates (for indications other than epilepsy), or narcotic analgesics.

23. Subject with concomitant treatment of felbamate or previous felbamate therapy within the last 6 months prior to Visit 1.

25. Subject is on a ketogenic diet.

If the investigator has any doubts concerning the subject's eligibility, he/she should consult the UCB Study Physician or representative for clarification.

Have been changed to:

1. Subject has previously been randomized in this study or subject has previously been assigned to treatment in a clinical study of LCM.

12. Subject has any history of alcohol, opioid, or other drug use disorder, as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), within the previous 2 years.

    Note: previous sporadic cannabis use is not exclusionary as long as subject is requested and agrees not to use cannabis during the study.

15. At Visit 1, subject has ≥2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or

>ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

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

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

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

17. Subject has a known cardiac channelopathy, such as Brugada syndrome.
22. Subject has been taking 1 or more of the following medications on a regular basis within 28 days prior to Visit 1: monoamine oxidase A (MAO-A) inhibitors, barbiturates (for indications other than epilepsy), or clozapine.
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 <12 months are excluded. Subjects treated with felbamate for ≥12 months prior to Visit 1 and who have not experienced serious toxicity issues are eligible.
25. Subject is on a ketogenic diet that has either changed within the 4 weeks prior to Visit 1 or is expected to change during the study.

Subjects may be rescreened with prior consultation and permission of the Medical Monitor. If the investigator has any doubts concerning the subject's eligibility, he/she should consult the UCB Study Physician or representative for clarification.

Change #16

Section 6.3, Exit criteria

Last paragraph

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within **1 week** of the subject's second seizure.

Has been changed to:

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within **1 week** of the subject's second seizure, with the following exception: if the 2 PGTC seizures occur during the first 6 weeks of the Treatment Period (after randomization), the subject should continue the Titration Period visits and wait for the end of the first 6 weeks of the Treatment Period to complete the ET Visit.

Change #17

Section 6.4, Withdrawal criteria

Bullet point 15

- 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 drug.

Investigators should attempt to obtain information on subjects, in the case of withdrawal or discontinuation. For subjects considered lost to follow-up the investigator should make an effort (at least 1 telephone call and 1 written message to the subject), and document his/her effort (date and summary of the telephone 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.

Has been changed to:

- Discontinuation criteria for potential drug-induced liver injury (PDILI) are described in Section 6.4.1.

Investigators should attempt to obtain information on subjects in the case of withdrawal. For subjects considered as lost to follow up, the investigator should make 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.

Change #18

A new section has been added:

Section 6.4.1, Potential drug-induced liver injury IMP discontinuation criteria

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

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

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

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

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

Evaluation of PDILI must be initiated as described in Section 10.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Change #19

Section 7.2, Treatments to be administered

Paragraph 2

At Visit 2, subjects will be randomized to receive either LCM (oral solution for pediatric subjects [≥4 to <18 years of age] weighing <50kg or tablets for adult subjects [≥18 years of age] and pediatric subjects weighing ≥50kg) or matching placebo. At the end of Visit 2, subjects should take the first dose of study drug while in the clinic.

Has been changed to:

At Visit 2, subjects will be randomized to receive either LCM (oral solution for pediatric subjects [≥4 to <18 years of age] weighing <50kg or tablets for adult subjects [≥18 years of age] and pediatric subjects weighing ≥50kg) or matching placebo. At the end of Visit 2, subjects should take the first dose of study drug while in the clinic. Treatment assigned will be determined by the subject's weight at Visit 2.

Paragraph 3

The following text has been added:

Tablets are 50mg and **must not be broken**; instead unequal dosing is allowed – if subjects are taking an odd number of tablets per day (eg, 7 tablets totaling 350mg), they should take the lower dose in the morning (eg, 150mg [3 tablets]) and the higher dose in the evening (eg, 200mg [4 tablets]).

Change #20

Section 7.2.3, Transition Period (for subjects who enter EP0012)

Paragraph 1

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period, or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. Two weeks after Visit 10 (Week 24) or the ET Visit, a Transition telephone contact is required; a subsequent Clinic Visit is at the discretion of the investigator (Table 5–2). The Final Clinic Visit is the same as Visit 1 of EP0012.

Has been changed to:

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. Two weeks after Visit 10 (Week 24) or the ET Visit, a Transition telephone contact is required; a subsequent Clinic Visit is at the discretion of the investigator (Table 5–2). The background AED may be adjusted during the Transition Period at the discretion of the investigator. The Final Clinic Visit is the same as Visit 1 of EP0012.

Change #21

Section 7.5, Handling and storage requirements

Paragraphs 1 to 3

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.

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

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) before further use of the IMP and communicated to the sponsor's designee in accordance with the pharmacy manual.

Have been changed to:

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

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log (showing actual and minimum/maximum temperatures reached over the time interval) in accordance with local requirements on a regular basis.

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

Change #22

Section 7.6, Drug accountability

Paragraph 1

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

Paragraph 5

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB's designee, preferably in their original package. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

Have been changed to:

Paragraph 1

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor'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.

Paragraph 5

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

Change #23

Section 7.8.1, Permitted concomitant treatments (medications and therapies)

Paragraph 1

Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 1 to 3 AEDs (with at least 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period with or without additional concurrent stable VNS.

Bullet point 2

- The chronic (daily dose) use of benzodiazepines is allowed regardless of indication and will be counted as 1 of the 3 allowed AEDs.

Paragraph 2

Contraceptive treatment is allowed as described in in Section 6.2 (Exclusion Criterion 21).

Have been changed to:

Paragraph 1

Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 1 to 3 AEDs (with 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period with or without additional concurrent stable VNS.

Bullet point 2

- The chronic (daily dose) use of a benzodiazepine is allowed regardless of indication and will be counted as 1 of the 3 allowed AEDs.

Paragraph 2

Contraceptive treatment is allowed as described in in Section 6.2 (Exclusion Criterion 21). Recommended contraception methods for subjects on enzyme-inducing antiepileptic drugs (EI-AEDs) or not on EI-AEDs are detailed in Section 17.8.

The following paragraph has been added (Paragraph 4):

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

Change #24

Section 7.8.2, Prohibited concomitant treatments (medications and therapies)

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

- Neuroleptics.
- MAO inhibitors.
- Barbiturates (except as antiepileptic medications).
- Narcotic analgesics.
- Only stable, low doses (<50% of the maximum daily dose recommended by the country-specific product label) of non-benzodiazepine anxiolytics or once-daily hypnotics are allowed for nonepilepsy indications.

Has been changed to:

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

- Clozapine.
- MAO-A inhibitors.

- Barbiturates (except as antiepileptic medications).
- Patients taking non-benzodiazepine anxiolytics or once-daily hypnotics must remain on stable doses of these medications throughout the study.

Change #25

Section 7.10, Randomization and numbering of subjects

First paragraph

An IVRS/IWRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB. The randomization schedule will be produced by the UCB Clinical Trial Supply Officer who is otherwise not involved in this study. The IVRS/IWRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Last paragraph

To randomize a subject (Visit 2), the investigator (or designee) will contact the IVRS/IWRS and provide brief details about the subject to be randomized. The IVRS/IWRS will automatically inform the investigator (or designee) of the subject's randomization number. The IVRS/IWRS will allocate kit numbers to the subject based on the subject number during the course of the study.

Has been changed to:

First paragraph

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB. The randomization schedule will be produced by the IRT Vendor who is otherwise not involved in this study. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Last paragraph

To randomize a subject (Visit 2), the investigator (or designee) will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the investigator (or designee) of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the eCRF.

Change #26

Section 8.1.1, Visit 1 (Week -4)

Paragraph 2

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 and the subject's parent/legal guardian (for subjects <18 years of age) by the investigator (or designee). The IRB-approved Informed Consent/Assent Form must be signed and dated by the subject, or his/her legal representative, and by the person who conducted the informed consent/assent discussion (investigator or designee).

Has been changed to:

Paragraph 3

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 and the subject's parent/legal guardian (for subjects <18 years of age) by the investigator (or designee). The IRB/IEC-approved Informed Consent/Assent form must be signed and dated by the subject, or his/her legal representative, and by the person who conducted the informed consent/assent discussion (investigator or designee). Participation in the study starts from the time of signing the IRB/IEC-approved Informed Consent/Assent form.

Paragraph 4

The following text has been added:

Sites may conduct prescreening EEGs and prior to this, subjects will read and sign a separate Informed Consent form that has been approved by an IRB/IEC and the Sponsor, and which complies with regulatory requirements.

Change #27

Section 9.3.1, Seizure frequency

During the study, subjects will keep a diary to record daily seizure activity from Visit 1 until the end of study participation. The subject should be reminded to bring the diary to each clinic visit. The following information will be recorded on a daily basis as applicable:

- Seizure type
- Number of seizures

Investigators should advise subjects and/or caregivers about the importance of reporting non-PGTC seizures. Subjects should be reminded that diaries must include daily entries even if no seizures have occurred.

Has been changed to:

Section 9.3.1, Seizure variables

Subjects will keep a diary to record daily seizure activity from Visit 1 until the end of study participation. Efficacy and safety variables will be assessed using the seizure count information recorded on the subject diaries. Subjects should be reminded that diaries must include daily entries even if no seizures have occurred. The subject should be reminded to bring the diary to each clinic visit.

9.3.1.1 PGTC seizures

The following information will be recorded on a daily basis as applicable:

- Seizure type
- Number of PGTC seizures

If more than one PGTC seizure occurs on a single day, each seizure should be counted separately, provided there is a complete recovery of consciousness between seizures.

9.3.1.2 Absence and myoclonic seizures

In the subject diary, the following information will be recorded on a daily basis:

- Seizure type
- Number of seizures to be recorded although for the purpose of data analysis, only the number of days with seizure will be analyzed.

Investigators should advise subjects and/or caregivers about the importance of reporting absence and myoclonic seizures.

Change #28

Section 9.3.6, Number of working or school days lost

The number of working or school days lost by the subject will be recorded, as applicable.

Section 9.3.7, Number of days with help from a caregiver

The number of days with help from a caregiver will be recorded, as applicable.

Have been changed to:

Section 9.3.6, Number of working or school days lost due to epilepsy

The number of working or school days lost due to epilepsy by the subject will be recorded, as applicable.

Section 9.3.7, Number of days with help from a caregiver due to epilepsy

The number of days with help from a caregiver due to epilepsy will be recorded, as applicable.

Working or school days lost and days of help from a caregiver are further specified as "due to epilepsy" throughout the protocol, eg, Table 5–1, Table 5–2, and Table 5–3 Schedules of study assessments, Section 8 STUDY PROCEDURES BY VISIT, etc.

Change #29

Section 10, ASSESSMENT OF SAFETY

A new section 10.1.1 Definitions has been added and 10.2.1 Definition of serious adverse event has been moved up to Section 10.1.1.2 Serious adverse event, following 10.1.1.1 Adverse event.

Section 10.5 Anticipated serious adverse events has been moved up to Section 10.1.1.2.1.

Section 10.3 Adverse events of special interest has been moved up to Section 10.1.1.3.

Section 10.1.5 Rule for repetition of an adverse event has been moved up to Section 10.1.2.2.

Section 10.2.2 Procedures for reporting serious adverse events has been moved up to Section 10.1.2.3 Additional procedures for reporting serious adverse events.

Change #30

Section 10.1.1.3, Adverse events of special interest

New bullet point added:

- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

Change #31

Section 10.1.4, Follow-up of adverse events

Paragraph 1

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.

Has been changed to:

Section 10.1.3, Follow-up of adverse events

Paragraphs 1 and 3

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. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events are provided in Section 10.2.1.4.

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

Change #32

The following section has been added:

Section 10.1.5, Suspected transmission of an infectious agent via a medicinal product

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

Change #33

Section 10.6.1, Liver function tests

Refer to Section 6.4 for LFT withdrawal criteria.

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

discontinuation of study drug and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

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

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 drug.

Has been changed to:

Section 10.2.1, Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.2.1.4).

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

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

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

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing

any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued. Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 10–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation - immediate IMP discontinuation not required (see Section 10.2.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 10.2.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

Table 10–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal a Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause). b If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor. c Details provided in Section 10.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. d Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.						

10.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 10.2.1.3) and SAE report (if applicable).

10.2.1.2 Immediate action: determination of IMP discontinuation

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

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.4.1 and Table 10–3 for details).

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

10.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 10–4 (laboratory measurements) and Table 10–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

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

The following measurements are to be assessed:

Table 10-4 PDILI laboratory measurements

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

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

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

The following additional information is to be collected:

Table 10–5: PDILI information to be collected

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

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

10.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10-3.

Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

Change #34

A new section has been added:

Section 10.3.3, New seizure types

Incidence of new seizure types, and increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period will be assessed using the seizure count information recorded on the subject diaries (see Section 9.3.1).

Change #35

Section 11, ASSESSMENT OF PHARMACOKINETICS

Paragraph 2

Each blood sample drawn for LCM plasma concentration determination will be centrifuged and split into 2 duplicate samples prior to freezing. The samples will be stored at -20°C until shipped to a central laboratory. The central laboratory will store the plasma samples at -70°C until analysis.

Has been changed to:

Each blood sample drawn for LCM plasma concentration determination will be centrifuged and split into 2 duplicate samples prior to freezing. The samples will be stored at -20°C until shipped to a central laboratory. The central laboratory will store the plasma samples at -20°C until analysis.

Change #36

Section 13.3.2, Secondary efficacy analyses

Analysis of the key secondary efficacy variable, seizure freedom for PGTC seizures for the 24-week Treatment Period, will be analyzed in the same manner as the primary endpoint using the FAS. The percentage of seizure-free subjects at the end of the 24-week Treatment Period will be estimated from the KM estimates of time to first seizure using 2-sided 95% confidence intervals. A gatekeeping strategy will be employed to control the Type I error (Marcus et al, 1976). If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

Analyses of the secondary efficacy variables will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1 13.3.1) and the analysis of the key secondary efficacy variable (as described above) will be exploratory only.

Time to the first PGTC seizure for the 24 week Treatment Period will be analyzed in the same manner as the primary endpoint using the FAS.

The percent change in log-transformed PGTC seizure frequency during the first 6 weeks of the Treatment Period will be analyzed using analysis of covariance, controlling for Baseline seizure frequency. The percent change in log-transformed PGTC seizure frequency during the 24-week Treatment Period will be analyzed in a similar manner. Further approaches for the analysis of the secondary variable will be described in a detailed SAP.

Has been changed to:

13.3.2.1 Key secondary efficacy variable

Analysis of the key secondary efficacy variable, seizure freedom for PGTC seizures for the 24-week Treatment Period, will be analyzed in the same manner as the primary endpoint using the FAS. The percentage of seizure-free subjects at 24 weeks will be estimated from the KM estimates of time to first seizure using 2-sided 95% confidence intervals. A gatekeeping strategy

will be employed to control the Type I error (Marcus et al, 1976). If the primary endpoint is statistically significant at the 5% level, then the key secondary efficacy endpoint will also be assessed at the 5% significance level. If the primary endpoint fails to reach statistical significance, then the key secondary efficacy endpoint will be exploratory only.

Section 13.3.2.2, Other secondary efficacy variables

Analyses of the other secondary efficacy variables will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described in Section 13.3.2.1) will be exploratory only.

Time to the first PGTC seizure for the Treatment Period will be analyzed in the same manner as the primary endpoint using the FAS.

The percent change in log-transformed PGTC seizure frequency during the first 6 weeks of the Treatment Period will be analyzed using analysis of covariance, controlling for Baseline PGTC seizure frequency. The percent change in log-transformed PGTC seizure frequency during the Treatment Period will be analyzed in a similar manner. Further approaches for the analysis of the secondary variable will be described in a detailed SAP.

Change #37

Section 13.4, Planned safety and other analyses

Paragraph 3

Observed values and changes from Baseline in vital signs, body weight, continuous laboratory parameters, and 12 lead ECG measurements will be summarized using continuous descriptive statistics. The number and percentage of subjects in each category will be summarized for categorical outcomes. The incidence of clinically relevant laboratory values will be summarized and shift tables summarizing the number and percentage of subjects having a different status (eg, abnormal laboratory result) post-Baseline compared to Baseline will be provided.

Has been changed to:

Observed values and changes from Baseline in vital signs, body weight, continuous laboratory parameters, and 12 lead ECG measurements will be summarized using continuous descriptive statistics. The number and percentage of subjects in each category will be summarized for the categorical outcomes. Shift tables summarizing the number and percentage of subjects having a different status (eg, abnormal laboratory result) post-Baseline compared to Baseline will be provided.

New last paragraph:

Incidence of new seizure types, and increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period will be summarized for each treatment group.

Change #38

Section 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.

Has been changed to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on outcomes for an individual subject.

Change #39

Section 13.7, Planned interim analysis and data monitoring

Paragraph 2, last sentence:

Analysis of the primary endpoint (time to second PGTC seizure) will only be examined at the planned futility assessment; an unblinded, descriptive review of safety and seizure frequency data will be provided for all IDMC meetings.

Has been changed to:

Analysis of the primary endpoint (time to second PGTC seizure) will only be examined at the planned futility assessment; an unblinded, descriptive review of safety, PGTC seizure frequency, and changes in days with absence and/or myoclonic seizures will be provided for all IDMC meetings.

Change #40

Section 13.8, Determination of sample size

Paragraph 1

Observing 125 events (subjects who had a second PGTC seizure during the 24-week Treatment Period) will provide 90% power to observe a hazard ratio of 0.56 at the 2-sided 5% level, assuming a nominal dropout rate of <10%. The observed hazard ratio was based on a 25.4% survival rate for placebo and 48.2% for lamotrigine from a previous study comparing lamotrigine and placebo (French et al, 2007). The observed hazard ratio in the lamotrigine study was 0.533; however, to provide a conservative margin, the hazard ratio was increased to 0.56 for estimating a sample size for the study. The rationale for the increase in the hazard ratio was 2-fold: different active compounds (LCM and lamotrigine) and a choice of time to second seizure as the primary efficacy endpoint (in the lamotrigine study, percent change in seizure frequency was the primary endpoint).

Has been changed to:

Observing 125 events (subjects who had a second PGTC seizure during the 24-week Treatment Period) will provide 90% power to observe a hazard ratio of 0.56 at the 2-sided 5% level, assuming a dropout rate of 15%. The observed hazard ratio was based on a 25.4% survival rate for placebo and 48.2% for lamotrigine from a previous study comparing lamotrigine and placebo (French et al, 2007). The observed hazard ratio in the lamotrigine study was 0.533; however, in order to account for the possibility of an increased placebo response, as has been documented in

recent clinical studies of AEDs, the hazard ratio was increased by 5% to 0.56 for estimating a sample size for this study. The rationale for the increase in the hazard ratio included the following considerations: different active compounds (LCM and lamotrigine) and a choice of time to second seizure as the primary efficacy endpoint (in the lamotrigine study, percent change in PGTC seizure frequency was the primary endpoint) (see rationale for second PGTC seizure in Section 5.4.2).

Change #41

Section 14.1, Informed consent/assent

Paragraph 3, first sentence

Prior to participation in the study, the written Informed Consent/Assent Form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the Informed Consent/Assent discussion (investigator or designee).

Has been changed to:

Prior to participation in the study (and prior to prescreening EEG, if applicable), the written Informed Consent/Assent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the Informed Consent/Assent discussion (investigator or designee).

Change #42

Section 14.2, Subject identification cards

Upon signing the Informed Consent/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 them at all times.

Has been changed to:

Prior to study participation at Visit 2, upon signing the Informed Consent/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 them at all times.

Change #43

Section 14.3, Institutional Review Boards and Independent Ethics Committees

Paragraph 2

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

Has been changed to:

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, Informed Consent/Assent form (including Informed Consent/Assent form for prescreening EEG, if applicable), 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.

Change #44

Section 16, REFERENCES

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

Has been changed to:

Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011;77(10):1005-12.

The following reference has been added:

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

17.7 Protocol Amendment 5

Rationale for the amendment

The primary purpose of this substantial amendment is to stop the subjects' study participation once 125 events have been observed to avoid exposing subjects to placebo unnecessarily and allow for flexible dosing of the treatment in the open-label follow-up study EP0012.

In addition, the following changes have been made:

- The initial plan was to enroll 20% pediatric subjects out of a total sample size of approximately 200 subjects, which would have resulted in 40 pediatric subjects enrolled in the study. Due to a fluctuating event rate, the study has now been changed to enroll subjects until the 125th event has occurred (defined as a subject experiencing the second primary generalized tonic-clonic [PGTC] seizure). Changing the number of pediatric subjects from 20% to 40 absolute ensures that at least 40 pediatric subjects are recruited while also limiting the number of required pediatric subjects in case more than 200 subjects will have to be enrolled. This is considered appropriate in light of the extremely challenging recruitment of pediatric subjects in this study. Additionally, from the biostatistical point of view, increasing the number of pediatric subjects from 40 to 45 or 50 is very unlikely to yield significantly new or different safety information.
- To update the introduction with regulatory information on the marketing authorization of Vimpat and to provide an update on the lacosamide clinical program.
- To appropriately align the Inclusion Criterion 7.a with the examples given in the supportive table.
- To clarify that Visit 5 is the beginning of the Maintenance Period (18 weeks).
- To remove some blood sampling details from the protocol and refer to the laboratory manual.
- To clarify the potential drug-induced liver injury (PDILI) criteria requiring immediate and permanent discontinuation of the investigational medicinal product (IMP).
- To clarify that if the monitor has no direct access to the source electronic medical records, certified copies should be generated by the investigator and verified by the monitor against the original medical record.
- To make a minor clarification to the sentence about pooling strategies for age strata for consistency with the Statistical Analysis Plan (SAP). Furthermore, title page and study physician contact details have been updated and minor editorial and formatting changes have been made throughout the protocol.

Modifications and changes

Specific changes

Change #1

Title page:

The title was updated from "Protocol SP0982 Amendment 4" to "Protocol SP0982 Amendment 5."

The information below was revised to include Protocol Amendment 5 and the type of protocol amendment:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	5 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial
Protocol Amendment 3	09 Jan 2015	Non-substantial
Protocol Amendment 4	08 Jun 2016	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	05 Aug 2011	N/A
Protocol Amendment 1	25 Sep 2012	Substantial
Protocol Amendment 2	11 Jul 2014	Substantial
Protocol Amendment 3	09 Jan 2015	Non-substantial
Protocol Amendment 4	08 Jun 2016	Substantial
Protocol Amendment 5	07 Nov 2017	Substantial

Change #2

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted], MD
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	

Has been changed to:

Sponsor Study Physician

Name:	[redacted], MD
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Change #3

Section 1 SUMMARY

Paragraph 2

Approximately 200 subjects across approximately 150 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 6

The primary efficacy variable is the time to the second PGTC seizure (also defined as an event) during the 24 week Treatment Period.

Paragraph 8

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs); withdrawal due to AEs; changes in hematology, chemistry, endocrinology, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; incidence of new seizure types; increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period; and changes in physical and neurological examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using a behavioral assessment (Achenbach Child Behavior Checklist [CBCL]) and a cognitive function assessment (Behavior Rating Inventory of Executive Function® [BRIEF®]/Behavior Rating Inventory of Executive Function Preschool Version [BRIEF-P]).

Has been changed to:

Paragraph 2

Up to 250 subjects across 150 to 180 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 6

The primary efficacy variable is the time to the second PGTC seizure (also defined as an event) during the 24-week Treatment Period. Once the 125th event occurs, the study will have met its protocol-defined endpoint or milestone; all subjects will transition into EP0012 or taper off study medication.

Paragraph 8

The secondary objective is to assess the safety and tolerability of LCM in subjects with IGE with uncontrolled PGTC seizures. Safety variables to be assessed are adverse events (AEs) as reported spontaneously by the subject and/or caregiver or observed by the investigator. Other safety variables are; withdrawal due to AEs; incidence of new seizure types; increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period; changes in physical and neurological examination findings; changes in hematology, chemistry, endocrinology, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); changes in vital sign measurements; for pediatric subjects <18 years of age, safety will be evaluated using a behavioral assessment (Achenbach Child Behavior Checklist [CBCL]) and a cognitive function assessment (Behavior Rating Inventory of Executive Function® [BRIEF®]/Behavior Rating Inventory of Executive Function Preschool Version [BRIEF-P]).

Change #4

Section 2 INTRODUCTION

Paragraph 7

Lacosamide has been approved in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older. Lacosamide has also been approved in the US (oral tablets, oral solution [syrup], and solution for iv infusion) as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older. The approved indication of LCM as adjunctive treatment for partial-onset seizures was based on 1327 subjects who received LCM in the pooled Phase 2 or Phase 3 studies during the development program. With the completion of the 3 open-label studies, the cumulative exposure to LCM during the clinical studies was 3297.4 subject-years. Further information on LCM nonclinical results, as well as the PK, efficacy, and safety profiles, can be obtained from the current version of the LCM Investigator's Brochure.

In addition, lacosamide is being evaluated in the following ongoing pediatric efficacy and safety studies:

- SP0967 (ages ≥1 month to <4 years) as adjunctive therapy in partial-onset seizures
- SP0969 (ages ≥4 to <17 years) as adjunctive therapy in partial-onset seizures

- EP0034, open-label extension study to SP0967 and SP0969
- SP0966 (ages ≥1 month to <18 years) as adjunctive therapy, exploratory study in subjects with epilepsy syndromes associated with generalized seizures

Has been changed to:

Paragraph 7

Lacosamide has been approved in the European Union (oral tablets, oral solution [syrup], and solution for intravenous [iv] infusion) as monotherapy or adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 4 years of age and older. Lacosamide has also been approved in the US (oral tablets, oral solution [syrup], and solution for iv infusion) as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older. The safety and efficacy of LCM has been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures. Excluding blinded ongoing studies and indications not currently pursued, as of the data cutoff of 31 Aug 2016, 4938 subjects have been exposed to LCM in the clinical development program.

New paragraph

Preliminary recent safety and PK data suggest that the exposure-response in pediatric and adult subjects treated with LCM will be similar. Lacosamide has been evaluated in 3 completed pediatric studies; 2 studies in subjects aged 1 month to 17 years, and in subjects with epilepsy ≥4 years to <17 years of age with uncontrolled partial-onset seizures. Subjects who completed the Maintenance Period were offered to participate in the open-label extension study.

In addition, LCM is being evaluated in the following ongoing pediatric efficacy and safety studies:

- SP0967 (ages ≥1 month to <4 years) as adjunctive therapy in partial-onset seizures
- EP0034, open-label extension study to SP0967 and SP0969
- SP0966 (ages ≥1 month to <18 years) as adjunctive therapy, exploratory study in subjects with epilepsy syndromes associated with generalized seizures

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

Change #5

Section 4.1.2 Secondary efficacy variables

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variables are:

- The percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline)

- The percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline
- Time to the first PGTC seizure during the Treatment Period

Has been changed to:

The key secondary efficacy variable is:

- Seizure freedom for PGTC seizures during the 24-week Treatment Period, estimated using Kaplan-Meier analysis

The other secondary efficacy variable is:

- Time to the first PGTC seizure during the Treatment Period

Change #6

Section 4.1.3 Other efficacy variables

The following variables have been added as the first three bullets (Note that the first and third variable have been moved from Secondary to Other and the second variable has been added):

- The percent change in PGTC seizure frequency per 28 days during the first 6 weeks of the Treatment Period (Titration Phase) relative to the Combined Baseline (combined 12-week Historical and 4-week Prospective Baseline)
- The percent change in PGTC seizure frequency per 28 days during the first 12 weeks of the Treatment Period relative to the Combined Baseline
- The percent change in PGTC seizure frequency per 28 days during the Treatment Period relative to the Combined Baseline

The following variable has been added as bullet 14:

- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency during the Titration Period compared to Combined Baseline

Change #7

Section 4.2 Safety variables

The safety variables are:

- AEs as reported spontaneously by the subject and/or caregiver or observed by the investigator.
- Subject withdrawal due to AE
- Changes in hematology, chemistry, endocrinology, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings
- Incidence of new seizure types during the Treatment Period

- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline

Other safety variables are:

- Behavioral assessment (Achenbach CBCL/1½-5 or CBCL/6-18)
- Cognitive function assessment (BRIEF-P or BRIEF)

Has been changed to:

The safety variable is:

- AEs as reported spontaneously by the subject and/or caregiver or observed by the investigator.

Other safety variables are:

- Subject withdrawal due to AE
- Incidence of new seizure types during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with absence seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in the days with myoclonic seizures per 28 days during the Treatment Period relative to the Prospective Baseline
- Changes in hematology, chemistry, endocrinology, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse rate) (including body weight and height) and physical and neurological examination findings
- Behavioral assessment (Achenbach CBCL/1½-5 or CBCL/6-18) for pediatric subjects only
- Cognitive function assessment (BRIEF-P or BRIEF) for pediatric subjects only

Change #8

Section 5.1 Study description

Paragraph 2

Approximately 200 subjects across approximately 150 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 12

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures

Paragraph 14

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit.

Paragraph 15

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. Following the End of Taper Visit, there will be a 30-day Safety Follow up Period (see Section 7.2.4).

Has been changed to:

Paragraph 2

Up to 250 subjects across 150 to 180 sites in the US, Europe, Asia, and Australia, with possible extension to other countries and regions, are planned to be randomized in this study.

Paragraph 12

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures
- The 125th event occurs in the study. A second PGTC seizure is defined as an event.

Paragraph 14

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period or if the 125th event occurs in the study (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012. Subjects completing Visit 10 (Week 24) or the ET Visit must complete a 4-week blinded transition followed by a Final Clinic Visit. The Final Clinic Visit is the same as Visit 1 of EP0012 (see Section 7.2.3). During the 4-week blinded transition, subjects receiving placebo during SP0982 will have their dose titrated to LCM (see Table 7-4).

Paragraph 15

If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. Following the End of Taper Visit, there will be a 30-day Safety Follow up Period (see Section 7.2.4). In case the 125th event occurs in the study, the subjects discontinuing treatment will complete the ET Visit or Visit 10 (Week 24), and an up

to 4-week blinded taper followed by an End of Taper Visit. However, the End of Taper Visit will be the same as Visit 1 of EP0012. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

Change #9

Section 5.1.1 Study duration per subject

The following paragraphs were added:

Titration Period

In case the 125th event occurs in the study while subjects are still in their 6-week Titration Period, these subjects will not have to proceed to Week 6 prior to initiating the Transition/Taper Period; these subjects will also be invited for their ET Visit at the next scheduled visit.

Maintenance Period

In case the 125th event occurs in the study while subjects are in their Maintenance Period, these subjects will also be invited for their ET Visit at the next scheduled visit and enter the Transition/Taper Period.

Transition Period

In case the subject is in the Transition/Taper Period, these subjects will proceed to their scheduled completion visit.

Screening Period

In case the 125th event occurs while a subject is in screening, the subject may proceed to the scheduled Baseline Visit if they are eligible or are a Baseline failure; these subjects will be able to enter EP0012 and will not proceed to randomization in SP0982 but will enter EP0012. For the subjects entering EP0012, their next visit will be Visit 1.

Change #10

Section 5.1.2 Study completers

The following subjects will be considered study completers:

- Subjects who meet any of the predetermined exit criteria (Section 6.3)
- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period

Has been changed to:

The following subjects will be considered study completers:

- Subjects who meet any of the predetermined exit criteria (Section 6.3)
- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period

Further information is provided in Section 6.3.

Change #11

Section 5.1.3 Planned number of subjects and sites

The number of screened subjects may vary according to the observed screen failure rate. Approximately 200 subjects (100 per treatment arm) will be randomized to achieve a total of 125 events, where an event is defined as the occurrence of the second PGTC seizure.

Subjects will be randomized in the following age categories:

- ≥4 years of age to <12 years of age (approximately 50 subjects)
- ≥12 years of age to <18 years of age (approximately 50 subjects)
- ≥18 years of age (approximately 100 subjects)

There will be approximately 150 sites in order to recruit the required subjects; additional sites will be added if deemed necessary. A target of approximately 50% of the randomized subjects should consist of subjects <18 years of age. Of these 100 subjects, 50% will be enrolled in each of the 2 age categories <18 years of age.

Has been changed to:

The number of screened subjects may vary according to the observed screen failure rate. Up to 250 subjects (100 to 125 per treatment arm) will be randomized to achieve a total of 125 events, where an event is defined as the occurrence of the second PGTC seizure.

Subjects will be randomized in the following age categories:

- (a) ≥4 years of age to <12 years of age
- (b) ≥12 years of age to <18 years of age
- (c) ≥18 years of age category

There will be approximately 150 to 200 sites in order to recruit the required subjects; additional sites will be added if deemed necessary. A target of at least 40 of the randomized subjects should consist of subjects <18 years of age.

Change #12

Section 5.2 Schedule of study assessments

Table 5–1: the line in front of the Maintenance Period (18 weeks) has been shifted one box to the left, so that V5 is the start of the Maintenance Period.

Table 5-1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Assessments	Prospective Baseline 4 weeks			Treatment Period[a]											Unscheduled[b]
				6 to 24 weeks (maximum)											NA
				Titration Period (6 weeks)[c]					Maintenance Period (18 weeks)						
Visit[c]	V1[bb]	TC	V2[d]	TC[e]	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ ET[f]	Visit
Study week	-4	-2		1	2	3	4	5	6	8	12	16	20	24	NA

Has been changed to:

Table 5-1: Schedule of study assessments for SP0982 (Prospective Baseline, Titration Period, Maintenance Period, ET Visit, and Unscheduled Visits)

Assessments	Prospective Baseline 4 weeks			Treatment Period[a]											Unscheduled[b]
				6 to 24 weeks (maximum)											NA
				Titration Period (6 weeks)[c]					Maintenance Period (18 weeks)						
Visit[c]	V1[bb]	TC	V2[d]	TC[e]	V3	TC	V4	TC	V5	V6	V7	V8	V9	V10/ ET[f]	Visit
Study week	-4	-2		1	2	3	4	5	6	8	12	16	20	24	NA

Change #13

Section 5.2 Schedule of study assessments

Table 5–3: Footnote c has been updated.

[c] There will be a 30-day (-1/+3 days) Safety Follow-up Period for subjects who complete the End of Taper Visit. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed 2 weeks later by a TC.

Has been changed to:

[c] There will be a 30-day (-1/+3 days) Safety Follow-up Period for subjects who complete the End of Taper Visit. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed 2 weeks later by a TC. After the 125th event occurs, the 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

Change #14

Section 5.3 Schematic diagrams for SP0982

Figure 5-2: Footnote b has been updated and footnote c has been added.

[b] If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit. There will be a 30-day Safety Follow-up Period for subjects who complete the End of Taper Visit.

Has been changed to:

[b] If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit. There will be a 30-day Safety Follow-up Period for subjects who complete the End of Taper Visit. After the 125th event occurs, the 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

[c] If the subject is in the Titration Period when the 125th event occurs, the subject will proceed to the Transition/Taper Period directly after their ET/V10 Visit.

Figure 5-3: Footnote a has been added.

[a] If a subject is in the Titration period and the next scheduled visit after the 125th event is not until Week 6, the subject will enter the Transition/Taper Period and the escalation will be adapted accordingly.

Change #15

Section 6.1 Inclusion criteria

Inclusion Criterion 7 has been updated

7. Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs OR 1 to 3 AEDs (with 1 AED identified as a benzodiazepine, see examples in the table below) for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS (see Section 7.8).

Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

Benzodiazepine AEDs	**Non-Benzodiazepine AEDs**	**Total AEDs**	**Is subject eligible?** (In terms of Inclusion Criterion 7)
0	1	1	Yes
0	2	2	Yes
1	1	2	Yes
1	2	3	Yes
1	0	1	**No**
0	3	3	**No**
2	1	3	**No**

AED=antiepileptic drug

Has been changed to:

7a. Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs with no benzodiazepine AEDs **OR** 1 benzodiazepine marketed AED with 1 to 2 non-benzodiazepine marketed AEDs (see examples in the table below) for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS (see Section 7.8)

Vagus nerve stimulation must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

Benzodiazepine AEDs	Non-Benzodiazepine AEDs	Total AEDs	Is subject eligible? (In terms of Inclusion Criterion 7)
0	1	1	Yes
0	2	2	Yes
1	1	2	Yes
1	2	3	Yes
1	0	1	**No**
0	3	3	**No**
2	1	3	**No**

AED=antiepileptic drug

Change #16

Section 6.2 Exclusion Criteria

Criterion 4 has been updated.

4. Subject has symptomatic generalized epilepsy ([ILAE, 1989] eg, Lennox Gastaut Syndrome) or evidence of both focal and generalized epilepsy.

Has been changed to:

4a. Subject has symptomatic generalized epilepsy ([ILAE, 1989] (eg, Lennox Gastaut Syndrome typically presenting with seizures including tonic seizures), some other related syndrome like Doose's syndrome (typically presenting with myoclonic-atonic seizures), or evidence of both focal and generalized epilepsy.

Change #17

Section 6.3 Exit Criteria

Subjects will be required to exit the study if either of the following events occurs:

- Subject completes the first 6 weeks of the Treatment Period (after randomization) and experiences ≥2 PGTC seizures during that time
- Subject experiences a second PGTC seizure after the first 6 weeks of the Treatment Period

Has been changed to:

Subjects will be required to exit the study if either of the following events occurs:

- Subject completes the first 6 weeks of the Treatment Period (after randomization) and experiences ≥2 PGTC seizures during that time
- Subject experiences a second PGTC seizure after the first 6 weeks of the Treatment Period
- The 125th event occurs in the study

Change #18

Section 6.4.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

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

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

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

Evaluation of PDILI must be initiated as described in Section 10.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Has been changed to:

Subjects with PDILI must be assessed to determine if IMP must be immediately and permanently discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

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

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

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

Evaluation of PDILI must be initiated as described in Section 10.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Change #19

Section 7.2.3 Transition Period (for subjects who enter EP0012)

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012.

Has been changed to:

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period or when the 125th event occurs in the study (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012.

Table 7-4: A note has been added.

Note: If a subject is in the Titration Period and the next scheduled visit after the 125th event occurs, dosing will be adapted to reach the target dosing at Week 4.

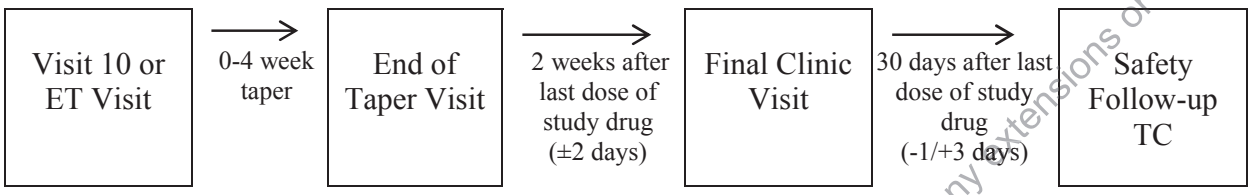
Change #20

Section 7.2.4 Taper Period

Paragraph 3

Following the End of Taper Visit, there will be a 30-day Safety Follow up Period. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-up telephone contact 30 days after the last dose of study drug.

The following schematic displays the scenario for subject dispensation:



Has been changed to:

Paragraph 3

Following the End of Taper Visit, there will be a 30-day Safety Follow up Period. The Safety Follow-up Period consists of a clinic visit 2 weeks after the End of Taper Visit followed by a Safety Follow-up telephone contact 30 days after the last dose of study drug. In case the 125th event occurs in the study, the subjects discontinuing treatment will complete the ET Visit or Visit 10 (Week 24), and an up to 4-week blinded taper followed by an End of Taper Visit. However, the End of Taper Visit will be the same as Visit 1 of EP0012. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

The following schematic displays the scenario for subject dispensation:

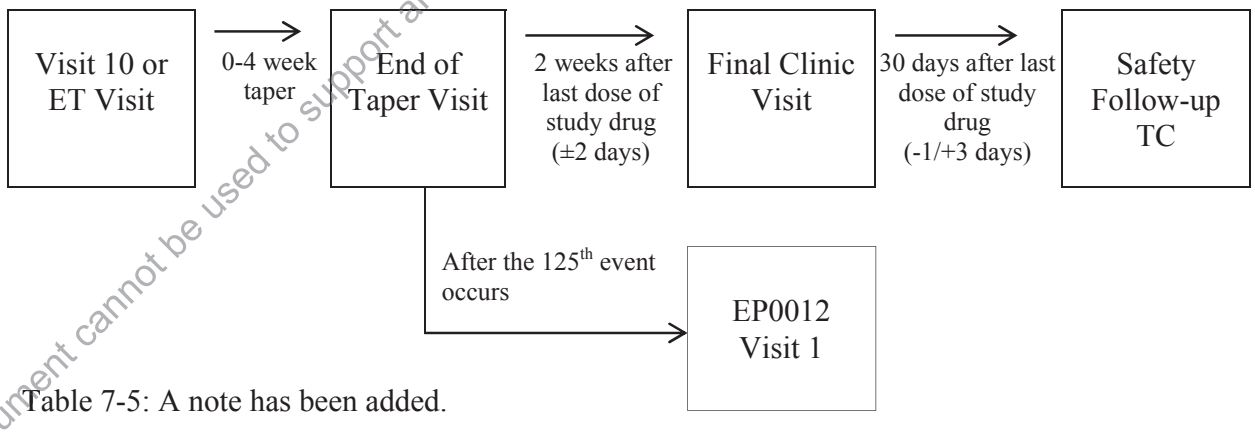


Table 7-5: A note has been added.

Note: Dosing for the Taper Period will be adapted depending on the dose subjects reached during the Titration Period when the 125th event occurs.

Change #21

Section 7.8.1 Permitted concomitant treatments (medications and therapies)

Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 1 to 3 AEDs (with 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period with or without additional concurrent stable VNS.

Has been changed to:

Subject has been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs **OR** 2 to 3 AEDs (with 1 AED identified as a benzodiazepine) for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period with or without additional concurrent stable VNS.

Change #22

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

- MAO-A inhibitors

Has been changed to:

- Any MAO inhibitors

Herbal medicines for epilepsy has been added.

- Herbal medicines for epilepsy

Change #23

Section 8.2 Treatment Period

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures

Has been changed to:

The Treatment Period continues until 1 of the following occurs (whichever occurs first):

- Completion of ≥6 weeks of the Treatment Period and occurrence of ≥2 PGTC seizures
- Completion of 24 weeks of the Treatment Period without occurrence of 2 PGTC seizures
- The 125th event occurs in the study

Change #24

Section 8.2.2.1.4 Visit 5 (end of Week 6)

The entire section has been moved from Section 8.2.2 Titration Period to Section 8.2.3 Maintenance Period as Section 8.2.3.1. The remainding subsections under Section 8.2.3 have been renumbered accordingly.

Change #25

Section 8.2.3.6 Visit 10/ET Visit (end of Week 24)

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure (see Section 6.3).

Has been changed to:

Once the subject has experienced 2 PGTC seizures, the site should contact the Medical Monitor to confirm whether the subject has met the exit criteria. If the exit criteria are met, sites will be advised to have subjects return for their ET Visit within 1 week of the subject's second seizure. Once the 125th event occurs subjects will return to the site at the next scheduled visit and the ET/Visit 10 will be performed (see Section 6.3).

Change #26

Section 8.3.1.2 Final Clinic Visit

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012.

Has been changed to:

After completing ≥6 weeks and experiencing the second PGTC seizure during the Treatment Period or after completing the 24-week Treatment Period or the 125th event occurs in the study (whichever comes first), eligible subjects may, at the ET Visit or Visit 10 (Week 24) respectively, choose to continue in EP0012.

Change #27

Section 8.3.2.2 Safety Follow-up Visit

Following the End of Taper Visit, the subject will return 2 weeks (±2 days) after the last dose of study drug for a Safety Follow-up Visit.

Has been changed to:

Following the End of Taper Visit, the subject will return 2 weeks (±2 days) after the last dose of study drug for a Safety Follow-up Visit. In case the 125th event occurs in the study, the subjects discontinuing treatment will complete a 30-day Safety Follow-up Period in the EP0012 study. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a

short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

Change #28

Section 8.3.2.3 Safety Follow-up telephone contact

Thirty days (-1/+3 days) after the last dose of study drug, the subject will receive a Safety Follow-up telephone contact.

Has been changed to:

Thirty days (-1/+3 days) after the last dose of study drug, the subject will receive a Safety Follow-up telephone contact. In case the 125th event occurs in the study, the subjects discontinuing treatment will complete a 30-day Safety Follow-up Period in the EP0012 study. The 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

Change #29

Section 10.2.1 Evaluation of PDILI

Paragraph 7

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued.

Has been changed to:

Paragraph 7

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued. Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Change #30

Section 10.2.1 Evaluation of PDILI

Table 10-3 Required investigations and follow up for PDILI, text under Actions column for the ALT or AST ≥3xULN WITH Symptoms of hepatitis or hypersensitivity row

Immediate, temporary or permanent, IMP discontinuation.

Has been changed to:

Immediate, permanent IMP discontinuation.

Change #31

Section 11 ASSESSMENT OF PHARMACOKINETICS

Blood samples for analysis of LCM plasma concentrations will be collected at any time between 2 successive bid doses, according to the schedule of study assessments in Table 5-1. The time the

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

Each blood sample drawn for LCM plasma concentration determination will be centrifuged and split into 2 duplicate samples prior to freezing. The samples will be stored at -20°C until shipped to a central laboratory. The central laboratory will store the plasma samples at -20°C until analysis.

Blood draws for these assessments will coincide with the blood collection times for assessment of the hematology and clinical chemistry parameters. Time and date of each blood draw will be documented on the eCRF.

Instructions on blood sample collection, processing, storage, and labeling/shipping will be provided in the laboratory manual for this study.

Has been changed to:

Blood samples for analysis of LCM plasma concentrations will be collected at any time between 2 successive bid doses, according to the schedule of study assessments in Table 5-1. The time the subject took the most recent dose of IMP and the time of blood sampling must be recorded. Actual dosing and sampling times will be recorded in the eCRF to the minute.

The central laboratory will store the plasma samples at -20°C until analysis. Blood draws for these assessments will coincide with the blood collection times for assessment of the hematology and clinical chemistry parameters. Time and date of each blood draw will be documented on the eCRF.

Instructions on blood sample collection, processing, storage, and labeling/shipping are provided in the laboratory manual for this study.

Change #32

Section 12.2.1 Definition of source data

Paragraph 3

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.

Has been changed to:

Paragraph 3

If the source documents are maintained by the investigator in a computerized system, the monitor should ensure that electronic records are ALCOA (attributable, legible, contemporaneous, original, and accurate) compliant and that there is proper access control, validation, and audit trail available upon request. If the monitor has no direct access to the original electronic medical records, the certified copies should be generated by the investigator and used for the study purposes. Accuracy and completeness of data on the certified copies should be verified by the monitor to maintain ongoing compliance.

Change #33

Section 13.3.1 Analysis of the primary efficacy variable

Paragraph 1, second sentence

Pooling strategies for strata with no events (ie, no subjects who had a second PGTC seizure) will be defined in the SAP prior to unblinding.

Has been changed to:

Paragraph 1, second sentence

Pooling strategies for strata with a low number of events will be defined in the SAP prior to unblinding.

Change #34

Section 13.3.2.2 Other secondary efficacy variables

Analyses of the other secondary efficacy variables will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described in Section 13.3.2.1) will be exploratory only.

Time to the first PGTC seizure for the Treatment Period will be analyzed in the same manner as the primary endpoint using the FAS.

The percent change in log-transformed PGTC seizure frequency during the first 6 weeks of the Treatment Period will be analyzed using analysis of covariance, controlling for Baseline PGTC seizure frequency. The percent change in log-transformed PGTC seizure frequency during the Treatment Period will be analyzed in a similar manner. Further approaches for the analysis of the secondary variable will be described in a detailed SAP.

Has been changed to:

Analyses of the other secondary efficacy variables will be performed using the FAS and will be descriptive in manner only. Any p-values or confidence limits provided other than those for the primary analysis of the primary variable (as described in Section 13.3.1) and the analysis of the key secondary efficacy variable (as described in Section 13.3.2.1) will be exploratory only.

Time to the first PGTC seizure for the Treatment Period will be analyzed in the same manner as the primary endpoint using the FAS.

Further approaches for the analysis of the secondary variable will be described in a detailed SAP.

Change #35

Section 13.4 Planned safety and other analyses

Analyses of other variables, eg, safety or plasma concentration data, will be descriptive in manner only. Lacosamide plasma concentrations will be summarized and evaluated by population PK; details will be provided in a separate analysis plan.

The incidence and frequency of TEAEs will be summarized for each treatment group and study period. The incidence of SAEs and TEAEs leading to premature discontinuation from study drug

will also be summarized for each treatment group and study period. Additional summaries will be provided by maximum intensity and relationship to study drug. All tables for AEs will be displayed by MedDRA® primary System Organ Class and Preferred Term. Further details on the analysis of AE data will be given in the SAP.

Observed values and changes from Baseline in vital signs, body weight, continuous laboratory parameters, and 12 lead ECG measurements will be summarized using continuous descriptive statistics. The number and percentage of subjects in each category will be summarized for the categorical outcomes. Shift tables summarizing the number and percentage of subjects having a different status (eg, abnormal laboratory result) post-Baseline compared to Baseline will be provided.

Incidence of new seizure types, and increase in absence seizure days per 28 days or myoclonic seizure days per 28 days during the Treatment Period will be summarized for each treatment group.

Has been changed to:

All safety analyses will be described in the SAP. Analyses of other variables, eg, safety or plasma concentration data, will be descriptive in manner only. Lacosamide plasma concentrations will be summarized and evaluated by population PK; details will be provided in a separate analysis plan.

The incidence and frequency of TEAEs will be summarized for each treatment group and study period. The incidence of SAEs and TEAEs leading to premature discontinuation from study drug will also be summarized for each treatment group and study period. Additional summaries will be provided by maximum intensity and relationship to study drug. All tables for AEs will be displayed by MedDRA® primary System Organ Class and Preferred Term. Further details on the analysis of AE data will be given in the SAP.

Change #36

Section 13.4.1 Other safety analysis

This section has been removed for consistency with the variables section

Change #37

Section 13.8 Determination of sample size

Paragraph 2

This is an event-driven study. The study will be closed to enrollment once 125 events have been observed. If 125 events are observed prior 200 randomized subjects, then enrollment will stop and fewer than 200 subjects will be randomized. However, if 125 events are not observed after 200 subjects are randomized, then the study will continue to enroll up to a maximum of 250 subjects randomized or 125 events, whichever occurs first.

Has been changed to:

Paragraph 2

This is an event-driven study. Enrollment in the study will continue up to 125 events occurring or a maximum of 250 subjects randomizing, whichever comes first.

17.8 International Classification of Epileptic Seizures (1981)

Adapted from the International Classification of Epileptic Seizures (1981)

Clinical seizure types

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)

III. 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.

17.9 Contraception table

Method	Abbreviation	no EI-AEDs	EI-AEDs
combined injectable contraceptives	CIC	ok	ok
combined patch	P	ok	needs barrier
combined vaginal ring	R	ok	needs second method
low-dose combined oral contraceptives	COC	ok	needs barrier
etonogestrel implant	ETG	ok	ok
levonorgestrel implant	LNG	ok	ok
depot medroxyprogesterone acetate	DMPA	ok	ok
norethisterone enantate	NET-EN	ok	ok
progestogen-only pills	POP	ok	needs barrier
emergency contraceptive pills	ECP	NA	NA
copper-bearing intrauterine devices	Cu-IUDs	ok	ok
levonorgestrel-releasing IUDs	LNG-IUDs	ok	ok
barrier methods	BARR	not eligible	not eligible
fertility awareness-based methods	FAB	not eligible	not eligible
lactational amenorrhoea method	LAM	not eligible	not eligible
coitus interruptus	CI	not eligible	not eligible
female and male sterilization	STER	ok	ok

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

_____ _____

Printed Name Date/Signature

19 SPONSOR DECLARATION

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

SP0982 Protocol Amendment 5

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	07-Nov-2017 13:43 GMT+0
	Clinical Approval	08-Nov-2017 12:09 GMT+0