PROTOCOL EP0012 AMENDMENT 5

AN OPEN-LABEL, MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY FOR UNCONTROLLED PRIMARY GENERALIZED TONIC-CLONIC SEIZURES IN SUBJECTS WITH IDIOPATHIC GENERALIZED EPILEPSY

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UCB BIOSCIENCES Inc.
8010 Arco Corporate Drive
Raleigh, NC 27617
UNITED STATES

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STUDY CONTACT INFORMATION

Sponsor

UCB BIOSCIENCES Inc.

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

Sponsor Study Physician

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Allée de la Recherche 60 1070 Brussels BELGIUM
Phone:	[redacted]
Email:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]
Email:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	Pharmaceutical Research Associates (PRA), Inc.
Address:	4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612 UNITED STATES
Phone:	+1 919 786 8200
Fax:	+1 919 786 8201

Interactive Response Technology

Name:	Perceptive eClinical Limited
Address:	Lady Bay House, Meadow Grove Nottingham, NG23HF UK
Phone:	+44 115 955 7333
Fax:	+44 115 955 7555

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

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
bid	twice daily
BMI	body mass index
BP	blood pressure
BRIEF®	Behavior Rating Inventory of Executive Function®
BRIEF-P®	Behavior Rating Inventory of Executive Function-Preschool Version®
CBCL	Child Behavior Checklist
CDMS	clinical data management system
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic Case Report form
EDC	electronic data capture
EI-AED	enzyme-inducing antiepileptic drug
EQ-5D-3L	3-level EuroQol-5 Dimension Quality of Life Assessment
ES	Enrolled Set
ET	Early Termination
GCP	Good Clinical Practice
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
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
LCM	lacosamide
LFT	liver function test
MAO-A	monoamine oxidase A
MAP	managed access program
PDILI	potential drug-induced liver injury
PedsQL™	Pediatric Quality of Life Inventory
PGTCS	primary generalized tonic-clonic seizure(s)
PK	pharmacokinetic
PS	Patient Safety
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Inventory-Form 31
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SFU	Safety Follow Up
SOP	Standard Operating Procedure
SS	Safety Set
TEAEs	treatment-emergent adverse events
TMF	trial master file
ULN	upper limit of normal
VAS	visual analogue scale

1 SUMMARY

This Phase 3, multicenter, open-label extension study is designed to assess the long-term safety and efficacy of oral lacosamide (LCM, VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) as an adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures (PGTCS) in subjects ≥4 years of age with idiopathic generalized epilepsy (IGE). This study will enroll subjects who have completed the LCM SP0982 study. In addition, subjects who completed the SP0982 Prospective Baseline Period and met all entry criteria except the minimum PGTCS criteria required for randomization into SP0982 may choose to enter EP0012 (eligible Baseline failures and completers are defined in Section 5.1). It is estimated that up to 250 subjects across approximately 150 to 180 sites will be enrolled in EP0012.

Once 125 subjects have had a second PGTCS in SP0982, that study will have met its protocol-defined stopping criteria and all subjects will transition into EP0012 or taper off study medication. Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg twice daily [bid]) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Baseline failures are required to complete Week 1 of dosing before LCM dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further LCM 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 target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets) within 14 days after Visit 1.

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects must remain on the dose for ≥7 days before a subsequent dose escalation.

EP0012 will consist of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. During the Treatment Period, Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinical visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur every 24 weeks thereafter until the end of the study. From Year 2 (Visit 11) to 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. The study duration and the total number of clinic visits will vary for each subject. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTCS in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or their parent(s)/legal representative(s).

The primary study objective is to assess the safety and tolerability of LCM as an adjunctive therapy for uncontrolled PGTCS in subjects with IGE during long-term exposure. Secondary objectives are to assess the efficacy of adjunctive LCM therapy during long-term exposure for the treatment of uncontrolled PGTCS in subjects with IGE, and to allow subjects who have completed SP0982 and eligible Baseline failures from SP0982 to receive LCM.

The primary safety variables are adverse events (AEs), subject withdrawals due to AEs, 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. Secondary safety variables are percentage of treatment-emergent marked abnormalities in hematology and chemistry parameters; percentage of treatment-emergent marked abnormalities in 12-lead electrocardiograms (ECGs); and percentage of treatment-emergent marked abnormalities in vital sign measurements (ie, blood pressure [BP] and pulse rate). Other safety variables include changes in hematology, chemistry, and urinalysis parameters, changes in 12-lead ECGs, and changes in in vital sign measurements (ie, BP and pulse rate), including height and weight and physical (including neurological) examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function-Preschool Version® [BRIEF®/BRIEF-P®]). The seizure efficacy variables are evaluations of seizure frequency, based on information included in subject diaries. The health outcome variables, including the Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), the Pediatric Quality of Life Inventory™ (PedsQL™), the 3-level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L), healthcare resource use, the number of working or school days lost by subjects due to epilepsy, and the number of days with help from a caregiver due to epilepsy will be assessed for the first 2 years of treatment.

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 unknown origin.

Generalized seizures are those in which the first clinical changes indicate initial involvement of both brain hemispheres. Consciousness typically is 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 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 PGTCS in IGE is complex because the patient population is heterogeneous, as PGTCS 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 antiepileptic drugs (AEDs) and vagus nerve stimulation. 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 (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 also 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 PGTCS, the efficacy and tolerability profiles for LCM were evaluated in a series of animal models followed by a Phase 2 pilot study of patients with IGE and uncontrolled PGTCS.

Lacosamide demonstrated significant seizure protection in animal models of seizures and epilepsy mimicking generalized epilepsy in humans. Of particular relevance for the PGTCS 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 and increased spike and wave discharges in the WAG/R and Genetic Absence Epilepsy Rats from Strasbourg models of absence epilepsy.

SP0961, the Phase 2, multicenter, open-label pilot study designed to assess the safety of adjunctive LCM (400mg/day) for uncontrolled PGTCS in subjects aged 16 to 65 years with IGE, is complete. The results of this pilot study showed reductions in PGTCS 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, cannot be distinguished between the drug versus 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.

SP0982 is a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of LCM for uncontrolled PGTCS in subjects ≥4 years of age with IGE.

The current study (EP0012) will assess the long-term safety, tolerability, and efficacy of LCM and will enroll subjects who have completed SP0982 as well as eligible Baseline failures from SP0982. At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

3 STUDY OBJECTIVE(S)

3.1 Primary objective

The primary objective is to assess the safety and tolerability of LCM as an adjunctive therapy for uncontrolled PGTCS in subjects with IGE during long-term exposure.

3.2 Secondary objectives

The secondary objectives are:

- To assess the efficacy of adjunctive LCM therapy during long-term exposure for the treatment of subjects with IGE experiencing uncontrolled PGTCS
- To allow subjects who have completed SP0982 and eligible Baseline failures from SP0982 to receive LCM

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variables are:

- The incidence of TEAEs over the duration of the Treatment Period.
- Subject withdrawals due to TEAEs
- Incidence of new appearance of absence and/or myoclonic seizures during the Treatment Period
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days compared to the Prospective Baseline
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days compared to the Prospective Baseline
- At least 50% worsening in days with absence seizures
- At least 50% worsening in days with myoclonic seizures

4.1.2 Secondary safety variables

Secondary safety variables are:

- Percentage of treatment-emergent marked abnormalities in hematology and chemistry parameters
- Percentage of treatment-emergent marked abnormalities in 12-lead ECGs

- Percentage of treatment-emergent marked abnormalities in vital sign measurements (ie, BP and pulse rate)

4.1.3 Other safety variables

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, BP and pulse rate), including weight and height and physical (including neurological) examination findings
- Achenbach CBCL1½-5 or CBCL/6-18 (for pediatric subjects only)
- Cognitive function assessment BRIEF/BRIEF-P (for pediatric subjects only)

4.2 Efficacy variables

4.2.1 Primary efficacy variable

No primary efficacy variables are defined for this study.

4.2.2 Secondary efficacy variable

The secondary efficacy variable is:

- Percent change in PGTCS frequency per 28 days from Combined Baseline, where Combined Baseline is defined as the combined 12-week Historical Baseline and 4-week Prospective Baseline periods immediately prior to randomization in the parent study (SP0982)

4.2.3 Other efficacy variables

The other efficacy variables are:

- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline
- Change in days with absence seizures per 28 days relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline
- At least a 50% reduction in PGTCS frequency compared to the Combined Baseline
- At least a 50% reduction in myoclonic seizure days compared to the Prospective Baseline
- At least a 50% reduction in absence seizure days compared to the Prospective Baseline
- Seizure-free status (yes/no) for PGTCS
- Seizure-free status (yes/no) for all generalized seizure types
- 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 for the first 2 years of treatment

- Change from Baseline in the EQ-5D-3L visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions (for subjects ≥12 years of age) for the first two years of treatment
- Healthcare resource use: medical procedures, hospitalizations, and healthcare provider visits for the first 2 years of treatment.
- Number of working or school days lost by subject due to epilepsy for the first two years of treatment.
- Number of days with help from a caregiver due to epilepsy for the first two years of treatment

5 STUDY DESIGN

5.1 Study description

This is a multicenter, open-label extension study to assess the long-term safety, tolerability and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTCS in subjects ≥4 years of age with IGE. This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 study (or have left the primary study at the time of the 125th event, whichever came first) as well as eligible Baseline failures from SP0982. Then, some subjects who tapered in SP0982 after the 125th event may enter EP0012 for the Safety Follow-Up only (ICF to be signed beforehand). Up to 250 subjects from 150 to 180 study sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, study completers from SP0982 who are eligible for inclusion in EP0012, SP0982 Safety Follow-Up subjects, and Other are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTCS criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTCS during that time or

Subjects who experience a second PGTCS after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTCS within the 24-week Treatment Period of SP0982
- Subjects who were ongoing in SP0982 when the 125th event occurred

SP0982 Safety Follow-Up subjects

- Subjects tapered in SP0982 after the 125th event occurs will enter EP0012 for the Safety Follow-Up Visit only

Other

- Subjects that enrolled in EP0012 that did not fall into the above categories

Randomized subjects meeting SP0982 exit criteria and subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. In addition, once 125 subjects have had a second PGTCS in SP0982 (ie, the 125th event has occurred), that study will have met its protocol-defined end. All subjects ongoing in SP0982 will transition into EP0012 for further long-term treatment or for a Safety Follow-Up.

Baseline failures are required to complete Week 1 of dosing before LCM dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further LCM 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 target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets) within 14 days after Visit 1.

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects must remain on the dose for ≥7 days before a subsequent dose escalation.

The LCM dose may be increased or decreased at the investigator's discretion after the subject receives the first dose of LCM in the study (see Table 7–1). Baseline failures must complete Week 1 of dosing before LCM may be increased or decreased. The maximum dose for pediatric subjects weighing <50kg is 12mg/kg/day (oral solution). The maximum dose for pediatric subjects weighing ≥50kg is 600mg/day (tablets) and for adult subjects is 800mg/day (tablets).

A clinic visit (scheduled or unscheduled) is required if:

- The dose is increased for the first time to any dose above 10mg/kg/day for pediatric subjects weighing <50 kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.
- The dose is increased for the first time to any dose above LCM 400mg/day for all adult subjects or pediatric subjects weighing ≥50kg. One week after the first time the dose is

increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

EP0012 will last at least 2 years and consist of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1. Visit 2 will occur 2 weeks after Visit 1 and Visit 3 will occur 4 weeks later (Week 6). Clinic visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur every 24 weeks thereafter until the end of the study. From Year 2 (Visit 11) to 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs, as well as to ensure subjects are compliant with LCM administration and diary completion.

Subjects and/or their caregiver will be dispensed a seizure diary to record all types of seizures, concomitant AEDs, and other pertinent health status information. Subjects must bring their diary to each visit. Baseline seizure frequency and type will be verified by a reliably documented seizure history collected (eg, in a seizure diary during SP0982).

New concomitant AEDs may be introduced to optimize treatment, if the concomitant medication has been approved by the regulatory authority for the respective patient indication in the subject's country. New AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM (Taper Visit and SFU) may not be required for some subjects who leave the study depending on the treatment option selected by the investigator in consultation with the subject and/or their parent(s)/legal representative(s).

5.1.1 Study duration per subject

For adult subjects, treatment will continue for at least 2 years. Once 2 years of participation are reached, adult subjects will continue to participate until 1 of the 2 following conditions are met.

- LCM is approved for use for the treatment of PGTCS in subjects with IGE in the subject's country for or until the latest approval is granted either by EMA, FDA, or PMDA.
- For pediatric subjects, treatment will continue until 1 of the following 2 conditions are met:

- up to 5 years of participation or
- until the approval of the extension of indication to cover the target age group is granted

Adult and pediatric subjects are completers if they continue in the study for the maximum duration in their respective region.

The following study periods are defined:

- A Treatment Period lasting for at least 5 years (238 weeks) for the population less than 18 years old at enrollment and will be shorter for adults leaving the study when the PGTCS indication approvals are being obtained during the course of the study.
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator and do not have to perform the tapering (Taper Visit and SFU).
  - Subjects tapering off LCM will do so over a period of up to 4 weeks (see taper schedule, Table 7–2).
  - An End of Taper Visit (latest 3 days after the final dose) will occur after the final LCM dose for subjects who taper off LCM. 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 same design will apply to some of the subjects tapered in SP0982 at the time of the 125th event and who entered EP0012 for the Safety Follow-Up Visit only and to subjects who entered EP0012 for a Safety Follow-up Visit after discontinuing SP0982 due to the study stopping.

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

Subjects who entered EP0012 as <18 years and become adults (≥18 years) during the study, will remain in the study for at least 5 years (238 weeks).

5.1.2 Planned number of subjects and site(s)

Up to 250 subjects across 150 to 180 international sites are planned to be enrolled in this study.

5.1.3 Anticipated regions and countries

This 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 for treatment Years 1 to 2 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5–1. An additional schedule of study assessments for treatment Years 3 to 5 (Treatment Period, Early Termination [ET]

Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5–2 for subjects <18 years and Table 5–3 for subjects ≥18 years. The schedule of study assessments for the Taper Period and Safety Follow-Up Visit (including subjects who tapered in SP0982 after the 125th event consented to enter EP0012 for the Safety Follow-up only) is provided in Table 5-4.

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

	Treatment Period[a]														Unscheduled[b]
Duration	**Open-label: at least 2 years**														**NA**
Year of study	**Year 1**								**Year 2**						
Visit[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6****	**V7****	**V8**	**Telephone Contact[d]**	**V9**	**V10****	**V11**	**ET Visit[e]**	**Termination Visit[f]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**NA**
Informed Consent/Assent	X														
Inclusion/Exclusion criteria	X														
Subject ID card dispensing	X														
Concomitant medications and AED(s)	X*	X	X	X	X			X	X	X		X	X	X	X
Medical history/Epilepsy history update	X														
Physical exam (complete)[g]	X*							X				X	X	X	
Physical exam (brief)[h]		X	X	X	X					X					X
Neurological exam (complete)[i]	X*							X				X	X	X	
Neurological exam (brief)[j]		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	X
Body weight and height[m]	X*			X				X		X		X	X	X	
Tanner Stage[n]	X							X				X	X	X	
Laboratory tests[o]	X*	X			X			X		X		X	X	X	

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

	Treatment Period[a]														Unscheduled[b]
Duration	**Open-label: at least 2 years**														**NA**
Year of study	**Year 1**								**Year 2**						
Visit[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6****	**V7****	**V8**	**Telephone Contact[d]**	**V9**	**V10****	**V11**	**ET Visit[e]**	**Termination Visit[f]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**NA**
Endocrinology[p]	X*												X	X	
Pregnancy test[q]	X	X	X	X	X			X		X		X	X	X	
Call IRT	X	X	X	X	X			X		X		X	X	X	X
C-SSRS[r]	X	X	X	X	X			X		X		X	X	X	X
Dispense subject diary	X	X	X	X	X			X		X		X	X	X	
Subject diary return/review		X	X	X	X			X		X		X	X	X	X
Dispense LCM	X	X	X	X	X			X		X		X	X	X	
LCM review/return		X	X	X	X			X		X		X	X	X	
Withdrawal criteria	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
EQ-5D-3L	X				X			X		X		X	X	X	
QOLIE-31-P/PedsQL[s]	X				X			X		X		X	X	X	
Achenbach CBCL[t]	X				X			X		X		X	X	X	
BRIEF-P/BRIEF[u]	X				X			X		X		X	X	X	
Healthcare resource use	X*	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	X	

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

	Treatment Period[a]														Unscheduled[b]
Duration	**Open-label: at least 2 years**														**NA**
Year of study	**Year 1**								**Year 2**						
Visit[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6****	**V7****	**V8**	**Telephone Contact[d]**	**V9**	**V10****	**V11**	**ET Visit[e]**	**Termination Visit[f]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**NA**
Days with help from a caregiver due to epilepsy	X*	X	X	X	X			X		X		X	X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-3L=3-level EuroQol-5 Dimension Quality of Life Assessment; ET=early termination; exam=examination; ID=identification; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; PedsQL=Pediatric Quality of Life Inventory; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; V=Visit

Note: For subjects who have completed SP0982, assessments marked (*) should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1; for eligible Baseline failures from SP0982, a full Visit 1 is required including all scheduled tasks and procedures.

Note: Visit 6, Visit 7 and Visit 10 (**) assessments will not be performed according to Protocol Amendment 3.

[a] The duration of the Treatment Period will continue for at least 2 years and vary by subject age group and is defined in Section 5.1.1.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks including Week 30 and Week 38 during the study, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, Week 78, and Week 86.

[e] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the early Termination Visit is the last visit in the study.

[f] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 17 if appropriate (see Table 5–2). For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[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 assessment of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.

[j] The brief neurological examination will include selected assessment 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) a 12-lead ECG (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] Height will be recorded at Visits 1 and 9, and at the ET and Termination Visit.

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

[o] Urinalysis will be required for all subjects.

[p] If the patient was treated in SP0982, endocrinology should be done if age was <18 years at SP0982 Visit 1. If the patient was a Baseline failure in SP0982, endocrinology should be done if age is <18 years at EP0012 Visit 1.

[q] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

[r] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[s] 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 PedsQL form appropriate for each subject's age should be completed, with the following exception: if a subject ages up to the next form of the PedsQL within 1 year after the Baseline assessment of the primary study, the form that was used at the Baseline assessment should be completed for 1 year after the Baseline assessment, and subsequently the form consistent with his/her age at the time of assessment should be completed. For each version of the PedsQL subjects must have at least 1 year of data before transitioning to the next age range (see Section 9.2.1).

[t] The Achenbach CBCL: CBCL/1½-5 for children 18 months to 5 years and 11 months of age and CBCL/6-18 for children ≥6 years to <18 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). The version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: for subjects who completed the CBCL/1½-5 at the Baseline assessment of the previous study and turn 6 years of age within 1 year after the Baseline assessment of the primary study, the CBCL/1½-5 should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the CBCL/6-18 should be completed. The Achenbach CBCL will only be administered in

countries where a validated translated version is available. For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range. The Achenbach CBCL should be completed by the same parent/legal representative, if possible (see Section 10.4.6).

[u] The BRIEF-P should be used for subjects who are <5 years of age at Visit 1, and the BRIEF should be used for subjects who are ≥5 years of age at Visit 1. For each developmentally appropriate version of the BRIEF, subjects must have at least 1 year of data before transitioning to the next age range (see Section 10.4.7).

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years at enrollment)

	Treatment period[a]								End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years								Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5 + Extended Period						
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**Vx[f]**	**ET Visit[g]**	**Term Visit[h]**	**LCM Solution Dispensation Visit[i]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**X**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X		X
Physical exam (complete)[j]			X		X		X	X (odd visits only)	X	X		
Neurological exam (brief)[k]		X		X		X	X	X (even visit only)	X	X		
12-lead ECG[l]			X		X		X	X (odd visits only)	X	X		
Vital signs (BP and pulse) including orthostatic assessments[m]		X	X	X	X	X	X	X	X	X		X
Body weight and height[n]		X	X	X	X	X	X	X (even visits only)	X	X		
Tanner Stage[o]			X		X		X	X (odd visits only)	X	X		
Laboratory tests		X		X		X	X[p]	X[p]	X	X		
Endocrinology[q]									X	X		
Pregnancy test[r]		X	X	X	X	X	X	X	X	X		

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years at enrollment)

	Treatment period[a]								End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years								Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5 + Extended Period						
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**Vx[f]**	**ET Visit[g]**	**Term Visit[h]**	**LCM Solution Dispensation Visit[i]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**X**				**NA**
Call IRT		X	X	X	X	X	X	X	X	X		X
C-SSRS[s]		X	X	X	X	X	X	X	X	X		X
Dispense subject diary		X	X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	X	
LCM 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
AE reporting	X	X	X	X	X	X	X	X	X	X		X
Achenbach CBCL[t]			X		X		X	X (odd visits only)	X	X		
BRIEF[u]			X		X		X	X (odd visits only)	X	X		

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; exam=examination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit; Vx=Visit X

Note: Subjects who turn 18 years during the course of this study will be considered as pediatrics, however these subjects will not need to complete the Achenbach CBCL and BRIEF assessments.

[a] The duration of the Treatment Period will vary by subject age group and is defined in Section 5.1.1.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230. If the subject remains in the study beyond Week 238, telephone contacts will continue at 8-week intervals.

[e] At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] Subjects may require additional routine visits (Visit X) if the study is still ongoing at Week 238 for the respective subject. Vx visits are to be performed every 24 weeks. Additional routine visits should be scheduled and performed in accordance with footnote 'b' to avoid visit window deviations. Assessments must be performed in accordance with Table 5–3.

[g] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the early Termination Visit is the last visit in the study.

[h] A Termination Visit must be completed for all subjects who complete the study. This can be performed in alignment of the date of the last scheduled visit if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[i] Dispensation Visit will occur 12 weeks after each 24-weekly visit from Year 2 (Visit 11) to Year 3 onwards and will be for the purpose of dispensing LCM solution for pediatric subjects <50kg.

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

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

[l] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[n] Height will be recorded at Visits 12, 14, 16, Visit X (even visits), and at the ET and Termination Visit.

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

[p] Laboratory tests are applicable for combined the last scheduled visit/Termination Visit. If the last scheduled visit is not the Termination Visit, laboratory tests are not required.

[q] If the patient was treated in SP0982, endocrinology should be done if age was <18 years at SP0982 Visit 1. If the patient was a Baseline failure in SP0982, endocrinology should be done if age is <18 years at EP0012 Visit 1.

[r] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

[s] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[t] The Achenbach CBCL: CBCL/6-18 for children ≥6 years to <18 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range. The Achenbach CBCL should be completed by the same parent/legal representative, if possible (see Section 10.4.6).

[u] The BRIEF should be used for subjects who are ≥5 years of age. For each developmentally appropriate version of the BRIEF, subjects must have at least 1 year of data before transitioning to the next age range (see Section 10.4.7).

Table 5–3: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects ≥18 years at enrollment)

	Treatment period[a]								End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years								Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5 +Extended Period						
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**Vx[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**X**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X		X
Laboratory tests[h]		X		X		X	X[i]	X[i]	X	X		
Pregnancy test[j]		X	X	X	X	X	X	X	X	X		
Dispense subject diary		X	X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X		X
Call IRT		X	X	X	X	X	X	Xe	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	X	
LCM 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

AE reporting	X	X	X	X	X	X	X	X	X	X		X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit; Vx=Visit X

[a] The duration of the Treatment Period will vary by patient age group and is defined in Section 5.1.1.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230. If the subject remains in the study beyond Week 238, telephone contacts will continue at 8-week intervals.

[e] Vx visits are to be performed every 24 weeks. When subjects leave the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the early Termination Visit is the last visit in the study. Investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[g] A Termination Visit must be completed for all subjects who complete the Treatment Period (Week 238 or extended treatment period). This can be performed in alignment of the date of the last scheduled visit if applicable. For subjects who will not continue on commercial LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study. A Termination Visit is to be done if the subject is leaving the study prior to Week 238 following the approval of the PGTCS indication in their respective region/country as follows: for US subjects, when the US approval is obtained; for EU subjects, if the EU approval is obtained; and for all other adults at the approval of the PGTCS indication in Japan (last targeted approval). When subjects leave the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[h] Laboratory tests include chemistry, hematology and, urinalysis.

[i] Laboratory tests are applicable for the combined last scheduled visit/Termination Visit. If the last scheduled visit is not the Termination Visit, laboratory tests are not required.

[j] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

Table 5-4:Schedule of study assessments (Taper Period and Safety Follow-Up Period)

Assessment	Taper Period[a] (up to 4 weeks)	Safety Follow-Up Period[b]	
	End of Taper Visit (maximum 3 days after the last dose)[c]	Safety Follow-Up Visit	Safety Follow-Up TC
		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)	X	X	
Neurological exam (brief)	X	X	
12-lead ECG[d]	X	X[e]	
Vital signs (BP and pulse) including orthostatic assessments	X	X	
Body weight	X	X	
Laboratory tests:			
Chemistry/hematology	X	X[e]	
Endocrinology		X[e]	
Urine pregnancy test[f]	X	X	
Contact IRT	X		
Subject diary return/review[g]	X		
LCM review/return	X		
Withdrawal criteria	X		
AE reporting	X	X	X
C-SSRS[h]	X	X	
Healthcare resource use[i]	X	X	
Work/school days lost due to epilepsy[i]	X	X	
Days with help from a caregiver due to epilepsy[i]	X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IRT=interactive response technology; LCM=lacosamide; TC=telephone contact
Note: The schedule of study assessments for the Taper Period and Safety Follow-Up Visit includes some of the subjects who tapered in SP0982 after the 125th event who consented to enter EP0012 for the Safety Follow-Up only.

[a] Subjects who will not continue on LCM must complete an End of Taper Visit and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the (Early) Termination Visit is the last visit in the study.

[b] 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 Visit.

[c] 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 7–2. 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 place at the ET or Termination Visit.

[d] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[f] Pregnancy tests will be performed for female subjects of childbearing potential only. A urine pregnancy test will be performed.

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

[h] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[i] Healthcare resource use, work/schools days lost due to epilepsy, and days with help from a caregiver due to epilepsy will be assessed only for patients completing the study after ≤2 years. These assessments are not applicable for patients tapering down or performing the SFU-visits during Years 3, 4 or 5).

5.3 Rationale for study design and selection of dose

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

The efficacy, safety, and tolerability of LCM as an adjunctive therapy have been demonstrated in the partial-onset seizure population. The approach for further LCM development is to evaluate the use of adjunctive LCM for the treatment of uncontrolled PGTCS in patients with IGE.

The goal of the Phase 3 LCM PGTCS program is to provide clinical evidence of the efficacy and safety of LCM as an adjunctive therapy for uncontrolled PGTCS in subjects with IGE as the basis for approval of this indication. SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of LCM for uncontrolled PGTCS in subjects ≥4 years of age with IGE. EP0012 will provide continued availability of LCM to subjects who have completed SP0982 and eligible Baseline failures from SP0982.

For adult subjects (≥18 years of age), 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 PGTCS 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 PGTCS with IGE. The maximum dose of LCM 800mg/day is the highest dose that has been used in previous clinical studies. Dose selection in EP0012 is based on the primary study (SP0982). During EP0012, investigators will be allowed to increase or

decrease the dose of LCM to optimize tolerability and seizure reduction for each subject. Lacosamide doses may be increased up to a maximum of LCM 12mg/kg/day (oral solution) for pediatric subjects weighing <50kg. The maximum dose for pediatric subjects (<18 years of age) ≥50kg is 600mg/day (tablets) and for adult subjects is 800mg/day (tablets).

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent/Assent form for the open-label extension study (EP0012) must be 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 must have completed or be an eligible Baseline failure from the parent study (SP0982), as defined in Section 5.1. Note: Other subjects screened for SP0982 may be considered for roll-over to EP0012 if the investigator considers that the subject could benefit from treatment with open-label LCM and based on prior discussion with and approval from the UCB Study Physician or representative.
3. Subject/legally acceptable representative considered as reliable and capable of adhering to the protocol (eg, able to understand and complete diaries and questionnaires), visit schedule, and medication intake according to the judgment of the investigator.

6.2 Exclusion criteria

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

1. Subject is receiving any investigational drugs or using any experimental devices in addition to LCM.
2. Subject meets the withdrawal criteria for SP0982 or is experiencing an ongoing serious adverse event (SAE).
3. Subject has an active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional.
4. 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 all subjects who entered EP0012 directly 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.

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

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 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Investigators should contact the Medical Monitor whenever possible to discuss the withdrawal of a subject in advance. All subjects discontinuing treatment with LCM for any reason should taper as described in Section 7.2. All subjects who withdraw due to an AE must be followed until resolution of the event or until the event is considered stable.

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

1. Tapered subjects from SP0982 who enter EP0012 after the 125th event will be withdrawn at the enrollment visit and enter directly into the Safety Follow-Up Period without and ET Visit being performed in EP0012.
2. The subject develops second or third degree atrioventricular (AV) block.
3. The subject becomes pregnant, as evidenced by a positive pregnancy test.
4. The sponsor or a regulatory agency requests withdrawal of the subject.
5. The subject is unwilling or unable to continue, or the legal representative is unwilling or unable to allow the subject to continue in the study.
6. In the case of liver function test (LFT) results of transaminases (ALT and/or aspartate AST) ≥3x ULN 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.
7. Subject ≥6 years of age has actual suicidal ideation since last visit 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.
8. Subject is unable to tolerate at least the minimum LCM target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets).

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

- The subject requires a medication that is not permitted (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.
- Discontinuation criteria for potential drug-induced liver injury (PDILI) are described in Section 6.3.1.

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.

After the decision to withdraw the subject, the investigator will provide the subject with information about available alternative treatments.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with PDILI must be assessed to determine if investigational medicinal product (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%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 10.3.1.2.1 are followed.

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 10.3.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately. See Section 6.3 for when and how to discontinue subjects from the IMP. See Section 8.2 for the procedures to be performed at the time of discontinuation.

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 CRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

Investigational medicinal product (IMP) will be provided as LCM oral solution (LCM 10mg/mL) and LCM tablets (LCM 50mg and LCM 100mg).

The oral solution formulation contains 10mg/mL of drug substance and is colorless to pale yellow in appearance.

The tablet formulation will be supplied in doses of 50mg and 100mg. The 50mg tablets are light pink, oval, film-coated tablets debossed with "SP" on 1 side and "50" on the other. The 100mg tablets are dark yellow, oval, film-coated tablets debossed with "SP" on 1 side and "100" on the other.

7.2 Treatment(s) to be administered

Lacosamide will be orally administered bid (at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses (oral solution for pediatric subjects weighing <50kg or tablets for adult subjects [≥18 years of age] and pediatric subjects [<18 years of age] weighing ≥50kg); during the study, subjects who initially started on oral solution may transfer to tablets at the investigator's discretion.

Tablets **must not be broken**. In rare cases where uneven dosing (e.g., 350mg/day, 450mg/day, 550mg/day, etc) is medically needed, although the interactive response technology (IRT) will not dispense the exact dose, please contact the Medical Monitor for additional instructions. 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]).

During the study, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject, within the dose range described in Table 7–1.

7.2.1 Treatment Period

At Visit 1, subjects who completed SP0982 will start on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Baseline failures are required to complete Week 1 of dosing before LCM dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further LCM 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 target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets).

Subjects who tapered in SP0982 after the 125th event will enroll at Visit 1 and proceed directly to the Safety Follow-up Period without receiving LCM.

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects must remain on the dose for ≥7 days before a subsequent dose escalation.

Table 7–1 provides the minimum and maximum LCM dose during the Treatment Period.

Table 7–1: Minimum and maximum LCM dose during the Treatment Period

Formulation	Minimum LCM dose	Maximum LCM dose
Oral solution (pediatric subjects <50 kg)	4mg/kg/day	12mg/kg/day
Tablets (pediatric subjects ≥50kg)	200mg/day	600mg/day
Tablets (adult subjects)	200mg/day	800mg/day

LCM=lacosamide

The LCM dose may be adjusted at the investigator's discretion after the subject receives the first dose of LCM in the study. Baseline failures must complete Week 1 of dosing before LCM may be increased or decreased. The maximum dose for pediatric subjects weighing <50kg is 12mg/kg/day (oral solution). The maximum dose for pediatric subjects weighing ≥50kg is 600mg/day (tablets) and for adult subjects is 800mg/day (tablets).

A clinic visit (scheduled or unscheduled) is required if:

- The dose is increased for the first time to any dose above 10mg/kg/day for pediatric subjects weighing <50kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.
- The dose is increased for the first time to any dose above LCM 400mg/day for all adult subjects or pediatric subjects weighing ≥50kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Subjects withdrawing from the study must complete the ET Visit and (if they do not proceed with commercially available LCM) an up to 4-week taper followed by an End of Taper Visit (see taper schedule, Table 7–2). 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. A slow taper is permitted if medically necessary. Whenever possible, these cases should be discussed with the Medical Monitor prior to withdrawing the subject from the study. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

At the completion of the Treatment Period, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent(s)/legal representative(s).

Subjects completing the Treatment Period and not continuing with commercially available LCM must complete the Termination Visit and also undergo taper, followed by an End of Taper Visit (see taper schedule, Table 7–2), and a 30-day Safety Follow-Up Period.

The following table summarizes the recommended LCM dose taper:

Table 7–2: Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	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
4mg/kg/day	2mg/kg/day	NA	NA	NA
800mg/day	600mg/day	400mg/day	200mg/day	100mg/day
700mg/day	500mg/day	300mg/day	200mg/day	100mg/day
600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
400mg/day	300mg/day	200mg/day	100mg/day	NA
300mg/day	200mg/day	100mg/day	NA	NA
200mg/day	100mg/day	NA	NA	NA

ET=early termination; LCM=lacosamide; NA=not applicable
Note: The oral solution is dosed as mg/kg/day and tablets are dosed as mg/day.
[a]Subjects will begin taper on ET/Termination Visit.

7.3 Packaging

Lacosamide (tablets and oral solution) 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. Oral solution will be packaged in amber polyethylene terephthalate bottles. Tablets will be supplied in high-density polyethylene bottles with child proof polypropylene screw caps.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice 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 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 Handing 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 the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (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 bottles. 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-PGTCS.

7.8 Concomitant medication(s)/treatment(s)

All concomitant medication and treatment must be recorded in the appropriate study documents (eg, eCRF and source document).

7.8.1 Permitted concomitant treatments (medications and therapies)

Female subjects not surgically sterile or 2 years postmenopausal should practice 1 highly effective method of contraception (according to 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. Recommended contraception methods for subjects on enzyme-inducing antiepileptic drugs (EI-AEDs) or not on EI-AEDs are detailed in Section 16.7. Subjects on EI-AEDs who do not use one of the highly effective contraception methods recommended for this group may practice 2 combined methods of contraception (ie, combined hormonal contraception plus barrier method with spermicidal agent).

The initiation of felbamate treatment while participating in EP0012 is prohibited.

The use of neuroleptics except for clozapine is allowed. The use of barbiturates and narcotic analgesics is also allowed. Stable use of benzodiazepines is allowed as concomitant AEDs, but intermittent use is only allowed as rescue medication for epilepsy indications (maximum 1 dose per week).

During the Treatment Period, new concomitant AEDs may be introduced, if the concomitant medication has been approved by the regulatory authority for the respective patient indication in the subject's country. For example, a new AED may be added when the subject has not optimally or adequately responded (lack of efficacy or tolerance) to LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

7.8.2 Prohibited concomitant treatments (medications and therapies)

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

- Clozapine
- MAO-A inhibitors
- Vigabatrin

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

This is an open-label study; there will be no blinding.

7.10 Randomization and numbering of subjects

This is an open-label study and subjects will not be randomized to any treatment groups. The unique identification number assigned to subjects during the previous SP0982 study will be used to identify subjects and to maintain subject confidentiality throughout the current study. An IRT will be used to assign the applicable LCM treatment. Further instructions will be provided in the IRT manual.

8 STUDY PROCEDURES BY VISIT

Prior to any study activities, the subject or legal representative will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and that complies with regulatory requirements. The subject or legal representative will be given adequate time to consider any information concerning the study, given to them by the investigator or designee. As part of the informed consent procedure, the subject or legal representative will be given the opportunity to ask the investigator any questions regarding potential risks and benefits of participation in the study. Additionally, if applicable (according to the subject's age and local requirements), the subject will sign an IRB/IEC Assent form.

All visits occur at the end of the respective week in the study and a window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

A detailed schedule of study assessments for treatment Years 1 to 2 is provided in Table 5–1, for treatment Years 3 to 5 in Table 5–2, Table 5–3 and for the Taper Period and Safety Follow-Up Period in Table 5-4.

8.1 Treatment Period

8.1.1 Visit 1 (Week 0)

The following tasks and procedures are to be performed at this visit (for subjects who have completed SP0982, assessments marked [*] should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1; for eligible

Baseline failures from SP0982, a full Visit 1 is required including all scheduled tasks and procedures). Tapered subjects from SP0982 will enter EP0012 for the Safety Follow-Up only and will be withdrawn at Visit 1 once Visit 1 assessments have been performed. Details of the Safety Follow-Up are provided in Section 8.4.2 and Section 8.4.3.

- Written Informed Consent/Assent
- Inclusion/exclusion criteria
- Subject identification card dispensed
- Concomitant medications and AEDs*
- Medical history/epilepsy history update
- Physical examination (complete)*
- Neurological examination (complete)*
- ECG (12-lead) assessment*
- Vital signs (pulse rate, BP) including orthostatic assessments*
- Body weight and height*
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential]).* Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.
- Contact IRT
- Dispense subject diary
- Dispense LCM
- Assess withdrawal criteria*
- AE reporting*
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age
- Healthcare resource use*
- Work/school days lost due to epilepsy*

- Days with help from a caregiver due to epilepsy*

8.1.2 Visits 2 to 8 (Weeks 2 to 46, Year 1, excluding Visit 6 and Visit 7)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 2, 3, 4, and 5; complete, Visit 8)
- Neurological examination (brief, Visit 2, 3, 4, and 5; complete, Visit 8)
- ECG (12-lead) assessment (Visit 2, 4, and 8 only)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight (Visit 4, and 8 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 8 only)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) [Visit 2, 5, and 8 only], and a urine pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 5 and 8) (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age) (Visit 5 and 8 only)
- Achenbach CBCL for subjects <18 years of age (Visit 5 and 8 only)
- BRIEF for subjects <18 years of age (Visit 5 and 8 only)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

8.1.3 Visits 9 and 11 (Weeks 62 and 94, Year 2, excluding Visit 10)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 9; complete, Visit 11)
- Neurological examination (brief, Visit 9; complete, Visit 11)
- ECG (12-lead) assessment (Visit 9 and 11)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 9 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 11 only)
- 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])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 9 and 11) (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age) (Visit 9 and 11 only)
- Achenbach CBCL for subjects <18 years of age (Visit 9 and 11 only)
- BRIEF for subjects <18 years of age (Visit 9 and 11 only)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

8.1.4 Visits 12, 13, 14, 15, 16, 17 and X (Weeks 118, 142, 166, 190, 214, 238, and X, Years 3 to 5 + Extended Period)

8.1.4.1 Subjects <18 years

The following tasks and procedures are to be performed at these visits (Visit X [Vx] visits are to be performed every 24 weeks):

- Concomitant medications and AEDs

- Physical examination (complete, Visit 13, 15, 17, and odd numbered visits thereafter)
- Neurological examination (brief, Visit 12, 14, 16, 17, and even numbered visits thereafter)
- ECG (12-lead) assessment (Visit 13, 15, 17, and odd numbered visits thereafter)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 12, 14, 16, and even numbered visits thereafter)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 13, 15, 17, and odd numbered visits thereafter)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required. Laboratory tests are not performed at Visit 13 and 15 according to Protocol Amendment 3.
- Urine pregnancy test (for women of childbearing potential)
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects ≥6 years to <18 years of age (Visit 13, 15, 17, and odd numbered visits thereafter)
- BRIEF for subjects ≥5 to <18 years of age (Visit 13, 15, 17, and odd numbered visits thereafter)

8.1.4.2 Subjects ≥18 years

The following tasks and procedures are to be performed at these visits, additional routine visits (Visit X) can be done after Visit 17 (Vx visits are to be performed every 24 weeks) with assessments described in Table 5–3.

- Concomitant medications and AEDs
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not

required. Laboratory tests are not performed at Visit 13 and 15 according to Protocol Amendment 3.

- Urine pregnancy test (for women of childbearing potential)
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting

8.1.5 Telephone Contact

Telephone contacts are required at Week 30 and Week 38 and every 8 weeks during Year 2 to Year 5, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, Week 78, and Week 86. Telephone contacts in Years 3 to 5 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 214, Week 222, Week 230, Week 238, and every 8 weeks during the Extended Period.

The investigator or designee should contact the subject by telephone. During the telephone contact the following assessments will be performed:

- Concomitant medications and AEDs
- Assess withdrawal criteria
- AE reporting

The investigator will also ensure subjects are compliant with LCM administration and diary completion during the telephone contact.

8.1.6 LCM Solution Dispensation Visit

From Year 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed, and empty LCM bottles will be returned.

8.2 Early Termination Visit

Subjects withdrawing from the study will complete the ET Visit, and LCM will be tapered over a period of up to 4 weeks if not continuing with commercially available LCM (see taper schedule, Table 7–2).

The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs

- Physical examination (complete), excluding subjects ≥18 years after the first 2 years
- Neurological examination (brief), excluding subjects ≥18 years after the first 2 years
- ECG (12-lead) assessment, excluding subjects ≥18 years after the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments, excluding subjects ≥18 years after the first 2 years
- Body weight and height, excluding subjects ≥18 years after the first 2 years
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study), excluding subjects ≥18 years after the first 2 years
- C-SSRS assessment (for subjects ≥6 years of age), excluding subjects ≥18 years after the first 2 years
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age

The following assessments are only applicable at the ET Visit for subjects early terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

8.3 Termination Visit

A Termination Visit will be completed by subjects who complete the Treatment Period and meet 1 of the following conditions:

1. The subject chooses to transition to commercial LCM.
2. The subject chooses not to continue treatment with LCM.

Subjects not continuing treatment with LCM will complete the Termination Visit, and LCM will be tapered over a period of up to 4 weeks (see taper schedule, Table 7–2). Subjects who continue treatment with commercial LCM must also complete the Termination Visit.

Taper of LCM is not required for subjects who leave the Termination Visit and transition to commercial LCM. Subjects transitioning to commercial LCM will do so immediately and will continue at a dose determined by the investigator. In this instance, the Termination Visit will serve as the subject's last visit in the study.

The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs
- Physical examination (complete), excluding subjects ≥18 years after the first 2 years
- Neurological examination (complete) Note: Complete neurological exam to be performed for subjects terminating the study during Years 1-2, for all subjects and brief exam for subjects <18 years terminating during Years 3-5. Neurological exam is excluded for subjects ≥18 years after the first 2 years.
- ECG (12-lead) assessment, excluding subjects ≥18 years after the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments excluding subjects ≥18 years after the first 2 years
- Body weight and height, excluding subjects ≥18 years after the first 2 years
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study), excluding subjects ≥18 years after the first 2 years
- C-SSRS assessment (for subjects ≥6 years of age), excluding subjects ≥18 years after the first 2 years
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary for subjects undergoing taper
- Subject diary return/review
- Dispense LCM for subjects undergoing taper
- LCM review/return
- Assess withdrawal criteria
- AE reporting

- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age

The following assessments are only applicable at the Termination Visit for subjects terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

8.4 Taper and Safety Follow-Up Period

8.4.1 End of Taper Visit

An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs
- Physical examination (complete)
- Neurological examination (brief)
- ECG (12-lead) assessment
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and a urine pregnancy test [for women of childbearing potential])
- Contact IRT
- Subject diary return/review
- LCM review/return
- Assess withdrawal criteria
- AE reporting

The following assessments are only applicable at the End of Taper Visit for subjects terminating/early terminating the study during the first 2 years (see Section 4.2.3):

- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Subjects who were already tapered in SP0982 after the 125th event occurred do not need to undergo the End of Taper Visit assessments in EP0012 as the assessments were performed in SP0982.

8.4.2 Safety Follow-Up Visit

Following the End of Taper Visit, the subject will return 2 weeks after the last dose of study drug for a Safety Follow-Up Visit (including subjects tapered in SP0982 after the 125th event occurs who enter EP0012 only for a Safety Follow-Up Visit). During the Safety Follow-Up Visit, the following assessments will be performed:

- Concomitant medications and AEDs
- Physical examination (complete)
- Neurological examination (brief)
- ECG (12-lead) assessment (only required for subjects with an abnormal reading at the previous clinic visit)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, [only required for subjects with an abnormal value at the previous clinic visit], and a urine pregnancy test [for women of childbearing potential])
- AE reporting

The following assessments are only applicable at the Safety Follow-Up Visit for subjects terminating/early terminating the study during the first 2 years (see Section 4.2.3):

- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

8.4.3 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. During the Safety Follow-Up telephone contact, the following assessments will be performed:

- Concomitant medications and AEDs
- AE reporting

8.5 Unscheduled Visit

Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. A clinic visit (scheduled or unscheduled) is required the first time the dose is increased above the dose of 10mg/kg/day (oral solution) for pediatric subjects weighing

<50kg or 400mg/day (tablets) for adult and pediatric subjects ≥50kg. One week after the first time the dose is increased above the dose of 10mg/kg/day or 400mg/day, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated. Similarly, a clinic visit (scheduled or unscheduled) is required for pediatric subjects weighing <50 kg the first time the dose is increased to 11mg/kg/day, or 12mg/kg/day, and all adult subjects or pediatric subjects weighing ≥50kg the first time the dose is increased to LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, and LCM 800mg/day. One week after the first time the dose is increased to 11mg/kg/day, or 12mg/kg/day for pediatric subjects <50kg, and LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, or LCM 800mg/day for all adult subjects or pediatric subjects weighing ≥50kg, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

During an Unscheduled Visit the following assessments are required:

- Concomitant medications and AEDs
- Physical examination (brief) during the first 2 years, excluding subjects ≥18 years after the first 2 years
- Neurological examination (brief) during the first 2 years, excluding subjects ≥18 years after the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments, excluding subjects ≥18 years after the first 2 years
- Contact IRT
- Subject diary return/review
- Assess withdrawal criteria
- AE reporting

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

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

9 ASSESSMENT OF EFFICACY

9.1 Seizure variables

Subjects will keep a diary to record all seizure activity from Visit 1 until the end of study participation. Efficacy variables will be assessed using the seizure count information recorded on the subject diaries. The subject should be reminded to bring the diary to each clinic visit. Should an adverse event involving a seizure be reported, it must be consistent with the seizure information (including specific type of seizure) reported in the seizure diary.

9.1.1 PGTCS

The following information will be recorded as applicable:

- Seizure type
- Number of PGTCS

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

9.1.2 Absence and myoclonic seizures

In the subject diary, the following information will be recorded:

- 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.

9.2 Health outcome variables

Health outcome variables will be evaluated during the first 2 years of treatment.

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

The QOLIE-31-P Version 2 (see Section 16.2) 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).

9.2.2 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 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 HRQoL is measured for pediatric subjects ≤4 years of age. The PedsQL appropriate for each subject's age should be completed, with the following exception: if a subject ages up to the next form of the PedsQL within 1 year after the Baseline assessment of the primary study, the form that was used at the Baseline assessment should be completed for 1 year after the Baseline assessment, and subsequently the form consistent with his/her age at the time of assessment should be completed.

For each version of the PedsQL, subjects must have at least 1 year of data before transitioning to the next age range.

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.

9.2.3 EuroQol-5D-3L Quality of Life Assessment

The EQ-5D-3L (EuroQol Group, 2011) (see Section 16.3) 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 VAS, anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

9.2.4 Healthcare resource use

Healthcare resource use will include concomitant medical procedures, hospitalizations, and healthcare provider visits during the first 2 years of treatment.

9.2.5 Number of working or school days lost due to epilepsy

The number of working or school days lost by the subject due to epilepsy will be recorded, as applicable during the first 2 years of treatment.

9.2.6 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 during the first 2 years of treatment.

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 a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

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

Should an AE involving a seizure be reported, it must be consistent with the seizure information (including specific type of seizure) reported in the seizure diary.

10.1.1.2 Serious adverse events

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

- Death
- Life-threatening

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

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 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 he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For

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

If commercial LCM is given during hospitalization, this needs to be recorded on the CRF.

10.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

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

Table 10–1: Anticipated serious adverse events 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

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 beats/min)
- Syncope or loss of consciousness (other than seizure related)

- Serious suspected multiorgan hypersensitivity reactions.

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

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

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

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

- Emergence of non-pre-existing 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 IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

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

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 10.3.1.4.

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 the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (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 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, UCB will ask the investigator or designee to contact the subject and his partner to request consent 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/contract research organization (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 CRF, 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 SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

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 New seizure types, increase in days with and worsening of days with absence or myoclonic seizures

Incidence of new seizure types, increase in absence seizure days or myoclonic seizure days per 28 days during the Treatment Period, and 50% worsening in days with absence seizures or myoclonic seizures per 28 days during the Treatment Period will be assessed using the seizure count information recorded on the subject diaries (see Section 9.1).

10.3 Laboratory measurements

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, Table 5–2, Table 5–3 and Table 5-4. A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.3.2). 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	Endocrinology	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	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 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; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cell

10.3.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 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 10.3.1.1). 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 10.3.1.4).

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 CRF pages.

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 10.3.1.2.1 are met, rechallenge with IMP may be appropriate.

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 10.3.1.3); 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 10.3.1.2).	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 10.3.1.3).	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 10.3.1.1. 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.

10.3.1.1 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 10.3.1.3) and SAE report (if applicable).

10.3.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring. The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 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.

10.3.1.2.1 IMP restart/rechallenge (if applicable)

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

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 10–3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 10.3.1.3 and Section 10.3.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.

Subject agrees to the investigator-recommended monitoring plan.

10.3.1.3 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 CRF. 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	Differential count, hematocrit, hemoglobin, platelet count, RBC and WBC
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Albumin, AST, ALT, ALP, GGT, serum CPK, and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

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

[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

10.3.1.4 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.

10.3.2 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, Table 5–3 and Table 5-4.

10.4 Other safety measurements

10.4.1 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, Table 5–3 and Table 5-4. 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 schedule of study assessments in Table 5–1, Table 5–2, Table 5–3 and Table 5-4.

10.4.2 12-lead ECG

Standard 12-lead ECGs will be performed according to the schedule of study assessments in Table 5–1, Table 5–2, Table 5–3 and Table 5-4.

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), a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

10.4.2.1 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 6.3). 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.

10.4.3 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess

suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the schedule of study assessments in Table 5–1, Table 5–2, Table 5–3 and Table 5-4.

The C-SSRS will be completed for subjects who are ≥6 years of age. The "Since Last Visit" version of the C-SSRS should be used. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used once, followed by the "Since Last Visit" version at subsequent visits.

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

10.4.4 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, Table 5–3 and Table 5-4. Clinically significant physical examination findings are to be reported as AEs.

10.4.4.1 Complete physical examination

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

10.4.4.2 Brief physical examination

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

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

10.4.5 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, Table 5–3 and Table 5-4. 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 PGTCS.

10.4.5.1 Complete neurological examination

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

10.4.5.2 Brief neurological examination

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

10.4.6 Achenbach CBCL

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems.

The Achenbach CBCL consists of the CBCL/1½ -5 for children <5 years and 11 months of age, and the CBCL/6-18 for children ≥6 years to <18 years of age. These are to be completed by the parent(s)/legal representative(s). The completion of the Achenbach CBCL will require approximately 45 minutes. The version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: for subjects who completed the CBCL/1½-5 at the Baseline assessment of the previous study and turn 6 years of age within 1 year after the Baseline assessment of the primary study, the CBCL/1½-5 should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the CBCL/6-18 should be completed. The Achenbach CBCL will only be administered in countries where a validated translated version is available. For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range.

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.

10.4.7 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 or BRIEF appropriate for each subject's age should be completed, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment of the previous study and turn 5 years of age within 1 year after the Baseline assessment of the primary study, the BRIEF-P should be completed for 1 year after the Baseline assessment of the primary study,

and subsequently the BRIEF should be completed. The BRIEF-P and BRIEF will be administered according to the tabular schedules of study procedures (Section 5.2). The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each developmentally appropriate version of the BRIEF subjects must have at least 1 year of data before transitioning to the next age range.

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.

10.4.8 Tanner stage

The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study, according to the schedule of study assessments in Table 5–1 and Table 5–2. The investigator or qualified designee will evaluate the subject's sexual development using the 3-item 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 the evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study).

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 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.

11.2 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.

11.2.1 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.

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.

11.2.2 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 11.2.1.

11.3 Data handling

11.3.1 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.

11.3.2 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 will be 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.

11.3.3 Subject Enrollment log/Subject Identification Code list

The subject's enrollment will be recorded in the Subject 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.

11.4 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.

11.5 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable

regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file (TMF).

11.6 Audit and inspection

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

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent/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).

11.7 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.

12 STATISTICS

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

12.1 Definition of analysis sets

12.1.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have a signed Informed Consent/ Assent form.

12.1.2 Safety Set

The Safety Set (SS) consists of all enrolled subjects who received at least 1 dose of LCM during EP0012.

12.1.3 Full Analysis Set

The Full Analysis Set is a subset of the SS and consists of all subjects with seizure diary data for at least 1 day during EP0012.

12.2 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 (SD), median, minimum, and maximum.

12.3 Planned safety and other analyses

12.3.1 Safety analyses

The incidence of all TEAEs, treatment emergent SAEs and TEAEs leading to premature discontinuation from study drug will also be summarized descriptively. Additional summaries will be provided by maximum intensity and relationship to study drug. All tables of TEAEs will include Medical Dictionary for Regulatory Activities primary System Organ Class and Preferred Term. Further details on the analysis of each variable will be given in the SAP.

Incidence of new seizure types, increase in days with absence seizure or myoclonic seizures per 28 days during the Treatment Period, and 50% worsening in days with absence seizures or myoclonic seizures per 28 days during the Treatment Period will be summarized. Laboratory measurements as described in Section 10.3 and other safety measurements as described in Section 10.4 will be presented.

12.3.2 Other analyses

Details of further analyses will be provided in the SAP.

12.4 Planned efficacy analyses

Seizure data will be summarized from diary assessments. The percent change from the combined Baseline Period in PGTCS frequency per 28 days will be summarized. Response, defined as at least a 50% reduction in PGTCS frequency per 28 days compared to the combined Baseline Period, and freedom from PGTCS during the study will also be presented descriptively.

Days with myoclonic or absence seizures are more clinically relevant endpoints; therefore, change in and percent change in days with myoclonic and/or absence seizures will be summarized. The percentage of subjects with 50% reduction in days with absence and/or myoclonic seizures per 28 days compared to the Prospective Baseline will be presented. Subjects who were seizure-free from all generalized seizures will also be tabulated.

Descriptive statistics including number of subjects, mean, SD, median, minimum, and maximum will be used to summarize continuous data including seizure frequencies per 28 days and days with seizures per 28 days. Frequency counts will be used to display categorical data, where appropriate.

12.5 Handling of protocol deviations

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

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

12.6 Handling of dropouts or missing data

All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter, unless otherwise specified in the SAP.

12.7 Planned interim analysis and data monitoring

No interim analysis or Data Monitoring Committee is planned. However, data may be reported prior to the completion of this study to support annual reports, regulatory submissions, and publications.

12.8 Determination of sample size

The sample size of this open-label extension study will be determined by the parent SP0982 study, where approximately 200 subjects are planned to be randomized.

SP0982 is an event-driven study. Up to 250 subjects may be enrolled to meet the required number of events. Baseline failures from SP0982 will also be eligible for EP0012, which may increase the sample size.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

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, the 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 US must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she 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.

13.2 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 him/her at all times.

13.3 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, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the

original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

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

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

13.4 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 during the previous SP0982 study.

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).

13.4.1 Processing of subject health data

The processing of the subject personal health data in this study is allowed for the purpose of scientific research to evaluate the efficacy and the safety of the tested drug, in accordance with legal requirements from:

- the laws governing the conduct of clinical studies (ie, the provisions of the French Public Health Code and the EU clinical trial regulation 536/2014 which requires sponsors to collect and analyze such data before they are submitted to health authorities)
- the EU regulation 1235/2010 on pharmacovigilance which requires follow-up and reporting of adverse events of medicinal products to the health authorities, and any other applicable law

This means that after the end of the study the subject coded personal data will be retained for at least 25 years to ensure the validity of the research.

The subjects will be informed that the Sponsor is legally entitled and obliged to keep, retain, and use your medical data to ensure the quality of scientific results and to comply with legal or judicial retention periods.

13.5 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.

14 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.

15 REFERENCES

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16 APPENDICES

16.1 Appendix 1: 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

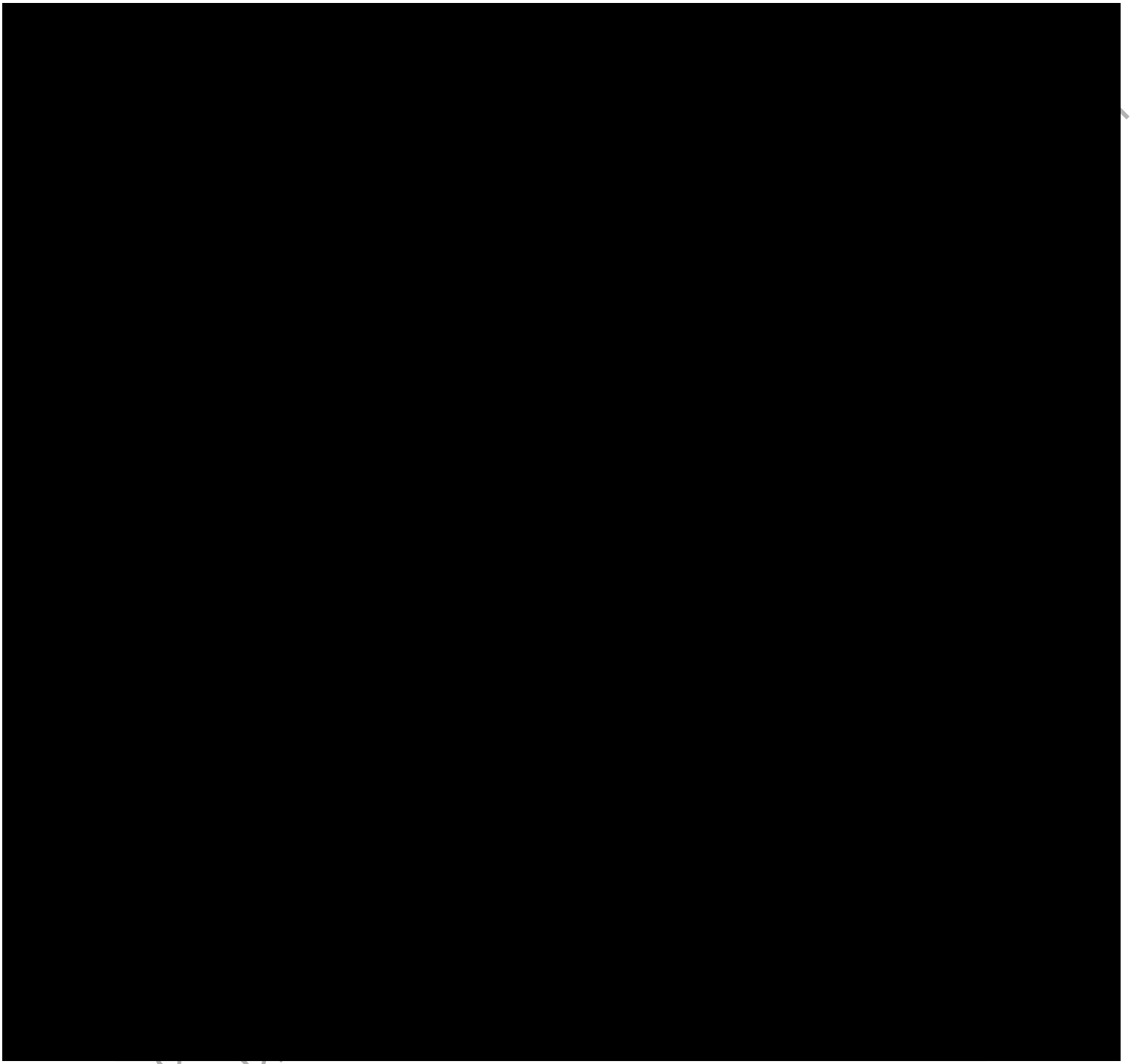
Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, eg, rhythmic eye movements, chewing, and swimming movements.

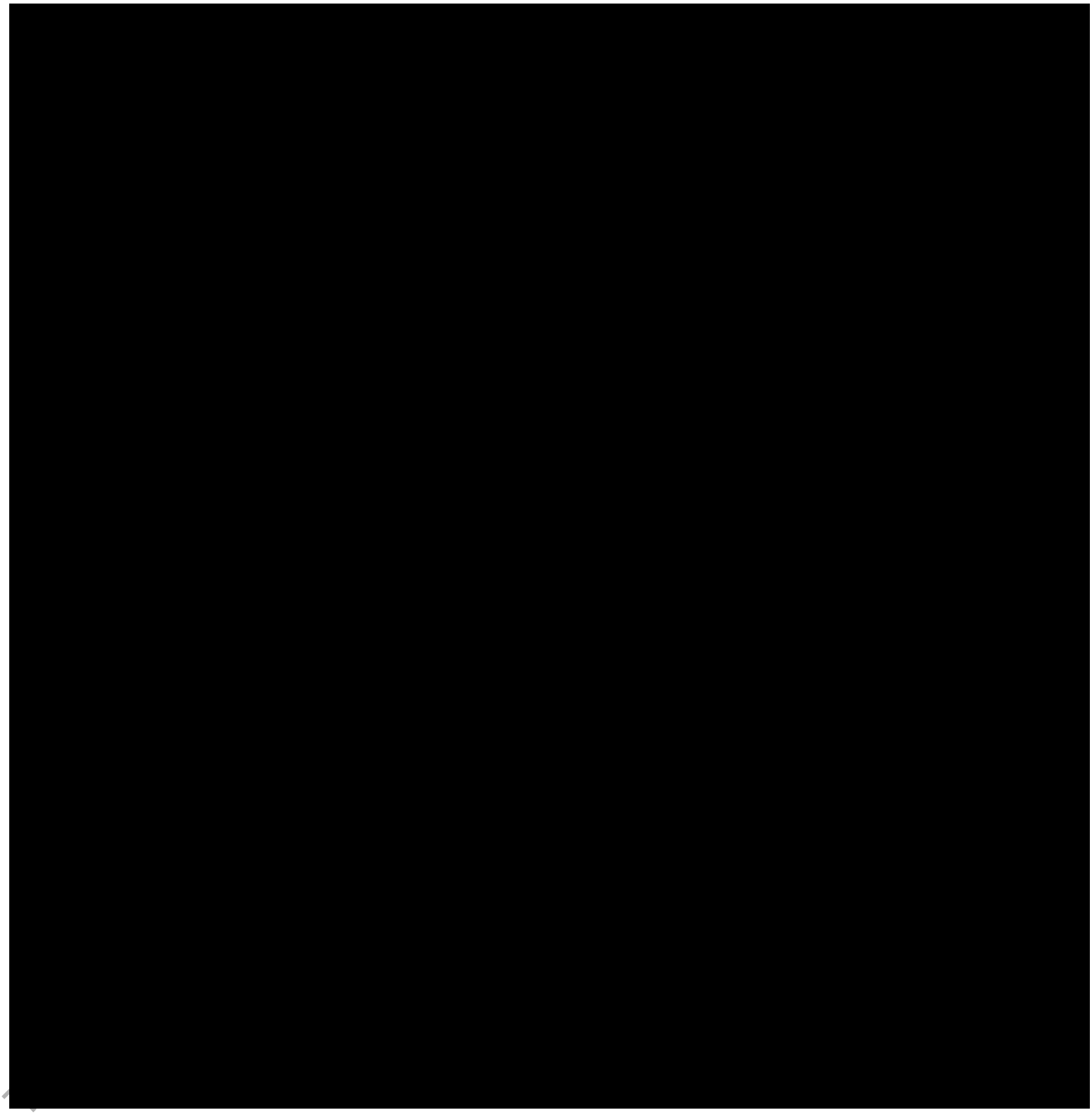
Status epilepticus

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.

[redacted]





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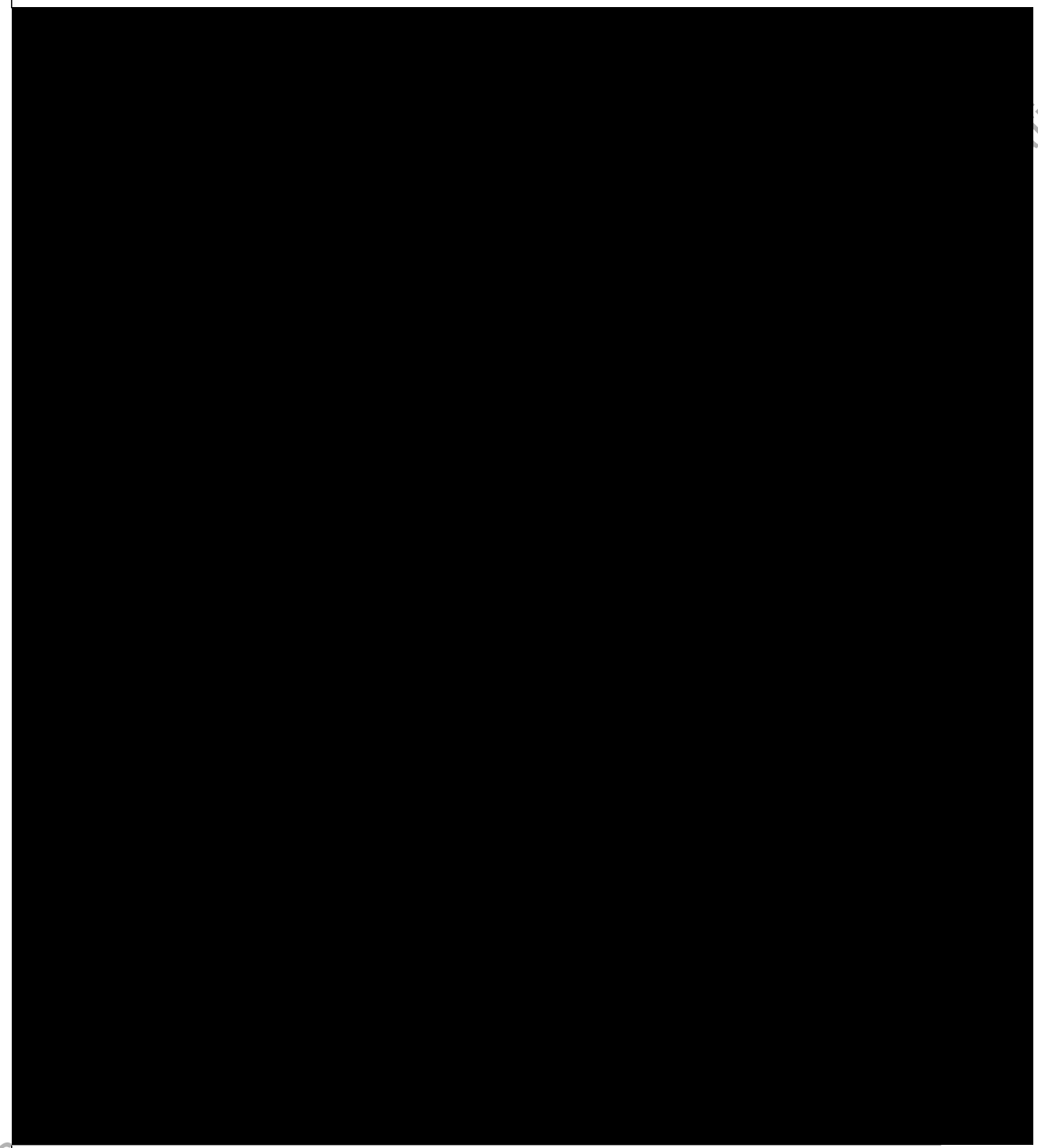

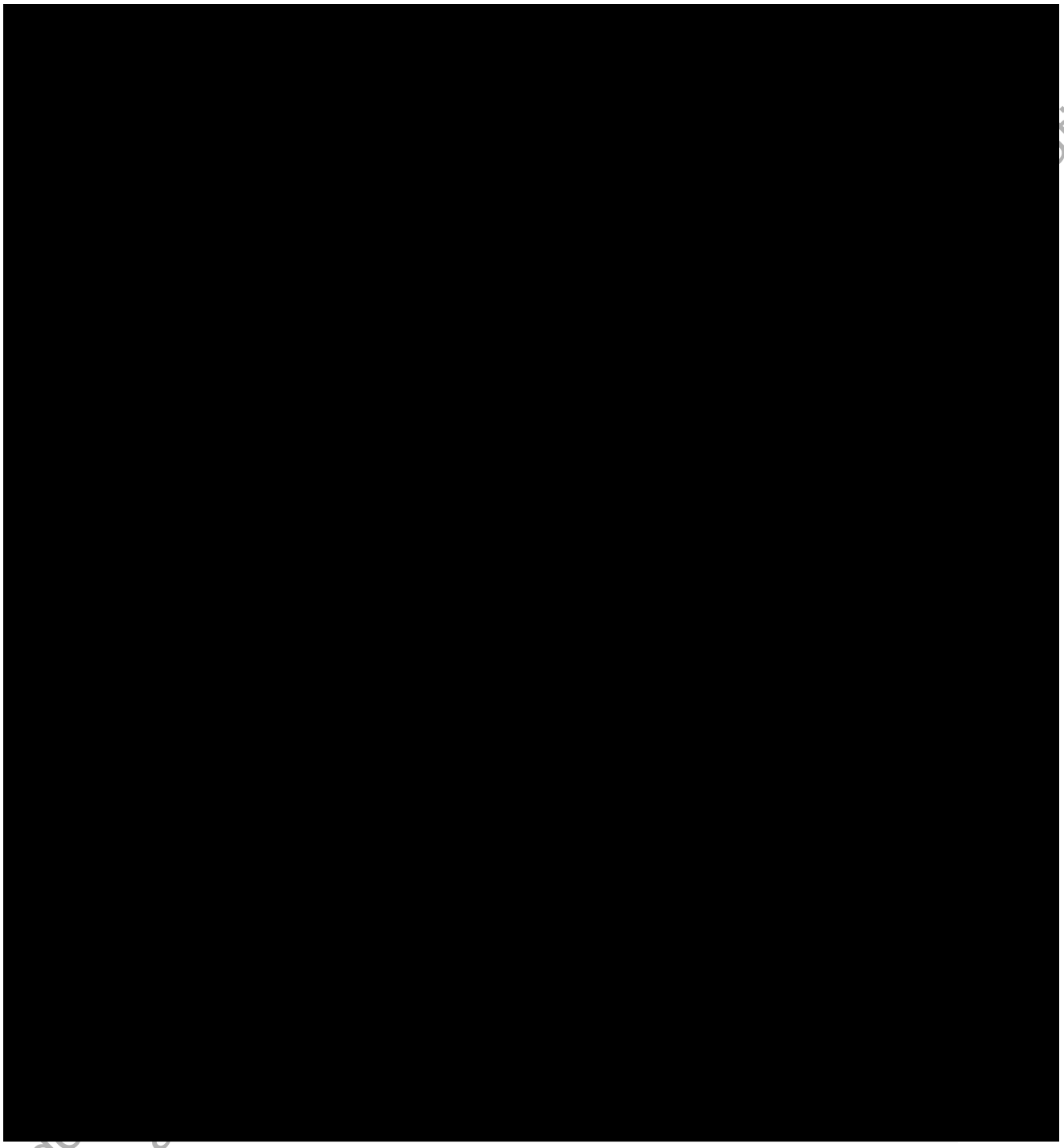

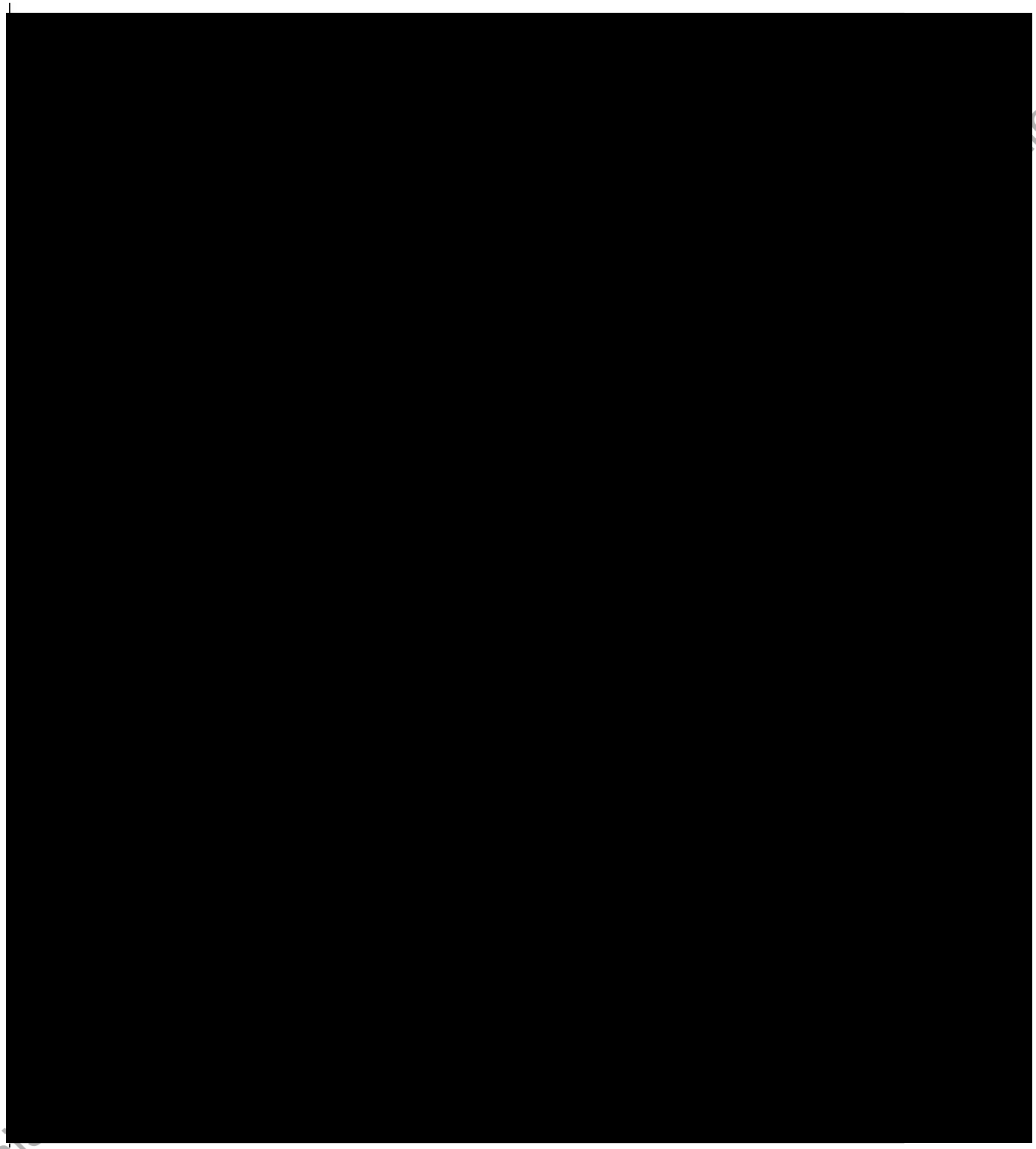

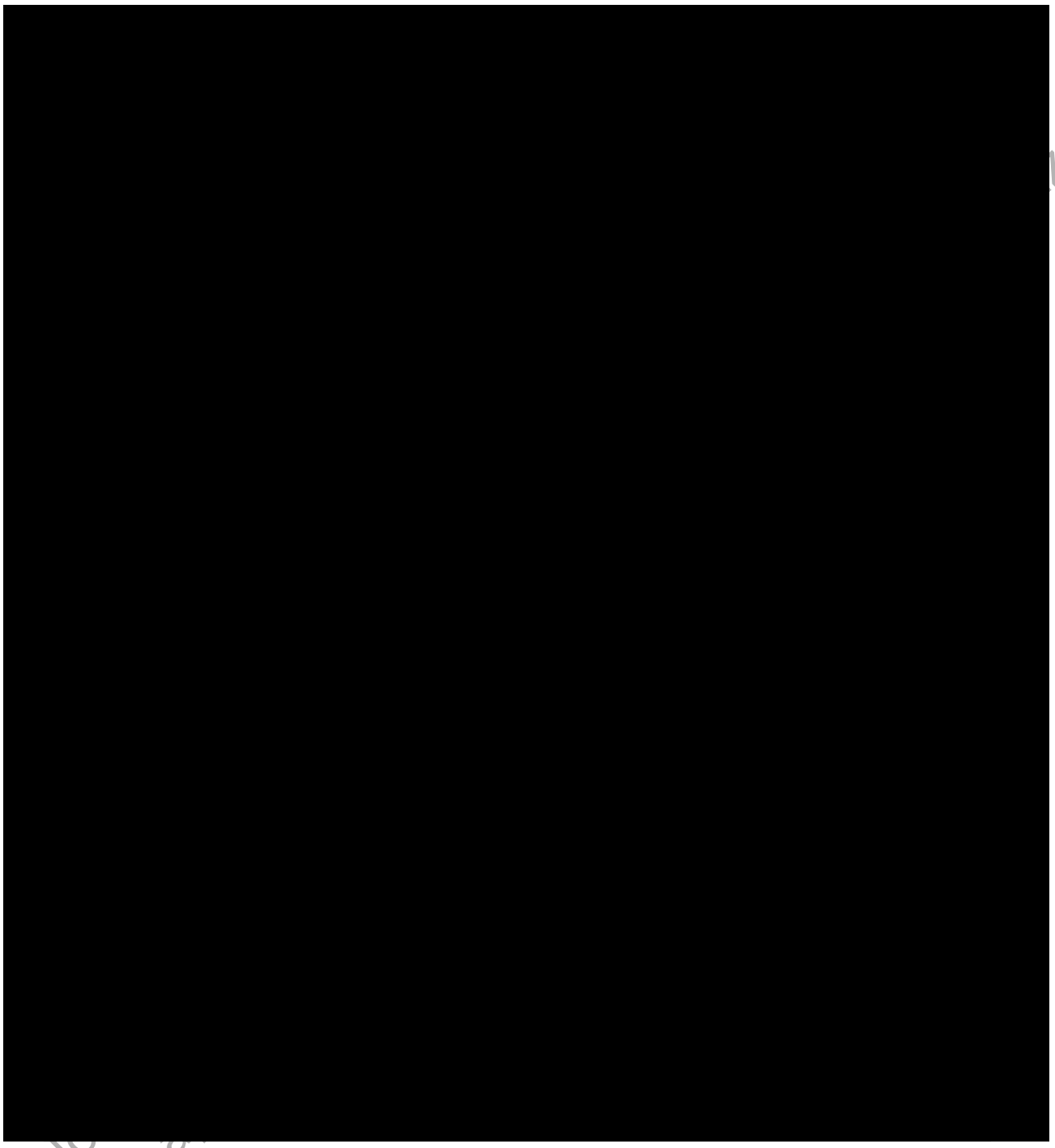

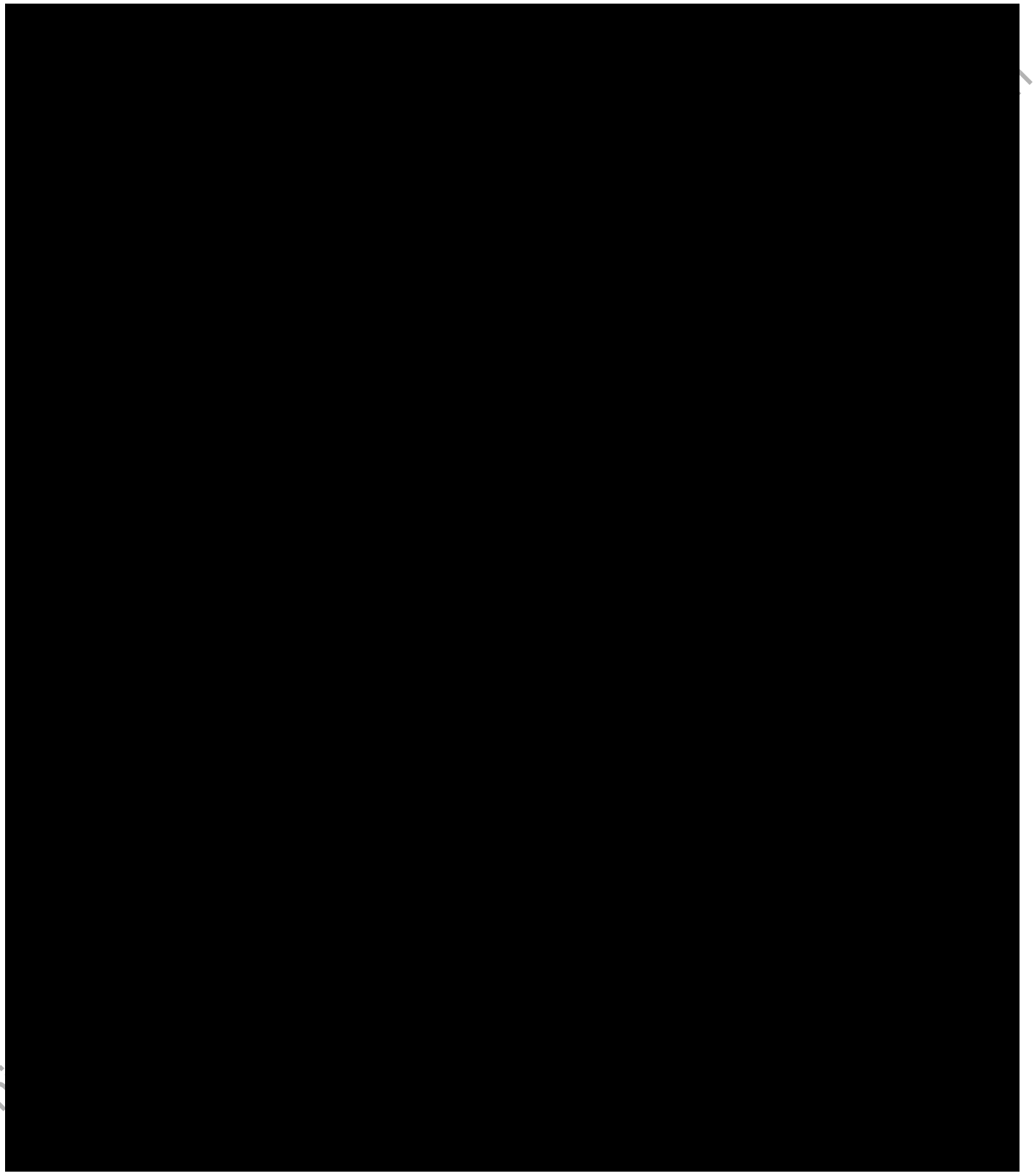

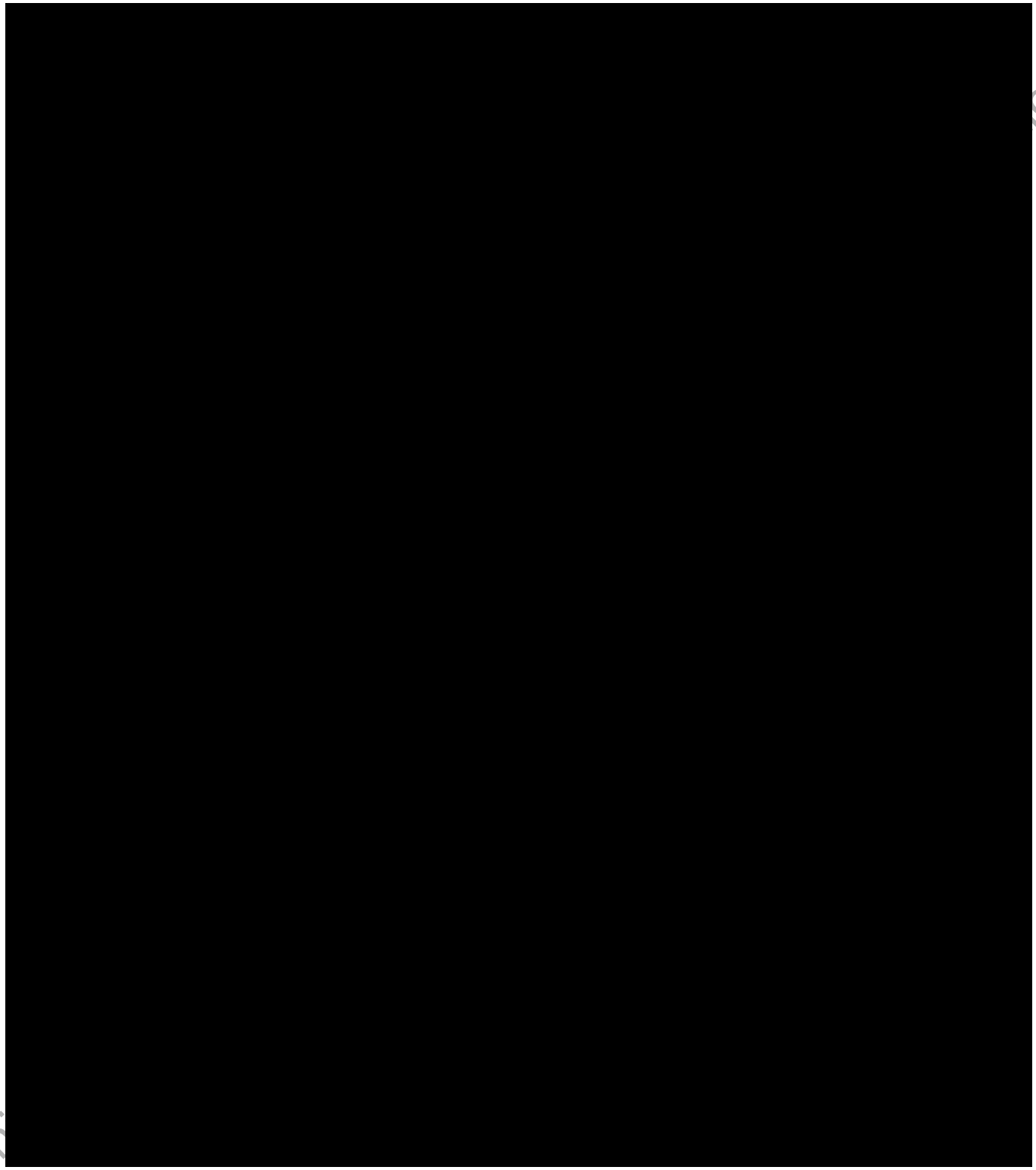

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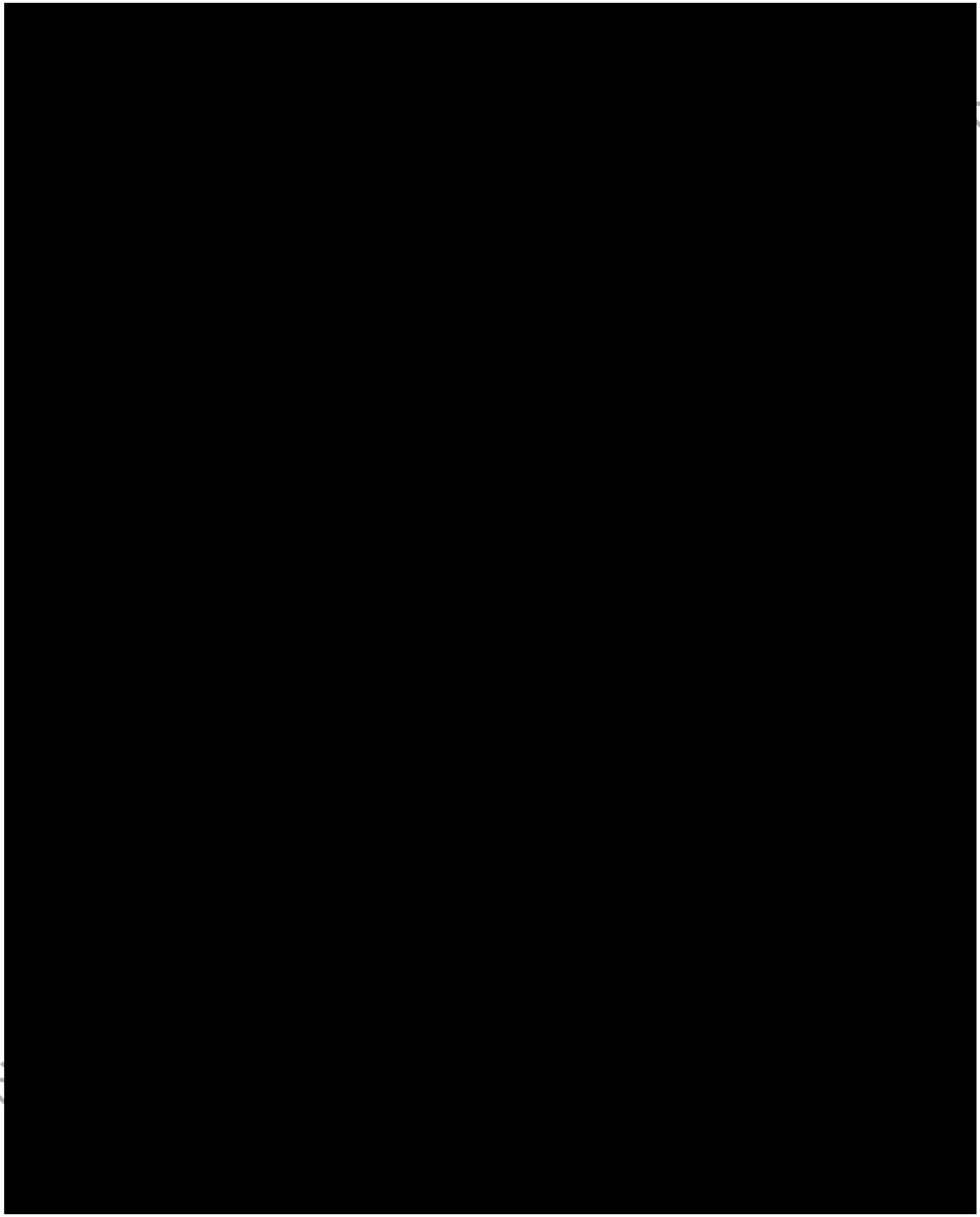

16.4 Appendix 4: Protocol Amendment 1

Rationale for the amendment

The primary purpose of this substantial amendment follows the amendment made to the SP0982 protocol, which is to identify significant changes to the study design and the inclusion of pediatric subjects (≥4 to 12 years of age).

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Duration of this study (EP0012) has been clarified as at least 2 years.
- Lacosamide plasma concentration analysis has been removed as it provides limited ability to interpret compliance and to perform an accurate PK modeling.
- Clarification on subjects being able to participate in a substudy at some sites, without being withdrawn from EP0012.
- For pediatric subjects <50kg, a Dispensation Visit has been added 12 weeks after each 24-weekly visit from Year 3 onwards, in order to dispense LCM solution.
- The use of concomitant medications and treatments has been clarified.
- Behavior Rating Inventory of Executive Function Preschool Version® (BRIEF-P®) has been added.
- Socio-professional data assessment has been removed in this study.
- Permitted and prohibited concomitant treatments have been clarified to be consistent with SP0982.
- In order to optimize study operations, ECGs will be evaluated locally and not centrally.
- Other changes made in this amendment are to provide clarification or are administrative in nature.

Specific changes

Change #1

Title page:

IND Number: 57939

Has been changed to:

IND Number (tablet): 57939

IND Number (oral solution): 73809

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	15 Oct 2012	Not applicable

Has been changed to:

Protocol/Amendment number	Date	Type of amendment
Final Protocol	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	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]
Address:	8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]
Fax:	[redacted]

Clinical Trial Biostatistician

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

Has been changed to:

Clinical Project Manager

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim

	GERMANY
Phone:	[redacted]
Fax:	[redacted]

Clinical Trial Biostatistician

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

Change #4

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 (24h)	
Fax	**Europe and Rest of the World (except Japan):** +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 (except Japan):** DSICT.-@ucb.com

Change #5

LIST OF ABBREVIATIONS

The following abbreviation has been added:

VAS visual analogue scale

Change #6

Section 1 SUMMARY

Paragraphs 1 through 8

This is a Phase 3, multicenter, open-label extension study designed to assess the long-term safety and efficacy of oral lacosamide (LCM, VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, AD 234037) as an adjunctive therapy for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects with idiopathic generalized epilepsy (IGE). This study will enroll subjects who have completed the LCM SP0982 study. In addition, subjects who completed the SP0982 Prospective Baseline Period and met all entry criteria except the minimum PGTC seizure criteria required for randomization into SP0982 may choose to enter EP0012 (eligible Baseline failures and completers are defined in Section 5.1). It is estimated that approximately 200 subjects across approximately 150 sites will be enrolled in EP0012. Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 400mg/day (200mg twice daily [bid]); subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 100mg/day (50mg bid). Investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction in a range from LCM 100mg/day to 800mg/day.

EP0012 will last up to approximately 6 years and consists of a Treatment Period and an End of Study Period lasting up to 5 weeks. During the Treatment Period, Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Visits will then occur every 8 weeks for the first year, every 4 months in the second year, and every 6 months thereafter until the end of the study. A telephone contact will occur every 8 weeks if no clinic visit is scheduled. The study duration and the total number of clinic visits will vary for each subject. Treatment will continue until LCM is commercially available in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until the sponsor decides to close the study.

Upon study completion, subjects must either transition to commercial LCM or taper off study drug. Subjects continuing treatment with commercial LCM will transition at their current dose. Subjects tapering off LCM will do so at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that safety concerns require a more rapid withdrawal of LCM.

Have been changed to:

This Phase 3, multicenter, open-label extension study is designed to assess the long-term safety and efficacy of oral lacosamide (LCM, VIMPAT®; SPM 927; previously referred to as harkoseride; (R) 2 acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) as an adjunctive therapy for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects ≥4 years of age with idiopathic generalized epilepsy (IGE). This study will enroll subjects who have completed the LCM SP0982 study. In addition, subjects who completed

the SP0982 Prospective Baseline Period and met all entry criteria except the minimum PGTC seizure criteria required for randomization into SP0982 may choose to enter EP0012 (eligible Baseline failures and completers are defined in Section 5.1). It is estimated that approximately 200 subjects across approximately 150 sites will be enrolled in EP0012.

Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg twice daily [bid]) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Baseline failures are required to complete Week 1 of dosing before LCM dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further LCM 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 target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets) within 14 days after Visit 1.

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects who have dose adjustments must remain on the dose for ≥3 days (in order to reach steady state) before a subsequent dose adjustment.

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4 week Taper Period, and a 30-day Safety Follow-Up Period. During the Treatment Period, Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinical visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur and every 24 weeks thereafter until the end of the study. From Year 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. The study duration and the total number of clinic visits will vary for each subject. At selected sites, subjects may also be able to participate in a substudy without withdrawing from EP0012. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or their parent(s)/legal representative(s).

Paragraph 10, third sentence:

In addition, for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function® [BRIEF®]).

Has been changed to:

In addition, for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function-Preschool Version® [BRIEF®/BRIEF-P®]).

Change #7

Section 2 INTRODUCTION

Paragraphs 1 through 3

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).

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 epilepsies can be further classified as primary/idiopathic and secondary/symptomatic epilepsies. Idiopathic generalized epilepsy is a category of disorders defined by strict clinical and electroencephalogram 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.

Have been changed to:

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). Epileptic seizures occur in the context of a wide range of epilepsy syndromes that may be of genetic, structural/metabolic, or unknown origin.

Generalized seizures are those in which the first clinical changes indicate initial involvement of both brain hemispheres. Consciousness typically is 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 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 in IGE is complex because the patient population is heterogeneous, as PGTC seizures can occur as an isolated seizure type or in association with other generalized seizure types.

Paragraph 5, first sentence

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);

Has been changed to:

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 (Bartolomei et al, 1997; Verrotti et al, 2007);

Paragraph 6

The following paragraph was deleted:

Of patients with IGE experiencing PGTC seizures, clinical experience has shown that up to 30% of patients 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.

Paragraph 8

The following paragraph was added:

Preliminary safety and PK data suggest that exposure-response in pediatric and adult subjects treated with LCM will be similar. Lacosamide is evaluated in pediatric subjects 1 month to 17

years of age in 2 completed studies and 1 ongoing study: SP847 (open-label, Phase 2, PK, tolerability, and safety study), SP1047 (PK study with a 1 day Evaluation Period), and SP848 (open-label long-term safety study).

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 patients 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 patients with IGE and uncontrolled PGTC seizures.

Paragraphs 11, 12, and 13

SP0961, the Phase 2, multicenter, open-label pilot study 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. 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, cannot be distinguished between the drug versus 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.

SP0982 is a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of LCM for uncontrolled PGTC seizures in subjects ≥12 years of age with IGE.

The current study (EP0012) will assess the long-term safety, tolerability, and efficacy of LCM and will enroll subjects who have completed SP0982 as well as eligible Baseline failures from SP0982. EP0012 will also allow subjects to receive LCM until it is approved for use in the subject's country for the treatment of PGTC seizures in IGE.

Have been changed to:

SP0961, the Phase 2, multicenter, open-label pilot study 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, cannot be distinguished between the drug versus 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.

SP0982 is a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of LCM for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE.

The current study (EP0012) will assess the long-term safety, tolerability, and efficacy of LCM and will enroll subjects who have completed SP0982 as well as eligible Baseline failures from SP0982. At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

Change #8

Section 4.1.2 Secondary safety variables

Secondary safety variables are:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, BP and pulse rate), including body weight and physical (including neurological) examination findings
- Achenbach CBCL
- Cognitive function assessment BRIEF

Has been changed to:

Secondary safety variables are:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, BP and pulse rate), including body weight and physical (including neurological) examination findings

Change #9

The following section has been added:

Section 4.1.3 Other safety variables

- Achenbach CBCL1½-5 or CBCL/6-18
- Cognitive function assessment BRIEF/BRIEF-P

Change #10

Section 4.2 Efficacy variables

Efficacy variables are:

- Percent change in PGTC seizure frequency per 28 days from Baseline, where Baseline is defined as the 12-week Historical Baseline and 4-week Prospective Baseline periods immediately prior to randomization in the parent study (SP0982)
- Percent change in days with myoclonic seizures per 28 days from Baseline

- Percent change in days with absence seizures per 28 days from Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency compared to Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Baseline
- Seizure-free status (yes/no) for PGTC seizures
- Seizure-free status (yes/no) for myoclonic seizures
- Seizure-free status (yes/no) for absence seizures
- Seizure-free status (yes/no) for all generalized seizure types
- 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
- EuroQol 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

Has been changed to:

Section 4.2.1 Primary efficacy variable

No primary efficacy variables are defined for this study.

Section 4.2.2 Secondary efficacy variable

The second efficacy variable is:

- Percent change in PGTC seizure frequency per 28 days from Baseline, where Baseline is defined as the 12-week Historical Baseline and 4-week Prospective Baseline periods immediately prior to randomization in the parent study (SP0982)

Section 4.2.3 Other efficacy variables

The other efficacy variables are:

- Percent change in days with myoclonic seizures per 28 days from Baseline
- Percent change in days with absence seizures per 28 days from Baseline

- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency compared to Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Baseline
- Seizure-free status (yes/no) for PGTC seizures
- Seizure-free status (yes/no) for myoclonic seizures
- Seizure-free status (yes/no) for absence seizures
- Seizure-free status (yes/no) for all generalized seizure types
- 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 in the 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

Change #11

The following section has been deleted

Section 4.3 Pharmacokinetic variables

The plasma concentrations of LCM will be assessed.

Change #12

Section 5.1 Study description

Paragraph 1

This is a multicenter, open-label extension study to assess the long-term safety and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTC seizures in subjects with IGE. This study will enroll consenting subjects who have completed the LCM SP0982 study as well as eligible Baseline failures from SP0982. Approximately 200 subjects from approximately 150 study sites will be enrolled in EP0012. For the purposes

of this study Baseline failures and study completers from SP0982 who are eligible for inclusion are defined as:

Has been changed to:

This is a multicenter, open-label extension study to assess the long-term safety and change in seizure frequency associated with long-term adjunctive oral LCM for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE. This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 study as well as eligible Baseline failures from SP0982. Approximately 200 subjects from approximately 150 study sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, and study completers from SP0982 who are eligible for inclusion in EP0012 are defined as:

Paragraph 2, bulleted items

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTC seizure criteria required for randomization (Baseline failures)
- Subjects who complete the end of the first 5 weeks of the Treatment Period (after randomization) of SP0982 and have experienced at least 2 PGTC seizures during that time or
- Subjects who experience a second PGTC seizure after the first 5 weeks of the Treatment Period of SP0982 or
- Subjects who do not have 2 PGTC seizures within the 24-week Treatment Period of SP0982

Have been changed to:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTC seizure criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTC seizures during that time or
- Subjects who experience a second PGTC seizure after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period of SP0982

Paragraph 3

Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 400mg/day (200mg bid); subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 100mg/day (50mg bid). During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject. The LCM dose may be adjusted after the subject receives the first dose of LCM in the study. Lacosamide doses may be increased up to a maximum of LCM 800mg/day or decreased to a minimum of LCM 100mg/day at the discretion of the investigator. A clinic visit (scheduled or unscheduled) is required the first time the dose is increased to LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, and LCM 800mg/day. One week after the first time the dose is increased to LCM 700mg/day or LCM 800mg/day, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Has been changed to:

Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Baseline failures are required to complete Week 1 of dosing before LCM dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further LCM 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 target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets) within 14 days after Visit 1.

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects who have dose adjustments must remain on the dose for ≥3 days (in order to reach steady state) before a subsequent dose adjustment.

To optimize tolerability and seizure reduction, the LCM dose may be increased or decreased at the investigator's discretion after the subject receives the first dose of LCM in the study (see Table 7–1). Baseline failures must complete Week 1 of dosing before LCM may be increased or decreased. The maximum dose for pediatric subjects weighing <50kg is 12mg/kg/day (oral solution). The maximum dose for pediatric subjects weighing ≥50kg is 600mg/day (tablets) and for adult subjects is 800mg/day (tablets).

A clinic visit (scheduled or unscheduled) is required if:

- The dose is increased for the first time to any dose above 10mg/kg/day for pediatric subjects weighing <50 kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.
- The dose is increased for the first time to any dose above LCM 400mg/day for all adult subjects or pediatric subjects weighing ≥50kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Paragraph 8

EP0012 will last up to approximately 6 years and consists of a Treatment Period and an End of Study Period lasting up to 5 weeks. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers. Eligible Baseline failures who choose to enter EP0012 will undergo a complete Visit 1 in EP0012. Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinical visits will then occur every 8 weeks for the first year, every 4 months in the second year, and every 6 months thereafter until the end of the study. A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs. The study duration and the total number of clinic visits will vary for each subject. Treatment will continue until LCM is commercially available in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until the sponsor decides to close the study.

Has been changed to:

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1. Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinic visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur and every 24 weeks thereafter until the end of the study. From Year 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs, as well as to ensure subjects are compliant with LCM administration and diary completion. The study duration and the total number of clinic visits will vary for each subject. At selected sites, subjects may also be able to participate in a substudy without withdrawing from EP0012. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

Paragraph 9, first sentence

Subjects will be dispensed a seizure diary to record all types of seizures, concomitant AEDs, and other pertinent health status information.

Has been changed to:

Subjects and/or their caregiver will be dispensed a seizure diary to record all types of seizures, concomitant AEDs, and other pertinent health status information.

Paragraphs 10 to 12

New concomitant AEDs may be introduced to optimize treatment, if the concomitant medication has been approved by the regulatory authority in the subject's country. New AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

Upon study completion, subjects must either transition to commercially available LCM or taper off study drug. Subjects continuing treatment with commercially available LCM will transition at their current dose.

Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent/legal guardian. Subjects tapering off LCM will do so at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that safety concerns require a more rapid withdrawal of LCM. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. The Medical Monitor should be contacted if a more rapid withdrawal is required. A Final Clinic Visit will occur 2 weeks after the final LCM dose for subjects who taper off LCM.

Have been changed to:

New concomitant AEDs may be introduced to optimize treatment, if the concomitant medication has been approved by the regulatory authority for the respective patient indication in the subject's country. New AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or their parent(s)/legal representative(s).

Change #13

Section 5.1.1 Study duration per subject

Paragraph 1

For each subject, the study will last from study entry until LCM is commercially available in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until the sponsor decides to close the study. It is anticipated that up to approximately 6 years of treatment will be performed to allow for the collection of long-term safety data. If LCM is not commercially available in the subject's country at the time the sponsor closes the study, access to LCM will be provided according to local laws.

Has been changed to:

For each subject, the study will last from study entry until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until the sponsor decides to close the study. It is anticipated that at least 2 years of treatment will be performed to allow for the collection of long-term safety data. If LCM is not approved for use in the subject's country at the time the sponsor closes the study, access to LCM will be provided according to local laws.

Paragraph 2

The following study periods are defined:

- A Treatment Period lasting up to approximately 6 years.
- An End of Study Period lasting up to 5 weeks.
  - Subjects continuing LCM treatment with commercial LCM will transition at their current dose (received in the Treatment Period).
  - Subjects tapering off LCM will do so over 1 to 3 weeks (see taper schedule, Table 7-1).
  - A Final Clinic Visit will occur 2 weeks after the final LCM dose for subjects who taper off LCM.

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 following study periods are defined:

- A Treatment Period lasting at least 2 years.
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator.
  - Subjects tapering off LCM will do so over a period of up to 4 weeks (see Taper Schedule, Table 7-2).
  - An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. 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 end of the study is defined as the date of the last visit/telephone contact of the last subject in the study.

Depending on the local regulations, after 2 years, subjects may continue to receive LCM in a named patient program.

Change #14

Section 5.1.2 Planned number of subjects and site(s)

Approximately 200 subjects across approximately 150 international sites will be eligible to enroll in this study.

Has been changed to:

Approximately 200 subjects across approximately 150 international sites are planned to be enrolled in this study.

Change #15

Section 5.1.3 Anticipated regions and countries

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

Has been changed to:

This 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

The schedule of study assessments for treatment Years 1 to 2 is provided in Table 5–1. An additional schedule of study assessments for treatment Years 3 to 6 is provided in Table 5–2.

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012

	Treatment Period[a]												End of Study Period			Unscheduled[b]
Duration	**Open-label: up to approximately 6 years**												**Up to 5 weeks[c]**			**NA**
Year of study	**Year 1**								**Year 2**							
Visit[d]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Telephone contact[e]**	**V9**	**V10**	**V11**	**ET Visit[f]**	**Termination Visit[g]**	**Final Clinic Visit[h]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**2 weeks after final LCM dose**	**NA**
Informed Consent/Assent	X															
Inclusion/Exclusion criteria	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 update	X															
Physical exam (complete)[i]	X*									X			X	X		
Physical exam (brief)[j]		X	X	X	X	X	X	X			X	X				X
Neurological exam (complete)[k]	X*									X			X	X		
Neurological exam (brief)[l]		X	X	X	X	X	X	X			X	X				X
12-lead ECG[m]	X*	X	X	X				X				X	X	X		

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012

	Treatment Period[a]												End of Study Period			Unscheduled[b]
Duration	**Open-label: up to approximately 6 years**												**Up to 5 weeks[c]**			**NA**
Year of study	**Year 1**								**Year 2**							
Visit[d]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Telephone contact[e]**	**V9**	**V10**	**V11**	**ET Visit[f]**	**Termination Visit[g]**	**Final Clinic Visit[h]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**2 weeks after final LCM dose**	**NA**
Vital signs (BP and pulse) including orthostatic assessments[n]	X*	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Body weight and height[o]	X*			X		X		X		X	X	X	X	X	X	
Tanner Stage[p]	X				X			X			X	X	X	X		
Laboratory tests	X*	X	X	X		X		X		X	X	X	X	X		
Pregnancy test[q]	X*	X	X	X	X	X	X	X		X	X	X	X	X	X	
LCM plasma concentration[r]		X				X							X	X		
Call IVRS/IWRS	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
C-SSRS	X*	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Dispense subject diary	X	X	X	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	X	X	X
Dispense LCM	X	X	X	X	X	X	X	X		X	X	X	X	X		
LCM review/return		X	X	X	X	X	X	X		X	X	X	X	X		
Withdrawal criteria	X*	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012

	Treatment Period[a]												End of Study Period			Unscheduled[b]
Duration	**Open-label: up to approximately 6 years**												**Up to 5 weeks[c]**			**NA**
Year of study	**Year 1**								**Year 2**							
Visit[d]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Telephone contact[e]**	**V9**	**V10**	**V11**	**ET Visit[f]**	**Termination Visit[g]**	**Final Clinic Visit[h]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**2 weeks after final LCM dose**	**NA**
AE reporting	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-3L	X				X					X			X	X		
QOLIE-31-P/PedsQL[s]	X				X			X		X		X	X	X		
Achenbach CBCL[t]	X				X			X		X		X	X	X		
BRIEF[u]	X				X			X		X		X	X	X		
Healthcare resource use	X*	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	X		
Days with help from a caregiver	X*	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; BRIEF=Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-3L=EuroQol-5 Dimension Quality of Life Assessment; ET=early termination; exam=examination; ID=identification; IVRS/IWRS=interactive voice/web response system; LCM=lacosamide; NA=not applicable; PedsQL=Pediatric Quality of Life Inventory; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; V=Visit; W=Week

Note: For subjects who have completed SP0982, assessments marked (*) should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1; for eligible Baseline failures from SP0982, a full Visit 1 is required including all scheduled tasks and procedures.

[a] The Treatment Period will continue for up to approximately 6 years or until LCM is otherwise available (eg, commercially), whichever is earlier.

[b] Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments listed 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.

[c] For subjects requiring taper, the LCM dose will be reduced by 200mg/day per week until discontinued, unless the investigator feels that safety concerns require a more rapid withdrawal of LCM. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary.

[d] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[e] Telephone contacts are required every 8 weeks during the study, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, and Week 86.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper and a Final Clinic Visit.

[g] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 19 if appropriate (see Table 5-2). For subjects who will not continue on LCM, this visit will be followed by LCM taper and a Final Clinic Visit. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[h] A Final Clinic Visit must be completed for all subjects who taper off LCM.

[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 assessment of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.

[m] The brief neurological examination will include selected assessment 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] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

[p] Height will be recorded at Visits 1 and 9, and at the ET and Termination Visit.

[q] The Tanner Stage will be performed only for subjects who are <18 years of age.

[r] Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, Termination Visit and Final Clinic Visit. All other pregnancy tests 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] 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. For each developmentally appropriate version of the PedsQL subjects must have at least 1 year of data before transitioning to the next age range.

[u] 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).

[v] The BRIEF should be used for subjects ≥12 to <18 years of age. For each developmentally appropriate version of the BRIEF subjects must have at least 1 year of data before transitioning to the next age range.

Table 5–2: Schedule of study assessments for Years 3 through 6 for EP0012

	Treatment Period[a]									End of Study Period			Unscheduled[b]
Duration	**Open-label: up to approximately 6 years**									**Up to 5 weeks[c]**			**NA**
Year of study	**Year 3**			**Year 4**		**Year 5**		**Year 6**					
Visit[d]	**Telephone contact[e]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19/ Term[f]**	**ET Visit[g]**	**Termination Visit[h]**	**Final Clinic Visit[i]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**262**	**286**			**2 weeks after final LCM dose**	**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (complete)[j]		X		X		X		X	X	X	X		
Physical exam (brief)[k]			X		X		X						X
Neurological exam (complete)[l]		X		X		X		X	X	X	X		
Neurological exam (brief)[m]			X		X		X						X
12-lead ECG[n]			X		X		X		X	X	X		
Vital signs (BP and pulse) including orthostatic assessments[o]		X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[p]		X	X	X	X	X	X	X	X	X	X	X	
Tanner Stage[q]		X	X	X	X	X	X	X	X	X	X		
Laboratory tests		X	X	X	X	X	X	X	X	X	X		
Pregnancy test[r]		X	X	X	X	X	X	X	X	X	X	X	
LCM plasma concentration[s]										X	X		
Call IVRS/IWRS		X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject diary		X	X	X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of study assessments for Years 3 through 6 for EP0012

	Treatment Period[a]									End of Study Period			Unscheduled[b]
Duration	**Open-label: up to approximately 6 years**									**Up to 5 weeks[c]**			**NA**
Year of study	**Year 3**			**Year 4**		**Year 5**		**Year 6**					
Visit[d]	**Telephone contact[e]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19/ Term[f]**	**ET Visit[g]**	**Termination Visit[h]**	**Final Clinic Visit[i]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**262**	**286**			**2 weeks after final LCM dose**	**NA**
Dispense LCM		X	X	X	X	X	X	X	X	X	X		
LCM 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
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-3L		X		X		X		X	X	X	X		
QOLIE-31-P/PedsQL[t]		X	X	X	X	X	X	X	X	X	X		
Achenbach CBCL[u]		X	X	X	X	X	X	X	X	X	X		
BRIEF[v]		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			

AE=adverse event; AED=antiepileptic drug; bid=twice daily; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-3L=EuroQol-5 Dimension Quality of Life Assessment; ET=early termination; exam=examination; IVRS/IWRS=interactive voice/web response system; LCM=lacosamide; NA=not applicable; PedsQL=Pediatric Quality of Life Inventory; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; Term=Termination; V=Visit; W=Week

[a] The Treatment Period will continue for up to approximately 6 years or until LCM is otherwise available (eg, commercially), whichever is earlier.

[b] Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments listed 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.

[c] For subjects requiring taper, the LCM dose will be reduced by 200mg/day per week until discontinued, unless the investigator feels that safety concerns require a more rapid withdrawal of LCM. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary.

[d] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[e] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230; Year 6 - Week 246, Week 254, Week 270, Week 278.

[f] At the completion of the study, subjects will choose to continue commercially available LCM (depending on launch and country availability) or taper off LCM until it has been discontinued.

[g] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper and a Final Clinic Visit.

[h] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 19 if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper and a Final Clinic Visit. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[i] A Final Clinic Visit must be completed for all subjects who taper off LCM.

[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 assessment of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.

[m] The brief neurological examination will include selected assessment 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] Blood pressure measurements should be taken with the proper placement and proper sized cuff to obtain accurate measurements.

[p] Height will be recorded at Visits 12, 14, 16 and 18, and at the ET and Termination Visit.

[q] The Tanner Stage will be performed only for subjects who are <18 years of age.

[r] Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, Termination Visit and Final Clinic Visit. All other pregnancy tests 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] 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. For each developmentally appropriate version of the PedsQL subjects must have at least 1 year of data before transitioning to the next age range.

[u] 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).

[v] The BRIEF should be used for subjects ≥12 to <18 years of age. For each developmentally appropriate version of the BRIEF subjects must have at least 1 year of data before transitioning to the next age range.

Has been changed to:

The schedule of study assessments for treatment Years 1 to 2 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5–1. An additional schedule of study assessments for treatment Years 3 to 5 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5–2. The schedule of study assessments for the Taper and Safety Follow-Up is provided in Table 5-3.

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit and Unscheduled Visit)

	Treatment Period[a]														Unscheduled[b]
Duration	**Open-label: at least 2 years**														**NA**
Year of study	**Year 1**								**Year 2**						
Visit[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Telephone Contact[d]**	**V9**	**V10**	**V11**	**ET Visit[e]**	**Termination Visit[f]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**NA**
Informed Consent/Assent	X														
Inclusion/Exclusion criteria	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 update	X														
Physical exam (complete)[g]	X*							X				X	X	X	
Physical exam (brief)[h]		X	X	X	X	X	X			X	X				X
Neurological exam (complete)[i]	X*							X		X		X	X	X	
Neurological exam (brief)[j]		X	X	X	X	X	X				X				X
12-lead ECG[k]	X*	X		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	X	X	X	X
Body weight and height[m]	X*			X		X		X		X	X	X	X	X	
Tanner Stage[n]	X							X				X	X	X	
Laboratory tests[o]	X*	X			X			X		X	X	X	X	X	
Pregnancy test[p]	X*	X	X	X	X	X	X	X		X	X	X	X	X	

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit and Unscheduled Visit)

	Treatment Period[a]														Unscheduled[b]
Duration	Open-label: at least 2 years														NA
Year of study	Year 1								Year 2						
Visit[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Telephone Contact[d]**	**V9**	**V10**	**V11**	**ET Visit[e]**	**Termination Visit[f]**	**Unscheduled Visit**
Week	**0**	**2**	**6**	**14**	**22**	**30**	**38**	**46**		**62**	**78**	**94**			**NA**
Call IVRS/IWRS	X	X	X	X	X	X	X	X		X	X	X	X	X	X
C-SSRS[q]	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Dispense subject diary	X	X	X	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	X	X
Dispense LCM	X	X	X	X	X	X	X	X		X	X	X	X	X	
LCM review/return		X	X	X	X	X	X	X		X	X	X	X	X	
Withdrawal criteria	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE reporting	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-3L	X				X			X		X		X	X	X	
QOLIE-31-P/PedsQL[r]	X				X			X		X		X	X	X	
Achenbach CBCL[s]	X				X			X		X		X	X	X	
BRIEF-P/BRIEF[t]	X				X			X		X		X	X	X	
Healthcare resource use	X*	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	X	
Days with help from a caregiver	X*	X	X	X	X	X	X	X		X	X	X	X	X	

AE=adverse event; AED=antiepileptic drug; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-3L=3-level EuroQol-5 Dimension Quality of Life Assessment; ET=early termination; exam=examination; ID=identification; IVRS/IWRS=interactive voice/web response system; LCM=lacosamide; NA=not applicable; PedsQL=Pediatric Quality of Life Inventory; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; V=Visit; W=Week

Note: For subjects who have completed SP0982, assessments marked (*) should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1; for eligible Baseline failures from SP0982, a full Visit 1 is required including all scheduled tasks and procedures.

[a] The Treatment Period will continue for at least 2 years.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, and Week 86.

[e] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-3.

[f] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 17 if appropriate (see Table 5–2). For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-3. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[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 assessment of mental status, sensory systems, motor functions, cranial nerves, reflexes, and coordination/cerebellar function.

[j] The brief neurological examination will include selected assessment 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) a 12-lead ECG (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] Height will be recorded at Visits 1 and 9, and at the ET and Termination Visit.

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

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

[p] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick.

[q] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.7.3).

[r] 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 PedsQL form appropriate for each subject's age should be completed, with the following exception: if a subject ages up to the next form of the PedsQL within 1 year after the Baseline assessment of the primary study, the form that was used at the Baseline assessment should be completed for 1 year after the Baseline

assessment, and subsequently the form consistent with his/her age at the time of assessment should be completed. For each version of the PedsQL subjects must have at least 1 year of data before transitioning to the next age range (see Section 9.2.1).

[s] The Achenbach CBCL: CBCL/1½-5 for children 18 months to 5 years and 11 months of age and CBCL/6-18 for children ≥6 years to <18 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). The version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: for subjects who completed the CBCL/1½-5 at the Baseline assessment of the previous study and turn 6 years of age within 1 year after the Baseline assessment of the primary study, the CBCL/1½-5 should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the CBCL/6-18 should be completed. The Achenbach CBCL will only be administered in countries where a validated translated version is available. For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range. The Achenbach CBCL should be completed by the same parent/legal representative, if possible (see Section 10.7.6).

[t] The BRIEF-P should be used for subjects who are <5 years of age at Visit 1, and the BRIEF should be used for subjects who are ≥5 years of age at Visit 1. For each developmentally appropriate version of the BRIEF, subjects must have at least 1 year of data before transitioning to the next age range (see Section 10.7.7).

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit and Unscheduled Visit)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit[h]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X		X
Physical exam (complete)[i]			X		X		X	X			
Physical exam (brief)[j]		X		X		X			X		X
Neurological exam (complete)[k]			X		X		X	X			
Neurological exam (brief)[l]		X		X		X			X		X
12-lead ECG[m]		X	X	X	X	X	X	X	X		
Vital signs (BP and pulse) including orthostatic assessments[n]		X	X	X	X	X	X	X	X		X
Body weight and height[o]		X	X	X	X	X	X	X	X		
Tanner Stage[p]			X		X		X	X	X		
Laboratory tests		X	X	X	X	X	X	X	X		
Pregnancy test[q]		X	X	X	X	X	X	X	X		
Call IVRS/IWRS		X	X	X	X	X	X	X	X		X
C-SSRS[r]		X	X	X	X	X	X	X	X		X
Dispense subject diary		X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit and Unscheduled Visit)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit[h]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**
LCM review/return		X	X	X	X	X	X	X	X	X	
Withdrawal criteria	X	X	X	X	X	X	X	X	X		X
AE reporting	X	X	X	X	X	X	X	X	X		X
EQ-5D-3L		X	X	X	X	X	X	X	X		
QOLIE-31-P/PedsQL[s]		X	X	X	X	X	X	X	X		
Achenbach CBCL[t]		X	X	X	X	X	X	X	X		
BRIEF[u]		X	X	X	X	X	X	X	X		
Healthcare resource use		X	X	X	X	X	X	X	X		
Work/school days lost		X	X	X	X	X	X	X	X		
Days with help from a caregiver		X	X	X	X	X	X	X	X		

AE=adverse event; AED=antiepileptic drug; 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; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-3L=3-level EuroQol-5 Dimension Quality of Life Assessment; ET=early termination; exam=examination; IVRS/IWRS=interactive voice/web response system; LCM=lacosamide; NA=not applicable; PedsQL=Pediatric Quality of Life Inventory; QOLIE-31-P=Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; Term=Termination; V=Visit; W=Week

[a] The Treatment Period will continue for at least 2 years.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230.

[e] At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-3.

[g] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 17 if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-3. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[h] Dispensation Visit will occur 12 weeks after each 24-weekly visit from Year 3 onwards and will be for the purpose of dispensing LCM solution for pediatric subjects <50kg.

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

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

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

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

[m] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[o] Height will be recorded at Visits 12, 14, and 16, and at the ET and Termination Visit.

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

[q] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick.

[r] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.7.3).

[s] 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. For each version of the PedsQL subjects must have at least 1 year of data before transitioning to the next age range (see Section 9.2.1).

[t] The Achenbach CBCL: CBCL/6-18 for children ≥6 years to <18 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range. The Achenbach CBCL should be completed by the same parent/legal representative, if possible (see Section 10.7.6).

[u] The BRIEF should be used for subjects who are ≥5 years of age. For each developmentally appropriate version of the BRIEF, subjects must have at least 1 year of data before transitioning to the next age range (see Section 10.7.7).

The following table has been added:

Table 5–3: Schedule of study assessments (Taper Period and Safety Follow-Up Period) for EP0012

Assessment	Taper Period[a] (up to 4 weeks)	Safety Follow-Up Period[b]	
	End of Taper Visit[c]	Safety Follow-Up Visit	Safety Follow-Up TC
		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)	X	X	
Neurological exam (complete)	X	X	
12-lead ECG[d]	X	X	
Vital signs (BP and pulse) including orthostatic assessments	X	X	
Body weight	X	X	
Laboratory tests:			
Chemistry/hematology	X	X[e]	
Endocrinology		X[e]	
Urine pregnancy test[f]	X	X	
Contact IVRS/IWRS	X		
Subject diary return/review[g]	X		
LCM review/return	X		
Withdrawal criteria	X		
AE reporting	X	X	X
C-SSRS[h]	X	X	
Healthcare resource use	X	X	
Work/school days lost	X	X	
Days with help from a caregiver	X	X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; IVRS/IWRS= interactive voice/web response system; LCM=lacosamide; TC=telephone contact

[a] All subjects who discontinue LCM must complete the End of Taper Visit.

[b] 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 Visit.

[c] 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 7-2. 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 place at the ET or Termination Visit.

[d] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[f] Pregnancy tests will be performed for female subjects of childbearing potential only. A urine pregnancy test will be performed.

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

[h] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.7.3).

Change #17

Section 5.3 Rationale for study design and selection of dose

Paragraph 2

The efficacy, safety, and tolerability of LCM as an adjunctive therapy have been demonstrated in the partial-onset seizure population. The approach for further LCM development is to evaluate the use of adjunctive LCM for the treatment of uncontrolled PGTC seizures in patients with IGE. The maximum dose of LCM 800mg/day is the highest dose that has been used in previous clinical studies. Preclinical evaluations of LCM in animal models of generalized seizures indicate that LCM may be an effective treatment. However, 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 (eg, myoclonic seizures, absence seizures). Primary generalized tonic-clonic seizures may also occur in such distinct syndromes as benign myoclonic epilepsy in infancy, juvenile myoclonic epilepsy, epilepsy with PGTC seizures on awakening, childhood and juvenile absence epilepsy, and reflex-induced PGTC seizures. Typically, PGTC seizures present initially in childhood, adolescence, or early adulthood.

Has been changed to:

The efficacy, safety, and tolerability of LCM as an adjunctive therapy have been demonstrated in the partial onset seizure population. The approach for further LCM development is to evaluate the use of adjunctive LCM for the treatment of uncontrolled PGTC seizures in patients with IGE.

Paragraph 3

The goal of the Phase 3 LCM PGTC seizure program is to provide clinical evidence of the efficacy and safety of LCM as an adjunctive therapy for uncontrolled PGTC seizures in subjects with IGE as the basis for approval of this indication. SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed 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 goal of the Phase 3 LCM PGTC seizure program is to provide clinical evidence of the efficacy and safety of LCM as an adjunctive therapy for uncontrolled PGTC seizures in subjects

with IGE as the basis for approval of this indication. SP0982 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of LCM for uncontrolled PGTC seizures in subjects ≥4 years of age with IGE. EP0012 will provide continued availability of LCM to subjects who have completed SP0982 and eligible Baseline failures from SP0982.

Paragraph 4

The following paragraph has been added:

For adult subjects (≥18 years of age), 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. The maximum dose of LCM 800mg/day is the highest dose that has been used in previous clinical studies. Dose selection in EP0012 is based on the primary study (SP0982). During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject. Lacosamide doses may be increased up to a maximum of LCM 12mg/kg/day (oral solution) for pediatric subjects weighing <50kg. The maximum dose for pediatric subjects (<18 years of age) ≥50kg is 600mg/day (tablets) and for adult subjects is 800mg/day (tablets).

Change #18

Section 6.2 Exclusion criteria

Exclusion criterion 3

3. 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.

Has been changed to:

3. Subject has an active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional.

Change #19

Section 6.3 Withdrawal criteria

Paragraph 2

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

- Subject develops second or third degree atrioventricular (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.
- A prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the investigator as serious enough to warrant discontinuation from the study.
- In the case of liver function test (LFT) results of transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) ≥3x upper limit of normal (ULN) 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 has actual suicidal ideation since last visit as indicated by a positive response "Yes" to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Has been changed to:

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

1. The subject develops second or third degree atrioventricular (AV) block.
2. The subject becomes pregnant, as evidenced by a positive pregnancy test.
3. The sponsor or a regulatory agency requests withdrawal of the subject.
4. The subject is unwilling or unable to continue, or the legal representative is unwilling or unable to allow the subject to continue in the study.
5. In the case of liver function test (LFT) results of transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) ≥3x upper limit of normal (ULN) 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.
6. Subjects ≥6 years of age has actual suicidal ideation since last visit 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.
7. Subject is unable to tolerate at least the minimum LCM target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets).

Paragraph 3, bulleted item 1

- The subject requires a medication that is not permitted

Has been changed to:

- The subject requires a medication that is not permitted (see Section 7.8).

Paragraph 3, bulleted item 3

- **The following bulleted item has been added:** 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.

Change #20

Section 7.1 Description of investigational medicinal product(s)

Oral tablets of LCM 50mg and 100mg will be used in the study and will be supplied in high-density polyethylene bottles with child proof polypropylene screw caps.

Has been changed to:

Investigational medicinal product (IMP) will be provided as LCM oral solution (LCM 10mg/mL) and LCM tablets (LCM 50mg and LCM 100mg).

The oral solution formulation contains 10mg/mL of drug substance and is colorless to pale yellow in appearance.

The tablet formulation will be supplied in doses of 50mg and 100mg. The 50mg tablets are light pink, oval, film-coated tablets debossed with "SP" on 1 side and "50" on the other. The 100mg tablets are dark yellow, oval, film-coated tablets debossed with "SP" on 1 side and "100" on the other.

Change #21

Section 7.2 Treatment(s) to be administered

Paragraphs 1 and 2

Lacosamide will be orally administered bid (at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses. During the study, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject.

At Visit 1 subjects who completed SP0982 will start on a dose of LCM 400mg/day (200mg bid); subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 100mg/day (50mg bid). The LCM dose may then be adjusted at the discretion of the investigator within the range of 100 to 800mg/day. The investigator should increase or decrease the dose no faster than LCM 100mg/day per week. A clinic visit (scheduled or unscheduled) is required the first time the dose is increased to LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, and LCM 800mg/day. One week after the first time the dose is increased to LCM 700mg/day or LCM 800mg/day, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Have been changed to:

Lacosamide will be orally administered bid (at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses (oral solution for pediatric subjects weighing <50kg or tablets for adult subjects [≥18 years of age] and pediatric subjects [<18 years of age] weighing ≥50kg); during the study, subjects who initially started on oral solution may transfer to tablets at the investigator's discretion.

During the study, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject, within the dose range described in Table 7–1.

Change #22

The following section header has been added:

Section 7.2.1 Treatment Period

Paragraphs 1 through 11

Subjects withdrawing from the study will complete the Early Termination (ET) Visit and LCM will be tapered over 1 to 3 weeks (see taper schedule, Table 7–1). Subjects completing the Treatment Period and not continuing with commercially available LCM will complete the Termination Visit and LCM will be tapered over 1 to 3 weeks (see taper schedule, Table 7-1). Lacosamide will be tapered off gradually at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that safety concerns require a more rapid withdrawal of LCM. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. The Medical Monitor should be contacted if a more rapid withdrawal is required. A Final Clinic Visit will occur 2 weeks after the final LCM dose for subjects who taper off LCM.

Has been changed to:

At Visit 1, subjects who completed SP0982 will start on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Baseline failures are required to complete Week 1 of dosing before LCM dosing flexibility based on tolerability is allowed. Investigators will assess whether a subject would tolerate a further LCM 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 target dose of 4mg/kg/day (oral solution) or 200mg/day (tablets).

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects who have dose adjustments must remain on the dose for ≥3 days (in order to reach steady state) before a subsequent dose adjustment.

Table 7-1 provides the minimum and maximum LCM dose during the Treatment Period.

Table 7-1: Minimum and maximum LCM dose during the Treatment Period

Formulation	Minimum LCM dose	Maximum LCM dose
Oral solution (pediatric subjects <50kg)	4mg/kg/day	12mg/kg/day
Tablets (pediatric subjects ≥50kg)	200mg/day	600mg/day
Tablets (adult subjects)	200mg/day	800mg/day

LCM=lacosamide

The LCM dose may be adjusted at the investigator's discretion after the subject receives the first dose of LCM in the study. Baseline failures must complete Week 1 of dosing before LCM may be increased or decreased. The maximum dose for pediatric subjects weighing <50kg is 12mg/kg/day (oral solution). The maximum dose for pediatric subjects weighing ≥50kg is 600mg/day (tablets) and for adult subjects is 800mg/day (tablets).

A clinic visit (scheduled or unscheduled) is required if:

- The dose is increased for the first time to any dose above 10mg/kg/day for pediatric subjects weighing <50kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.
- The dose is increased for the first time to any dose above LCM 400mg/day for all adult subjects or pediatric subjects weighing ≥50kg. One week after the first time the dose is increased, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Subjects withdrawing from the study must complete the Early Termination (ET) Visit and an up to 4-week taper followed by an End of Taper Visit (see taper schedule, Table 7–2). 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. A slow taper is permitted if medically necessary. Whenever possible, these cases should be discussed with the Medical Monitor prior to withdrawing the subject from the study. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

At the completion of the study, investigators should discuss treatment options with the subject and/or their legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or their legal representative(s).

Subjects completing the Treatment Period and not continuing with commercially available LCM must complete the Termination Visit and also undergo taper, followed by an End of Taper Visit (see taper schedule, Table 7–2), and a 30-day Safety Follow-Up Period.

Subjects completing the Treatment Period and not continuing with commercially available LCM must complete the Termination Visit and also undergo taper, followed by an End of Taper Visit (see taper schedule, Table 7–2), and a 30-day Safety Follow-Up Period.

The following table summarizes the recommended LCM dose taper:

Table 7–1: Lacosamide dosing for subjects requiring taper

Table 7–1: Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule		
	Week 1	Week 2	Week 3
LCM 800mg/day	LCM 600mg/day	LCM 400mg/day	LCM 200mg/day
LCM 700mg/day	LCM 500mg/day	LCM 300mg/day	LCM 100mg/day
LCM 600mg/day	LCM 400mg/day	LCM 200mg/day	LCM 0mg/day
LCM 500mg/day	LCM 300mg/day	LCM 100mg/day	LCM 0mg/day
LCM 400mg/day	LCM 200mg/day	LCM 0mg/day	-
LCM 300mg/day	LCM 100mg/day	LCM 0mg/day	-
LCM 200mg/day	LCM 0mg/day	-	-
LCM 100mg/day	LCM 0mg/day	-	-

ET=early termination; LCM=lacosamide

[a] Subjects will begin taper on ET/Termination Visit.

Has been changed to:

Table 7–2: Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	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
750 to 800mg/day	600mg/day	400mg/day	200mg/day	100mg/day
650 to 700mg/day	500mg/day	300mg/day	200mg/day	100mg/day
550 to 600mg/day	500mg/day	300mg/day	200mg/day	100mg/day

Table 7–2: Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	Week 1	Week 2	Week 3	Week 4
450 to 500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
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

ET=early termination; LCM=lacosamide
Note: The oral solution is dosed as mg/kg/day and tablets are dosed as mg/day.
[a] Subjects will begin taper on ET/Termination Visit.

Change #23

Section 7.3 Packaging

Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. The investigational medicinal product (IMP) is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage. Lacosamide will be packaged in high-density polyethylene bottles with child proof polypropylene screw caps.

Has been changed to:

Lacosamide (tablets and oral solution) 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. Oral solution will be packaged in amber polyethylene terephthalate bottles. Tablets will be supplied in high density polyethylene bottles with child proof polypropylene screw caps.

Change #24

Section 7.5 Handling and storage requirements

Paragraphs 2 through 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 #25

Section 7.6 Drug accountability

Paragraph 1, second sentence

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, first sentence

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 #26

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 #27

Section 7.8 Concomitant medication(s)/treatment(s)

The following paragraphs have been added:

All concomitant medication and treatment must be recorded in the appropriate study documents (eg, eCRF and source document).

Contraceptive treatment is allowed for female subjects of childbearing potential.

The use of neuroleptics, monoamine oxidase inhibitors, barbiturates (except for treatment of epilepsy), and narcotic analgesics is prohibited throughout the study. However, in the case of narcotics or marijuana, certain limited usage may become necessary (eg, acute medical situation, perioperative period for subjects requiring surgery). Upon learning of such situations, the investigator should consult the medical monitor to determine whether the narcotic or marijuana use should result in discontinuation of a subject's further participation in the study.

The use of vigabatrin and felbamate is also prohibited throughout the study.

Only stable use of amphetamines and sedative antihistamines is allowed during the study. Also, only stable, low doses of anxiolytics or hypnotics are allowed for nonepilepsy indications.

Stable use of benzodiazepines is allowed as concomitant AEDs, but intermittent use is only allowed as rescue medication for epilepsy indications (maximum 1 dose per week).

During the Treatment Period, new concomitant AEDs may be introduced, if the concomitant medication has been approved by the regulatory authority for the respective patient indication in the subject's country. For example, a new AED may be added when the subject has not optimally or adequately responded (lack of efficacy or tolerance) to LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

Change #28

The following section has been deleted:

Section 7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are restricted during the study:

- Use of benzodiazepines
  - The chronic (daily dose) use of benzodiazepines is allowed for treatment of epilepsy and will be counted as 1 of the AEDs.
  - The stable use of benzodiazepines for non-epilepsy indications is allowed during the study and will be counted as 1 of the AEDs.
  - The intermittent use of benzodiazepines is allowed only for rescue therapy for epilepsy indications, but limited to 4 doses per 28 days.

During the Treatment Period, new concomitant AEDs may be introduced to optimize treatment, if the concomitant medication has been approved by the regulatory authority in the subject's country. New AEDs should be added only when the subject has not optimally or adequately

responded to a maximum tolerated dose of LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

Change #29

Section 8 STUDY PROCEDURES BY VISIT

Paragraph 3

A detailed schedule of study assessments for treatment Years 1 to 2 is provided in Table 5–1 and for treatment Years 3 to 6 in Table 5–2.

Has been changed to:

A detailed schedule of study assessments for treatment Years 1 to 2 is provided in Table 5–1, for treatment Years 3 to 5 in Table 5–2, and for the Taper Period and Safety Follow-Up Period in Table 5–3.

Change #30

Section 8.1.1 Visit 1 (Week 0)

The following bulleted item has been deleted

- Socio-professional data

Bulleted items number 11, 12, 19, and 20

- Tanner staging (for subjects <18 years of age)
- C-SSRS assessment*
- EQ-5D-3L
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age)

Have been changed to:

- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- C-SSRS assessment (for subjects ≥6 years of age)
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)

Change #31

Section 8.1.2 Visits 2 to 8 (Weeks 2 to 46, Year 1)

Bulleted items number 1 through 19

- Concomitant medications and AEDs
- Physical examination (brief)
- Neurological examination (brief)

- ECG (12-lead) assessment (Visit 2, 3, 4 and 8 only)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight (Visit 4, 6 and 8 only)
- Tanner staging (for subjects <18 years of age) (Visit 5 and 8 only)
- C-SSRS assessment
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis) [Visit 2, 3, 4, 6 and 8 only], and a urine pregnancy test [for women of childbearing potential])
- LCM plasma concentration (Visit 2 and 6 only)
- Contact IVRS/IWRS
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 5 only)
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age) (Visit 5 and 8 only)

Have been changed to:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 2, 3, 4, 5, 6, and 7; complete, Visit 8)
- Neurological examination (brief, Visit 2, 3, 4, 5, 6, and 7; complete, Visit 8)
- ECG (12-lead) assessment (Visit 2, 4, 6, and 8 only)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight (Visit 4, 6, and 8 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 8 only)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis) [Visit 2, 5, and 8 only], and a urine pregnancy test [for women of childbearing potential])
- Contact IVRS/IWRS

- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 5 and 8) (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age) (Visit 5 and 8 only)

Change #32

Section 8.1.3 Visits 9 to 11 (Weeks 62 to 94, Year 2)

Bulleted items 1 through 18

- Concomitant medications and AEDs
- Physical examination (complete, Visit 9; brief, Visit 10 and 11)
- Neurological examination (complete, Visit 9; brief, Visit 10 and 11)
- ECG (12-lead) assessment (Visit 11 only)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 9 only)
- Tanner staging (for subjects <18 years of age) (Visit 10 and 11 only)
- 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])
- Contact IVRS/IWRS
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 9 only)
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age) (Visit 9 and 11 only)

Have been changed to:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 9 and 10; complete, Visit 11)
- Neurological examination (brief, Visit 9 and 10; complete, Visit 11)
- ECG (12-lead) assessment (Visit 9, 10, and 11)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 9 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 11 only)
- 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])
- Contact IVRS/IWRS
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 9 and 11) (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age) (Visit 9 and 11 only)

Change #33

Section 8.1.4 Visits 12 to 19 (Weeks 118 to 286, Years 3 to 6)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (complete, Visit 12, 14, 16, 18 and 19; brief, Visit 13, 15, and 17)
- Neurological examination (complete, Visit 12, 14, 16, 18 and 19; brief, Visit 13, 15, and 17)
- ECG (12-lead) assessment (Visit 13, 15, 17, and 19)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 12, 14, 16 and 18)
- Tanner staging (for subjects <18 years of age)

- 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])
- Contact IVRS/IWRS
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 12, 14, 16, 18 and 19)
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age)
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Has been changed to:

Section 8.1.4 Visits 12, 13, 14, 15, 16, and 17 (Weeks 118, 142, 166, 190, 214, and 238, Years 3 to 5)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 12, 14, and 16; complete, Visit 13, 15, and 17)
- Neurological examination (brief, Visit 12, 14, and 16; complete, Visit 13, 15, and 17)
- ECG (12-lead) assessment
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 12, 14, and 16)
- Tanner staging (for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 13, 15, and 17)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and a urine pregnancy test [for women of childbearing potential])

- Contact IVRS/IWRS
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Achenbach CBCL for subjects ≥6 years to <18 years of age
- BRIEF for subjects ≥5 to <18 years of age
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Change #34

Section 8.1.5 Telephone Contact (Years 2 to 6)

Has been changed to:

Section 8.1.5 Telephone Contact

Paragraph 1

Telephone contacts are required every 8 weeks during Year 2 to Year 6, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, and Week 86. Telephone contacts in Years 3 to 6 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230; Year 6 - Week 246, Week 254, Week 270, Week 278.

Has been changed to:

Telephone contacts are required every 8 weeks during Year 2 to Year 5, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, and Week 86. Telephone contacts in Years 3 to 5 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230.

Paragraph 2

The following paragraph has been deleted:

One week after the first time the dose is increased to LCM 700mg/day or LCM 800mg/day, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Paragraph 3

The following paragraph has been added:

The investigator will also ensure subjects are compliant with LCM administration and diary completion during the telephone contact.

Change #35

The following section has been added:

Section 8.1.6 LCM solution Dispensation Visit

From Year 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

Change #36

The following section header has been deleted:

Section 8.2 End of Study Period

Change #37

Section 8.2.1 Early Termination Visit (Years 1 to 6)

Has been changed to:

Section 8.2 Early Termination Visit

Paragraph 1

Subjects withdrawing from the study will complete the ET Visit and LCM will be tapered over 1 to 3 weeks (see taper schedule, Table 7–1).

Has been changed to:

Subjects withdrawing from the study will complete the ET Visit, and LCM will be tapered over a period of up to 4 weeks (see taper schedule, Table 7–2).

Paragraph 2, bulleted items number 7 through 19

- Tanner staging (for subjects <18 years of age)
- 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])
- LCM plasma concentration
- Contact IVRS/IWRS
- Dispense subject diary

- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age)

Have been changed to:

- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- 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])
- Contact IVRS/IWRS
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)

Change #38

Section 8.2.2 Termination Visit (Years 1 to 6)

Has been changed to:

Section 8.3 Termination Visit

Paragraphs 1 and 2

Subjects completing the Treatment Period and not continuing with commercially available LCM will complete the Termination Visit, and LCM will be tapered over 1 to 3 weeks (see taper schedule, Table 7–1).

Once LCM becomes commercially available and the subject elects to continue treatment, they must also complete the Termination Visit and transition to commercially available LCM. Taper of LCM is not required for subjects who complete the study and continue on commercially

available LCM. Subjects transitioning to commercially available LCM will do so immediately and will continue with the dose they were taking at the Termination Visit.

Have been changed to:

Subjects completing the Treatment Period and not continuing with commercially available LCM will complete the Termination Visit, and LCM will be tapered over a period of up to 4 weeks (see taper schedule, Table 7–2).

Once LCM is approved for use and the subject elects to continue treatment, they must also complete the Termination Visit and transition to commercially available LCM. Taper of LCM is not required for subjects who complete the study and continue on commercially available LCM. Subjects transitioning to commercially available LCM will do so immediately and will continue at a dose determined by the investigator.

Note: this visit can be combined with Visit 17 if appropriate.

Paragraph 4, bulleted items number 7 through 24

- Tanner staging (for subjects <18 years of age)
- 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])
- LCM plasma concentration
- Contact IVRS/IWRS
- Dispense subject diary for subjects undergoing taper
- Subject diary return/review
- Dispense LCM for subjects undergoing taper
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L
- QOLIE-31-P (subjects ≥18 years of age)/PedsQL (subjects <18 years of age)
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age
- Healthcare resource use (Years 1 to 2 only)
- Work/school days lost (Years 1 to 2 only)
- Days with help from a caregiver (Years 1 to 2 only)

Have been changed to:

- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- 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])
- Contact IVRS/IWRS
- Dispense subject diary for subjects undergoing taper
- Subject diary return/review
- Dispense LCM for subjects undergoing taper
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Change #39

Section 8.2.3 Final Clinic Visit

A Final Clinic Visit will occur 2 weeks after the final LCM dose for subjects who taper off LCM. The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight
- C-SSRS assessment
- Blood sample for a serum pregnancy test (for women of childbearing potential)
- Contact IVRS/IWRS
- Subject diary return/review
- AE reporting

Has been changed to:

Section 8.4.1 End of Taper Visit

An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs
- Physical examination (complete)
- Neurological examination (complete)
- ECG (12-lead) assessment
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and a urine pregnancy test [for women of childbearing potential])
- Contact IVRS/IWRS
- Subject diary return/review
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Change #40

Section 8.3 Unscheduled Visit

Has been changed to:

Section 8.5 Unscheduled Visit

Paragraph 1

Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. A clinic visit (scheduled or unscheduled) is required the first time the dose is increased to LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, and LCM 800mg/day. One week after the first time the dose is increased to LCM 700mg/day or LCM 800mg/day, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Has been changed to:

Unscheduled Visits may be performed at any time after Visit 1, at the discretion of the investigator. A clinic visit (scheduled or unscheduled) is required the first time the dose is

increased above the dose of 10mg/kg/day (oral solution) for pediatric subjects weighing <50kg or 400mg/day (tablets) for adult and pediatric subjects ≥50kg. One week after the first time the dose is increased above the dose of 10mg/kg/day or 400mg/day, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated. Similarly, a clinic visit (scheduled or unscheduled) is required for pediatric subjects weighing <50 kg the first time the dose is increased to 11mg/kg/day, or 12mg/kg/day, and all adult subjects or pediatric subjects weighing ≥50kg the first time the dose is increased to LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, and LCM 800mg/day. One week after the first time the dose is increased to 11mg/kg/day, or 12mg/kg/day for pediatric subjects <50kg, and LCM 500mg/day, LCM 600mg/day, LCM 700mg/day, or LCM 800mg/day for all adult subjects or pediatric subjects weighing ≥50kg, an unscheduled telephone contact must be conducted to ensure that the dose is well tolerated.

Paragraph 3

If unscheduled visit is due to an AE, then the C-SSRS is required.

Has been changed to:

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

Change #41

The following header section was added:

Section 8.4 Taper and Safety Follow-Up Period

Change #42

The following section has been added:

Section 8.4.2 Safety Follow-Up Visit

Following the End of Taper Visit, the subject will return 2 weeks 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:

- Concomitant medications and AEDs
- Physical examination (complete)
- Neurological examination (complete)
- ECG (12-lead) assessment (only required for subjects with an abnormal reading at the previous clinic visit)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology, [only required for subjects with an abnormal value at the previous clinic visit], and a urine pregnancy test [for women of childbearing potential])

- AE reporting
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Change #43

The following section has been added:

Section 8.4.3 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. During the Safety Follow-Up telephone contact, the following assessments will be performed:

- Concomitant medications and AEDs
- AE reporting

Change #44

Section 9.1 Seizure frequency

The following paragraph was added:

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 #45

Section 9.2.1 Patient-Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P)

Paragraphs 1 and 2

The QOLIE-31-P Version 2 (see Section 17.2) will be used to evaluate the health-related quality of life (HRQoL) of study subjects (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.

Have been changed to:

The QOLIE-31-P Version 2 (see Section 16.2) 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.

Change #46

Section 9.2.2 Pediatric Quality of Life Inventory

Paragraphs 2 through 4

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. For each developmentally appropriate version of the PedsQL subjects must have at least 1 year of data before transitioning to the next age range.

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.

Have been changed to:

The PedsQL Measurement Model consists of 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 HRQoL is measured for pediatric subjects ≤4 years of age. The PedsQL appropriate for each subject's age should be completed, with the following exception: if a subject ages up to the next form of the PedsQL within 1 year after the Baseline assessment of the primary study, the form that was used at the Baseline assessment should be completed for 1 year after the Baseline assessment, and subsequently the form consistent with his/her age at the time of assessment should be completed.

For each version of the PedsQL subjects, must have at least 1 year of data before transitioning to the next age range.

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 #47

Section 9.2.3 EuroQol-5D-3L Quality of Life Assessment

Paragraph 1, first sentence

The EQ-5D-3L (EuroQol Group, 2011) (see Section 17.3) is a self-administered questionnaire designed to measure health status.

Has been changed to:

The EQ-5D-3L (EuroQol Group, 2011) (see Section 16.3) is a self-administered questionnaire designed to measure health status in subjects ≥12 years of age.

Paragraph 2

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.

Has been changed to:

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

Change #48

Section 9.2.5 Number of working 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 #49

Section 9.2.6 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 #50

The following section has been deleted

Section 9.2.7 Socio-professional data

Socio-professional data, such as highest level of education, current professional status, housing status, and regular assistance will be collected according to the schedule of study assessments in Table 5–1.

Change #51

The following section has been deleted:

Section 10 ASSESSMENT OF PHARMACOKINETIC VARIABLE(S)

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 5-1and Table 5–

2. 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 -70°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.

Change #52

Section 11.3 Adverse events of special interest

Has been changed to:

Section 10.3 Adverse events of special interest

Paragraph 2, bulleted item number 3

- Serious suspected multiorgan hypersensitivity reactions; serious suspected multiorgan hypersensitivity cases may be identified and reported to the sponsor by the investigator using the following algorithm as agreed with the US Food and Drug Administration:
  - An AE or laboratory value (as defined in the following text) suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia

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

    ◦ Eosinophils % ≥10%

    ◦ Eosinophils absolute ≥0.5G/L

    ◦ Neutrophils absolute <1.5G/L

    ◦ Platelets ≤100G/L

    ◦ ALT ≥2xULN

    ◦ AST ≥2xULN

Has been changed to:

- Serious suspected multiorgan hypersensitivity reactions.

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

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

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

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

Bulleted item number 4 has been added

- Emergence of non-pre-existing or worsening of any existing epileptic seizure types

Change #53

Section 11.6 Laboratory measurements

Has been changed to:

Section 10.6 Laboratory measurements

Paragraph 1, 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 and Table 5–2.

Has been changed to:

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, Table 5–2, and Table 5-3.

Table 11-2: Laboratory tests

Table 11–2: 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	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	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
			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; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cell

Change #54

Section 11.6.1 Liver function tests

Has been changed to:

Section 10.6.1 Liver function tests

Paragraph 4

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

Has been changed to:

In all cases of transaminases (AST, ALT, or both) ≥3xULN, testing for hepatitis A, B, and C will be performed. In all cases of transaminases (AST, ALT, or both) ≥8xULN or a potential case of drug-induced liver injury (ie, Hy's law), testing for hepatitis E immunoglobulin M antibodies will be performed.

Change #55

Section 11.6.2 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 and Table 5–2.

Has been changed to:

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, Table 5–2, and Table 5-3.

Change #56

Section 11.7.1 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 and Table 5–2. Assessment of orthostatic changes will be as follows: after the 3-minute measurement in a supine position, the subject is asked to stand 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 schedule of study assessments in Table 5–1 and Table 5–2.

Has been changed to:

Section 10.7.1 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 schedule of study assessments in Table 5–1, Table 5–2, and Table 5-3.

Change #57

Section 11.7.2 12-lead ECG

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

Section 11.7.2.1 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 6.3). The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

Has been changed to:

Section 10.7.2 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), a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

Section 10.7.2.1 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 6.3). 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.

Change #58

Section 11.7.3 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the schedule of study assessments in Table 5–1 and Table 5–2.

Has been changed to:

Section 10.7.3 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the schedule of study assessments in Table 5–1, Table 5–2, and Table 5-3.

The C-SSRS will be completed for subjects who are ≥6 years of age. The "Since Last Visit" version of the C-SSRS should be used. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used once, followed by the "Since Last Visit" version at subsequent visits.

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders 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 #59

Section 11.7.4 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 and Table 5–2. Clinically significant physical examination findings are to be reported as AEs.

Has been changed to:

Section 10.7.4 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.

Change #60

Section 11.7.4.1 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:

Section 10.7.4.1 Complete physical examination

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

Change #61

Section 11.7.5 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 and Table 5–2. If possible, the same clinician should conduct all neurological examinations for the same subject during the study. The investigator or subinvestigator is responsible for confirming the diagnosis of IGE with PGTC seizures.

Has been changed to:

Section 10.7.5 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.

Change #62

Section 11.7.5.2 Brief neurological examination

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

Has been changed to:

Section 10.7.5.2 Brief neurological examination

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

Change #63

Section 11.7.6 Achenbach CBCL

Has been changed to:

Section 10.7.6 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 completion of the Achenbach CBCL will require approximately 45 minutes.

Has been changed to:

The Achenbach CBCL is a widely used validated questionnaire to evaluate a child's competencies and behavioral/emotional problems.

The Achenbach CBCL consists of the CBCL/1½ -5 for children <5 years and 11 months of age, and the CBCL/6 18 for children ≥6 years to <18 years of age. These are to be completed by the parent(s)/legal representative(s). The completion of the Achenbach CBCL will require approximately 45 minutes. The version of the Achenbach CBCL appropriate to each subject's age should be administered with the following exception: for subjects who completed the CBCL/1½-5 at the Baseline assessment of the previous study and turn 6 years of age within 1 year after the Baseline assessment of the primary study, the CBCL/1½-5 should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the CBCL/6-18 should be completed. The Achenbach CBCL will only be administered in countries where a validated translated version is available. For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range.

Change #64

Section 11.7.7 BRIEF

The BRIEF is a validated tool that will be used for the evaluation of subjects ≥5 years of age.

The BRIEF includes Rating forms used by parents to assess subjects' executive functioning and include validity scales to measure negativity and inconsistency of responses. For each developmentally appropriate version of the BRIEF subjects must have at least 1 year of data before transitioning to the next age range.

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:

Section 10.7.7 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 or BRIEF appropriate for each subject's age should be completed, with the following exception: For subjects who completed the BRIEF-P at the Baseline assessment of the previous study and turn 5 years of age within 1 year after the Baseline assessment of the primary study, the BRIEF-P should be completed for 1 year after the Baseline assessment of the primary study, and subsequently the BRIEF should be completed. The BRIEF-P and BRIEF will be administered

according to the tabular schedules of study procedures (Section 5.2). The BRIEF-P and BRIEF will be used only in countries where a translated scale is available. For each developmentally appropriate version of the BRIEF subjects must have at least 1 year of data before transitioning to the next age range.

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 #65

Section 11.7.8 Tanner stage

The Tanner Stage will be performed for subjects who are <18 years of age, according to the schedule of study assessments in Table 5–1 and Table 5–2. The investigator or qualified designee will evaluate the subject's sexual development using the 3-item scale.

Has been changed to:

Section 10.7.8 Tanner stage

The Tanner Stage will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study, according to the schedule of study assessments in Table 5–1 and Table 5–2. The investigator or qualified designee will evaluate the subject's sexual development using the 3-item 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 the evaluation of Tanner Stage (ie, those subjects who are pubescent at Visit 1 or who will enter puberty during the course of the study).

Change #66

Section 12.3.2 Database entry and reconciliation

Has been changed to:

Section 11.3.2 Database entry and reconciliation

Paragraph 1, third sentence

The study will be performed using remote data capture; the data are entered into the eCRFs once and are subsequently verified.

Has been changed to:

This study will be performed using remote data capture; the data are entered into the eCRFs once and are subsequently verified.

Change #67

The following section has been deleted

Section 13.1.3 Pharmacokinetic Set

The Pharmacokinetic Set is a subset of the SS and consists of all subjects with at least 1 evaluable assessment of plasma concentration data.

Change #68

Section 13.5 Handling of protocol deviations

After all eCRFs have been retrieved and entered, all queries issued and answered to the extent possible, and prior to locking the clinical database, a Data Review Meeting will be held. Important protocol deviations (ie, those considered to have an impact on interpretation of safety, efficacy, or study conduct) will be identified and reviewed by a panel consisting of the Clinical Program Manager, the study biostatistician, study physician, a representative of the monitoring team, and other appropriate team members.

Has been changed to:

Section 12.5 Handling of protocol deviations

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

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

Change #69

Section 13.7 Planned interim analysis and data monitoring

No interim analysis is planned for this study.

Has been changed to:

Section 12.7 Planned interim analysis and data monitoring

No interim analysis or Data Monitoring Committee is planned. However, data may be reported prior to the completion of this study to support annual reports, regulatory submissions, and publications.

Change #70

Section 13.8 Determination of sample size

Has been changed to:

Section 12.8 Determination of sample size

Paragraph 1

The sample size of this open-label extension study will be determined by the parent SP0982 study, where approximately 200 subjects will be randomized.

Has been changed to:

The sample size of this open-label extension study will be determined by the parent SP0982 study, where approximately 200 subjects are planned to be randomized.

Change #71

Section 16 References

Has been changed to:

Section 15 References

The following reference was deleted:

Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;34:453-68.

16.5 Appendix 5: Protocol Amendment 2

Rationale for the amendment

The protocol was amended following a request from the Taiwanese MoH, that for dose escalation, subjects who are eligible Baseline failures from SP0982 must remain on the dose for ≥7 days before a subsequent dose escalation. Additionally, the purpose of the amendment was to remove superfluous description of a substudy, to clarify the requirement for ECG at subsequent visits, requirement for endocrinology and timing of endocrinology assessments, pregnancy testing, definition of contraceptive methods, and seizure count, and to add a definition of the Enrolled Set. Several assessments will not be done in Years 3-5, including brief physical examination (complete physical examination will be done), complete neurological examination (brief neurological examination will be done), and health outcome measures. 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 EP0012 Amendment 1" to "Protocol EP0012 Amendment 2."

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	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial

Change #2

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Clinical Trial Biostatistician

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

Interactive Voice/Web Response System

Name:	Perceptive eClinical Limited
Address:	Lady Bay House, Meadow Grove Nottingham, NG23HF UK
Phone:	+44 115 955 7333
Fax:	+44 115 955 7555

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World (except Japan):** +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 (except Japan):**

Has been updated to:

Sponsor Study Physician

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]
Email:	[redacted]

Interactive Response Technology

Name:	Perceptive eClinical Limited
Address:	Lady Bay House, Meadow Grove Nottingham, NG23HF UK
Phone:	+44 115 955 7333
Fax:	+44 115 955 7555

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
BMI	body mass index
EDC	electronic data capture
EI-AED	enzyme-inducing antiepileptic drug
ES	Enrolled Set
ICH	International ~~Conference on~~ Council for Harmonisation
IRT	interactive response technology
~~IVRS/IWRS~~	~~interactive voice/web response system~~
MAO-A	monoamine oxidase A
MAP	managed access program
PDILI	potential drug-induced liver injury
PS	patient safety
SFU	Safety Follow Up
TMF	trial master file

These abbreviations have also been changed wherever they occur throughout the protocol.

Change #4

Section 1, SUMMARY

Paragraph 5

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects who have dose adjustments must remain on the dose for ≥3 days (in order to reach steady state) before a subsequent dose adjustment.

Has been changed to:

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects must remain on the dose for ≥7 days before a subsequent dose escalation.

Change #5

Section 1 SUMMARY

Paragraph 7

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. The study duration and the total number of clinic visits will vary for each subject. At selected sites, subjects may also be able to participate in a substudy without withdrawing from EP0012. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

Has been changed to:

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. The study duration and the total number of clinic visits will vary for each subject. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

Change #6

Section 1, SUMMARY

Paragraph 10

The primary safety variables are adverse events (AEs) and subject withdrawals due to AEs. Secondary safety variables are changes in hematology, chemistry, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); and changes in vital sign measurements (ie, blood pressure [BP] and pulse rate), including body weight and physical (including neurological) examination findings. In addition, for pediatric subjects <18 years of age, safety will be

evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function-Preschool Version® [BRIEF®/BRIEF-P®]). Efficacy variables are evaluations of seizure frequency, based on information included in subject diaries, and health outcome variables, including the Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), the Pediatric Quality of Life Inventory™ (PedsQL™), the 3-level EuroQol 5 Dimension Quality of Life Assessment (EQ-5D-3L) Quality of Life Assessment, healthcare resource use, the number of working or school days lost by subjects, and the number of days with help from a caregiver.

Has been changed to:

The primary safety variables are adverse events (AEs), subject withdrawals due to AEs, 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. Secondary safety variables are changes in hematology, chemistry, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); and changes in vital sign measurements (ie, blood pressure [BP] and pulse rate), including body weight and physical (including neurological) examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function-Preschool Version® [BRIEF®/BRIEF-P®]). The seizure efficacy variables are evaluations of seizure frequency, based on information included in subject diaries. The health outcome variables, including the Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), the Pediatric Quality of Life Inventory™ (PedsQL™), the 3-level EuroQol 5 Dimension Quality of Life Assessment (EQ-5D-3L), healthcare resource use, the number of working or school days lost by subjects due to epilepsy, and the number of days with help from a caregiver due to epilepsy will be assessed for the first 2 years of treatment.

Change #7

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 unknown origin.

Has been changed to:

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 unknown origin.

Change #8

Section 2, INTRODUCTION

Paragraph 8

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

Has been changed to:

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 #9

Section 4.1.1, Primary safety variables

The primary safety variables are:

- Adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs

Has been changed to:

The primary safety variables are:

- Adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- 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 days with absence seizures per 28 days during the Treatment Period as compared to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days during the Treatment Period as compared to the Prospective Baseline

Change #10

Section 4.1.2, Secondary safety variables

Bullet point 3

- Changes in vital sign measurements (ie, BP and pulse rate), including body weight and physical (including neurological) examination findings

Has been changed to:

- Changes in vital sign measurements (ie, BP and pulse rate), including BMI and physical (including neurological) examination findings

Change #11

Section 4.2.2, Secondary efficacy variable

The secondary efficacy variable is:

- Percent change in PGTC seizure frequency per 28 days from Baseline, where Baseline is defined as the 12-week Historical Baseline and 4-week Prospective Baseline periods immediately prior to randomization in the parent study (SP0982)

Has been changed to:

The secondary efficacy variable is:

- Percent change in PGTC seizure frequency per 28 days from Combined Baseline, where Combined Baseline is defined as the combined 12-week Historical Baseline and 4-week Prospective Baseline periods immediately prior to randomization in the parent study (SP0982)

Change #12

Section 4.2.3, Other efficacy variables

The other efficacy variables are:

- Percent change in days with myoclonic seizures per 28 days from Baseline
- Percent change in days with absence seizures per 28 days from Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency compared to Baseline

- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to Baseline
- Seizure-free status (yes/no) for PGTC seizures
- Seizure-free status (yes/no) for myoclonic seizures
- Seizure-free status (yes/no) for absence seizures
- Seizure-free status (yes/no) for all generalized seizure types
- 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 in the 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

Has been changed to:

The other efficacy variables are:

- Change in days with myoclonic seizures per 28 days relative to the Prospective Baseline
- Percent change in days with myoclonic seizures per 28 days relative to the Prospective Baseline
- Change in days with absence seizures per 28 days relative to the Prospective Baseline
- Percent change in days with absence seizures per 28 days relative to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in PGTC seizure frequency compared to the Combined Baseline
- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to the Prospective Baseline
- Seizure-free status (yes/no) for PGTC seizures
- Seizure-free status (yes/no) for all generalized seizure types

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

Change #13

Section 5.1, Study description

Paragraph 3

Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Paragraph 6

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects who have dose adjustments must remain on the dose for ≥3 days (in order to reach steady state) before a subsequent dose adjustment.

Have been changed to:

Paragraph 3

Randomized subjects meeting SP0982 exit criteria and subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for

pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Paragraph 6

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects must remain on the dose for ≥7 days before a subsequent dose escalation.

Change #14

Section 5.1, Study description

Paragraph 10

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs, as well as to ensure subjects are compliant with LCM administration and diary completion. The study duration and the total number of clinic visits will vary for each subject. At selected sites, subjects may also be able to participate in a substudy without withdrawing from EP0012. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

Paragraph 11

Subjects and/or their caregiver will be dispensed a seizure diary to record all types of seizures, concomitant AEDs, and other pertinent health status information. Subjects must bring their diary to each visit. Seizure frequency and type will be verified by a reliably documented seizure history collected (eg, in a seizure diary).

Have been changed to:

Paragraph 10

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs, as well as to ensure subjects are compliant with LCM administration and diary completion. The study duration and the total number of clinic visits will vary for each subject. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

Paragraph 11

Subjects and/or their caregiver will be dispensed a seizure diary to record all types of seizures, concomitant AEDs, and other pertinent health status information. Subjects must bring their diary to each visit. Baseline seizure frequency and type will be verified by a reliably documented seizure history collected (eg, in a seizure diary during SP0982).

Change #15

Section 5.1.1, Study duration per subject

Last paragraph

Depending on the local regulations, after 2 years, subjects may continue to receive LCM in a named patient program.

Has been changed to:

Depending on the local regulations, after 2 years, subjects may continue to receive LCM in a managed access program (MAP).

Change #16

Section 5.1.3, Anticipated regions and countries

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

Has been changed to:

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

Change #17

Table 5–1: Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

Rows

A row was added to schedule laboratory tests for endocrinology at Visit 1, ET and Termination Visits.

Work/school days lost and Days with help from a caregiver were changed to Work/school days lost due to epilepsy, and Days with help from a caregiver due to epilepsy.

Footnotes

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

p Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick.

Have been changed to:

o Urinalysis will be required for all subjects.

p If the patient was treated in SP0982, endocrinology should be done if age was <18 years at SP0982 Visit 1. If the patient was a Baseline failure in SP0982, endocrinology should be done if age is <18 years at EP0012 Visit 1.

q Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

Change #18

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

Rows

A row was added to schedule laboratory tests for endocrinology at ET and Termination Visits.

The following assessments have been removed from the schedule for Years 3 through 5: Physical exam (brief), Neurological exam (complete), EQ-5D-3L, QOLIE-31-P/PedsQLs, Healthcare resource use, Work/school days lost, and Days with help from a caregiver.

The following assessments will now be done at Visits 13, 15, and 17 only: 12-lead ECG, Achenbach CBCL, and BRIEF.

Footnotes

b Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

q Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick.

Has been changed to:

b Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

o Laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required.

p If the patient was treated in SP0982, endocrinology should be done if age was <18 years at SP0982 Visit 1. If the patient was a Baseline failure in SP0982, endocrinology should be done if age is <18 years at EP0012 Visit 1.

q Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination

Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

Change #19

Table 5–3: Schedule of study assessments (Taper Period and Safety Follow-Up Period) for EP0012

Rows

Neurological exam (complete), Work/school days lost, and Days with help from a caregiver were changed to Neurological exam (brief), Work/school days lost due to epilepsy, and Days with help from a caregiver due to epilepsy.

The following footnote has been added:

i Healthcare resource use, work/schools days lost due to epilepsy, and days with help from a caregiver due to epilepsy will be assessed only for patients completing the study after ≤2 years. These assessments are not applicable for patients tapering down or performing the SFU-visits during Years 3, 4 or 5).

Change #20

Section 6.1, Inclusion criteria

2. Subject must have completed or be an eligible Baseline failure from the parent study (SP0982), as defined in Section 5.1.

Has been changed to:

2. Subject must have completed or be an eligible Baseline failure from the parent study (SP0982), as defined in Section 5.1. Note: Other subjects screened for SP0982 may be considered for roll-over to EP0012 if the investigator considers that the subject could benefit from treatment with open-label LCM and based on prior discussion with and approval from the UCB Study Physician or representative.

Change #21

Section 6.2, Exclusion criteria

A new criterion has been added:

4. 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 Case Report form (CRF).

   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.

Change #22

Section 6.3, Withdrawal criteria

Bullet point 5

- 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 will decide whether or not to stop the study drug.

Has been changed to:

- Discontinuation criteria for potential drug-induced liver injury (PDILI) are described in Section 6.3.1.

Change #23

A new section has been added:

Section 6.3.1, 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%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 10.3.1.2.1 are followed.

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 10.3.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately. See Section 6.3 for when and how to discontinue subjects from the IMP. See Section 8.2 for the procedures to be performed at the time of discontinuation.

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 CRF must document the primary reason for IMP discontinuation.

Change #24

Section 7.2, Treatment(s) to be administered

New paragraph 2:

Tablets **must not be broken**. In rare cases where uneven dosing (e.g., 350mg/day, 450mg/day, 550mg/day, etc) is medically needed, although the interactive response technology (IRT) will not dispense the exact dose, please contact the medial monitor for additional instructions.

Change #25

Section 7.2.1, Treatment Period

Paragraph 4

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects who have dose adjustments must remain on the dose for ≥3 days (in order to reach steady state) before a subsequent dose adjustment.

Table 7–2: Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	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
750 to 800mg/day	600mg/day	400mg/day	200mg/day	100mg/day

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	Week 1	Week 2	Week 3	Week 4
650 to 700mg/day	500mg/day	300mg/day	200mg/day	100mg/day
550 to 600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
450 to 500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
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

Has been changed to:

Paragraph 4

During EP0012, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. Lacosamide doses may be increased or decreased in steps of no more than 2mg/kg/day (oral solution) or 100mg/day (tablets). Subjects must remain on the dose for ≥7 days before a subsequent dose escalation.

Table 7–2: Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	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
800mg/day	600mg/day	400mg/day	200mg/day	100mg/day
700mg/day	500mg/day	300mg/day	200mg/day	100mg/day
600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
400mg/day	300mg/day	200mg/day	100mg/day	NA
300mg/day	200mg/day	100mg/day	NA	NA
200mg/day	100mg/day	NA	NA	NA

Change #26

Section 7.5, Handling and storage requirements

Paragraphs 1 through 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 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 Handing Manual

Change #27

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 #28

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 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.

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.

Change #29

Section 7.8, Concomitant medication(s)/treatment(s)

All concomitant medication and treatment must be recorded in the appropriate study documents (eg, eCRF and source document).

Contraceptive treatment is allowed for female subjects of childbearing potential.

The use of neuroleptics, monoamine oxidase inhibitors, barbiturates (except for treatment of epilepsy), and narcotic analgesics is prohibited throughout the study. However, in the case of narcotics or marijuana, certain limited usage may become necessary (eg, acute medical situation, perioperative period for subjects requiring surgery). Upon learning of such situations, the

investigator should consult the medical monitor to determine whether the narcotic or marijuana use should result in discontinuation of a subject's further participation in the study.

The use of vigabatrin and felbamate is also prohibited throughout the study.

Only stable use of amphetamines and sedative antihistamines is allowed during the study. Also, only stable, low doses of anxiolytics or hypnotics are allowed for nonepilepsy indications.

Stable use of benzodiazepines is allowed as concomitant AEDs, but intermittent use is only allowed as rescue medication for epilepsy indications (maximum 1 dose per week).

During the Treatment Period, new concomitant AEDs may be introduced, if the concomitant medication has been approved by the regulatory authority for the respective patient indication in the subject's country. For example, a new AED may be added when the subject has not optimally or adequately responded (lack of efficacy or tolerance) to LCM. Concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

Section 7.8.1, Rescue medication

The intermittent use of benzodiazepines is allowed only for epilepsy indications (see Section 7.8).

Have been changed to:

Section 7.8, Concomitant medication(s)/treatment(s)

All concomitant medication and treatment must be recorded in the appropriate study documents (eg, eCRF and source document).

7.8.1 Permitted concomitant treatments (medications and therapies)

Female subjects not surgically sterile or 2 years postmenopausal should practice 1 highly effective method of contraception (according to 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. Recommended contraception methods for subjects on enzyme-inducing antiepileptic drugs (EI-AEDs) or not on EI-AEDs are detailed in Section 16.6. Subjects on EI-AEDs who do not use one of the highly effective contraception methods recommended for this group may practice 2 combined methods of contraception (ie, combined hormonal contraception plus barrier method with spermicidal agent).

The initiation of felbamate treatment while participating in EP0012 is prohibited.

The use of neuroleptics except for clozapine is allowed. The use of barbiturates and narcotic analgesics is also allowed. Stable use of benzodiazepines is allowed as concomitant AEDs, but intermittent use is only allowed as rescue medication for epilepsy indications (maximum 1 dose per week).

During the Treatment Period, new concomitant AEDs may be introduced, if the concomitant medication has been approved by the regulatory authority for the respective patient indication in the subject's country. For example, a new AED may be added when the subject has not optimally or adequately responded (lack of efficacy or tolerance) to LCM. Concomitant AEDs may be

carefully tapered and discontinued to achieve LCM monotherapy, if clinically appropriate. The Medical Monitor must be consulted prior to initiation of concomitant AED withdrawal.

7.8.2 Prohibited concomitant treatments (medications and therapies)

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

- Clozapine
- MAO-A inhibitors
- Vigabatrin

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 #30

Section 8.1.1, Visit 1 (Week 0)

Bullet points 13, 24, and 25

- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a serum pregnancy test [for women of childbearing potential])*.
- Work/school days lost*
- Days with help from a caregiver*

Have been changed to:

- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects ≤18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])*. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.
- Work/school days lost due to epilepsy*
- Days with help from a caregiver due to epilepsy*

Change #31

Section 8.1.2, Visits 2 to 8 (Weeks 2 to 46, Year 1)

Bullet points 22 and 23

- Work/school days lost
- Days with help from a caregiver

Have been changed to:

- Work/school days lost due to epilepsy

- Days with help from a caregiver due to epilepsy

Change #32

Section 8.1.3, Visits 9 to 11 (Weeks 62 to 94, Year 2)

Bullet points 22 and 23

- Work/school days lost
- Days with help from a caregiver

Have been changed to:

- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #33

Section 8.1.4, Visits 12, 13, 14, 15, 16, and 17 (Weeks 118, 142, 166, 190, 214, and 238, Years 3 to 5)

Bullet points 2, 3, 4, 9, and 17 through 23

- Physical examination (brief, Visit 12, 14, and 16; complete, Visit 13, 15, and 17)
- Neurological examination (brief, Visit 12, 14, and 16; complete, Visit 13, 15, and 17)
- ECG (12-lead) assessment
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and a urine pregnancy test [for women of childbearing potential])
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Achenbach CBCL for subjects ≥6 years to <18 years of age
- BRIEF for subjects ≥5 to <18 years of age
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Have been changed to:

Bullet points 2, 3, 4, 9, 10, 18, and 19

- Physical examination (complete, Visit 13, 15, and 17)
- Neurological examination (brief, Visit 12, 14, and 16)
- ECG (12-lead) assessment (Visit 13, 15, and 17)

- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required)
- Urine pregnancy test [for women of childbearing potential])
- Achenbach CBCL for subjects ≥6 years to <18 years of age (Visits 13, 15, and 17)
- BRIEF for subjects ≥5 to <18 years of age (Visits 13, 15, and 17)

EQ-5D-3L, QOLIE-31-P, Healthcare resource use, Work/school days lost, and Days with help from a caregiver were removed from Table 5-2 as health outcome variables will be assessed only during the first 2 years of treatment.

Change #34

Section 8.2 Early Termination Visit

Bullet points 3 and 9, and health outcome bullets

- Neurological examination (complete)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Have been changed to:

- Neurological examination (brief)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])

The following assessments are only applicable at the ET Visit for subjects early terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #35

Section 8.3 Termination Visit

Paragraph 2

Taper of LCM is not required for subjects who complete the study and continue on commercially available LCM. Subjects transitioning to commercially available LCM will do so immediately and will continue at a dose determined by the investigator.

Bullet points 3 and 9, and health outcome bullets

- Neurological examination (complete)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Have been changed to:

Paragraphs 2 and 3

Patients transitioning to the MAP will complete the Treatment Period after 2 years but continue their treatment with MAP LCM.

Taper of LCM is not required for subjects who complete the study and continue on MAP LCM or commercially available LCM. Subjects transitioning to MAP LCM or commercially available LCM will do so immediately and will continue at a dose determined by the investigator.

Bullet points 3 and 9, and health outcome bullets

- Neurological examination (complete) Note: Complete neurological exam to be performed for patients terminating the study during Years 1-2, brief exam for patients terminating during Years 3-5.
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])

The following assessments are only applicable at the Termination Visit for subjects terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use

- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #36

Section 8.4.1, End of Taper Visit

Bullet points 3, 14, 15, and 16

- Neurological examination (complete)
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Have been changed to:

- Neurological examination (brief)

The following assessments are only applicable at the End of Taper Visit for subjects terminating/early terminating the study during the first 2 years (see Section 4.2.3):

- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #37

Section 8.4.2, Safety Follow-Up Visit

Bullet points 3, 10, 11, and 12

- Neurological examination (complete)
- Healthcare resource use
- Work/school days lost
- Days with help from a caregiver

Have been changed to:

- Neurological examination (brief)

The following assessments are only applicable at the Safety Follow-Up Visit for subjects terminating/early terminating the study during the first 2 years (see Section 4.2.3):

- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #38

Section 8.5, Unscheduled Visit

Bullet points 2 and 3

- Physical examination (brief)
- Neurological examination (brief)

Paragraph 3

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

Have been changed to:

- Physical examination (brief) during the first 2 years
- Neurological examination (brief) during the first 2 years

Paragraph 3

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

Change #39

Section 9.1, Seizure frequency

Subjects will keep a diary to record daily seizure activity from Visit 1 until the end of study participation. Efficacy variables will be assessed using the seizure count information recorded on the subject diaries. 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:

9.1 Seizure variables

Subjects will keep a diary to record seizure activity from Visit 1 until the end of study participation. Efficacy variables will be assessed using the seizure count information recorded on the subject diaries. The subject should be reminded to bring the diary to each clinic visit.

9.1.1 PGTC seizures

The following information will be recorded 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.

9.1.2 Absence and myoclonic seizures

In the subject diary, the following information will be recorded:

- 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 #40

9.2 Health outcome variables

The following text has been added:

Health outcome variables will be evaluated during the first two years of treatment.

Change #41

9.2.4 Healthcare resource use

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

9.2.5 Number of working or school days lost

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

9.2.6 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:

9.2.4 Healthcare resource use

Healthcare resource use will include concomitant medical procedures, hospitalizations, and healthcare provider visits during the first 2 years of treatment.

9.2.5 Number of working or school days lost due to epilepsy

The number of working or school days lost by the subject due to epilepsy will be recorded, as applicable, during the first 2 years of treatment.

9.2.6 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, during the first 2 years of treatment.

Change #42

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 #43

Section 10.1.1.3, Adverse events of special interest

A bullet point has been 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 #44

Section 10.1.3, 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:

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 10.3.1.4.

New paragraph 3

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

Change #45

Section 10.1.6, Pregnancy

Paragraph 1

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 should be scheduled 2 weeks after the subject has discontinued her IMP.

Paragraphs 3 through 6

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.

Have been changed to:

Section 10.1.4, Pregnancy

Paragraph 1

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 Patient Safety (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 should be scheduled 2 weeks after the subject has discontinued her IMP.

Paragraphs 3 through 5

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, UCB will ask the investigator or designee to contact the subject and his partner to request consent 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/contract research organization (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.

Change #46

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 CRF, 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 #47

The following section has been added:

Section 10.2, 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 9.1).

Change #48

Section 10.6.1, Liver function tests

Refer to Section 6.3 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 performed. In all cases of transaminases (AST, ALT, or both) ≥8xULN or a potential case of drug-induced liver injury (ie, Hy's law), testing for hepatitis E immunoglobulin M antibodies will be performed.

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 10.3.1, Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 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 10.3.1.1). 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 10.3.1.4).

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 CRF pages.

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 10.3.1.2.1 are met, rechallenge with IMP may be appropriate.

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 10.3.1.3); 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 10.3.1.2).	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 10.3.1.3).	

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 10.3.1.1. 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.

10.3.1.1 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 10.3.1.3) and SAE report (if applicable).

10.3.1.2 Immediate action: determination of IMP discontinuation

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

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 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.

10.3.1.2.1 IMP restart/rechallenge (if applicable)

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

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 10-3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 10.3.1.3 and Section 10.3.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.

- Subject agrees to the investigator-recommended monitoring plan.

10.3.1.3 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 CRF. 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

10.3.1.4 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 #49

Section 12.1, Definition of analysis sets

The following subsection has been added:

12.1.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have a signed Informed Consent/ Assent form.

Change #50

Section 12.3.1, Safety analyses

A new Paragraph 2 has been added:

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. Laboratory measurements as described in Section 10.3 and other safety measurements as described in Section 10.4 will be presented.

Change #51

Section 12.4, Planned efficacy analyses

Paragraph 2

Days with myoclonic or absence seizures are more clinically relevant endpoints; therefore, days with myoclonus and absence will be summarized separately using the same method for PGTC seizures. Subjects who were seizure-free from all generalized seizures will also be tabulated (PGTC, myoclonic and absence seizures combined).

Has been changed to:

Days with myoclonic or absence seizures are more clinically relevant endpoints; therefore, change in and percent change in days with myoclonus and absence will be summarized. The percentage of subjects with 50% reduction in days with absence and myoclonic seizures per 28 days compared to the Prospective Baseline will be presented. Subjects who were seizure free from all generalized seizures will also be tabulated.

Change #52

Section 15, 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. doi: 10.1212/WNL.0b013e31822cfc90.

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.

Change #53

Appendix 6: Contraception Table was added in Section 16.6.

16.6 Appendix 6: Protocol Amendment 3

Rationale for the amendment

The primary purpose of this amendment is to simplify the assessments and procedures for all subjects during the first 94 weeks of study and to simplify the assessments and procedures for adults after Week 94. Pediatric assessments will be kept as they are after Week 94 for regulatory purposes.

In addition, the following changes have been made:

- To allow the Safety Follow-Up for subjects tapered in SP0982 after the 125th event occurs in SP0982, this will be performed at Visit 1 of EP0012 and subjects will have their 4-week Safety Follow-Up in EP0012.
- To restructure the safety variables
- The planned number of subject is aligned with the pivotal study SP0982
- To update the introduction section with regulatory information on the marketing authorization of Vimpat and to provide an update on the lacosamide (LCM) clinical program.
- To clarify the potential drug-induced liver injury (PDILI) criteria requiring immediate and permanent discontinuation of the investigational medicinal product (IMP).
- To update the 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 EP0012 Amendment 2" to "Protocol EP0012 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	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial
Protocol Amendment 3	29 Nov 2017	Substantial

Change #2

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Email:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Allée de la Recherche 60 1070 Brussels BELGIUM
Phone:	[redacted]
Email:	[redacted]

Change #3

Section 1 SUMMARY

Paragraph 1 (last sentence)

It is estimated that approximately 200 subjects across approximately 150 sites will be enrolled in EP0012.

Paragraph 2

Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg twice daily [bid]) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Paragraph 10

The primary safety variables are adverse events (AEs), subject withdrawals due to AEs, 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. Secondary safety variables are changes in hematology, chemistry, and urinalysis parameters; changes in 12-lead electrocardiograms (ECGs); and changes in vital sign measurements (ie, blood pressure [BP] and pulse rate), including body mass index (BMI) and physical (including neurological) examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function-Preschool Version® [BRIEF®/BRIEF-P®]). The seizure efficacy variables are evaluations of seizure frequency, based on information included in subject diaries. The health outcome variables, including the Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), the Pediatric Quality of Life Inventory™ (PedsQL™), the 3-level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L), healthcare resource use, the number of working or school days lost by subjects due to epilepsy, and the number of days with help from a caregiver due to epilepsy will be assessed for the first 2 years of treatment.

Has been changed to:

Paragraph 1 (last sentence)

It is estimated that up to 250 subjects across approximately 150 to 180 sites will be enrolled in EP0012.

Paragraph 2

Once 125 subjects have had a second PGTC seizure in SP0982, that study will have met its protocol-defined stopping and all subjects will transition into EP0012 or taper off study medication. Subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg twice daily [bid]) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Paragraph 10

The primary safety variables are adverse events (AEs), subject withdrawals due to AEs, 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. Secondary safety variables are percentage of treatment-emergent marked abnormalities in hematology, and chemistry parameters; percentage of treatment-emergent marked abnormalities in 12-lead electrocardiograms (ECGs); and percentage of treatment-emergent marked abnormalities in vital sign measurements (ie, blood pressure [BP] and pulse rate). Other safety variables include changes in hematology, chemistry, and urinalysis parameters, changes in 12-lead ECGs, and changes in in vital sign measurements (ie, BP and pulse rate), including weight and height and physical (including neurological) examination findings. In addition, for pediatric subjects <18 years of age, safety will be evaluated using behavioral assessments (Achenbach Child Behavior Checklist [CBCL]), and cognitive function assessments (Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function-Preschool Version® [BRIEF®/BRIEF-P®]). The seizure efficacy variables are evaluations of seizure frequency, based on information included in subject diaries. The health outcome variables, including the Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P), the Pediatric Quality of Life Inventory™ (PedsQL™), the 3-level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-3L), healthcare resource use, the number of working or school days lost by subjects due to epilepsy, and the number of days with help from a caregiver due to epilepsy will be assessed for the first 2 years of treatment.

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 monotherapy and 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.

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

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 also 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.

Paragraph 8

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.

Change #5

Section 4.1.2 Secondary safety variables

Secondary safety variables are:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, BP and pulse rate), including BMI and physical (including neurological) examination findings

Has been changed to:

Secondary safety variables are:

- Percentage of treatment-emergent marked abnormalities in hematology and chemistry parameters
- Percentage of treatment-emergent marked abnormalities in 12-lead ECGs
- Percentage of treatment-emergent marked abnormalities in vital sign measurements (ie, BP and pulse rate)

Change #6

Section 4.1.3 Other safety variables

- Achenbach CBCL1½-5 or CBCL/6-18
- Cognitive function assessment BRIEF/BRIEF-P

Has been changed to:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, BP and pulse rate), including weight and height and physical (including neurological) examination findings

- Achenbach CBCL1½ 5 or CBCL/6 18 (for pediatric subjects only)
- Cognitive function assessment BRIEF/BRIEF-P (for pediatric subjects only)

Change #7

Section 5 Study design

Paragraph 1

This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 study as well as eligible Baseline failures from SP0982. Approximately 200 subjects from approximately 150 study sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, and study completers from SP0982 who are eligible for inclusion in EP0012 are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTC seizure criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTC seizures during that time or
- Subjects who experience a second PGTC seizure after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period of SP0982

Randomized subjects meeting SP0982 exit criteria and subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Has been changed to:

Paragraph 1

This study will enroll consenting subjects, or subjects whose legal representatives have given consent, who have completed the LCM SP0982 (or have left the primary study at the time of the 125th event, whichever came first) as well as eligible Baseline failures from SP0982. Then, some subjects who tapered in SP0982 after the 125th event may enter EP0012 for the

Safety Follow-Up only (ICF to be signed beforehand). Up to 250 subjects from 150 to 180 study sites are planned to be enrolled in EP0012.

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, and study completers from SP0982 who are eligible for inclusion in EP0012 are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTC seizure criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTC seizures during that time or
- Subjects who experience a second PGTC seizure after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period of SP0982
- Subjects who were ongoing in SP0982 when the 125th event occurred

SP0982 Safety Follow-Up subjects

- Subjects tapered in SP0982 after the 125th event occurs will enter EP0012 for the Safety Follow-Up Visit only.

Randomized subjects meeting SP0982 exit criteria and subjects who completed SP0982 will start at Visit 1 on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. In addition, once 125 subjects have had a second PGTC seizure in SP0982 (ie, the 125th event has occurred), that study will have met its protocol-defined end. All subjects ongoing in SP0982 will transition into EP0012 for further long term treatment for a Safety Follow-Up.

Change #8

Section 5.1.1 Study duration per subject

Bullet 5 has been updated.

- An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. 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.

Has been changed to:

– An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. 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 same design will apply to some of the subjects tapered in SP0982 at the time of the 125th event and who entered EP0012 for the Safety Follow-Up Visit only and to subjects who entered EP0012 for a Safety Follow-up Visit after discontinuing SP0982 due to the study stopping.

Change #9

Section 5.1.2 Planned number of subjects and site(s)

Up to 200 subjects across approximately 150 international sites are planned to be enrolled in this study.

Has been changed to:

Up to 250 subjects across 150 to 180 international sites are planes to be enrolled in this study.

Change #10

Section 5.2 Schedule of study assessments

The schedule of study assessments for treatment Years 1 to 2 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5–1. An additional schedule of study assessments for treatment Years 3 to 5 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5–2. The schedule of study assessments for the Taper and Safety Follow-Up is provided in Table 5–3.

Has been changed to:

The schedule of study assessments for treatment Years 1 to 2 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5-1. An additional schedule of study assessments for treatment Years 3 to 5 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit) is provided in Table 5-2 for subjects <18 years and Table 5-3 for subjects ≥18 years. The schedule of study assessments for the Taper Period and Safety Follow-Up Visit (including subjects who tapered in SP0982 after the 125th event consented to enter EP0012 for the Safety Follow-up only) is provided in Table 5-4.

Table 5-1

A has been added to explain that Visit 6, Visit 7 and Visit 10 will not be performed according to Protocol Amendment 3. Footnote 'b' has 'vital signs' removed and for footnote 'd' Week 30 Week 38 and Week 78 has been added to footnote for consistency.

Note: Visit 6, Visit 7 and Visit 10 (**) assessments will not be performed according to Protocol Amendment 3.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

[d] Telephone contacts are required every 8 weeks including Week 30 and Week 38 during the study, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, Week 78, and Week 86.

Has been changed to:

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

[d] Telephone contacts are required every 8 weeks including Week 30 and Week 38 during the study, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, Week 78, and Week 86.

Table 5-2

Table title has been updated for pediatrics only, a note has been added and footnote 'b' and 'h' have been updated.

Table 5-2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	TC[d]	V12	V13	V14	V15	V16	V17/ Term[e]	ET Visit[f]	Term Visit[g]	LCM Solution Dispensation Visit[h]	Unscheduled Visit
Week		118	142	166	190	214	238				NA

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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, etc. The C-SSRS must be performed if the Unscheduled Visit is due to an AE.

[h] Dispensation Visit will occur 12 weeks after each 24-weekly visit Year 3 onwards and will be for the purpose of dispensing LCM solution for pediatric subjects <50kg.

Has been changed to

Table 5-2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit[h]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**

Note: Subjects who turn 18 years during the course of this study will be considered as pediatric, however these subjects will not need to complete the Achenbach CBCL and BRIEF assessments.

[h] Dispensation Visit will occur 12 weeks after each 24-weekly visit from Year 2 (Visit 11) to Year 3 onwards and will be for the purpose of dispensing LCM solution for pediatric subjects <50kg.

Change #11

The following table has been added for adult subjects for Years 3 to 5.

Table 5-3: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects ≥18 years)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	**Open-label: up to approximately 5 years**							**Up to 5 weeks**			
Year of study	**Year 3**			**Year 4**		**Year 5**					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit[h]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X		X
Laboratory tests[h]		X		X		X	X	X	X		
Pregnancy test[i]		X	X	X	X	X	X	X	X		
Dispense subject diary		X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X		X
Call IRT		X	X	X	X	X	X	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	
LCM review/return		X	X	X	X	X	X	X	X	X	
Withdrawal criteria	X	X	X	X	X	X	X	X	X		X
AE reporting	X	X	X	X	X	X	X	X	X		X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit

[a] The Treatment Period will continue for at least 2 years.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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

physical or neurological examination, ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230.

[e] At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4.

[g] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 17 if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[h] Laboratory tests include chemistry, hematology and urinalysis.

[i] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion

Change #12

Table 5-4

A note and footnote 'b' have been amended.

[b] There will be a 30-day (-1/+3 days) Safety Follow-Up Period for subjects who complete the End of Taper Visit for SP0982 and EP0012. 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 Visit.

Has been changed to

Note: The schedule of study assessments for the Taper Period and Safety Follow-Up Visit includes some of the subjects who tapered in SP0982 after the 125th event who consented to enter EP0012 for the Safety Follow-Up only.

[b] 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 Visit.

Change #13

Section 6.3 Withdrawal criteria

The following new criterion has been added

1. Tapered subjects from SP0982 who enter EP0012 after the 125th event will be withdrawn at the enrollment visit and enter directly into the Safety Follow-Up Period without and ET Visit being performed in EP0012.

Change #14

Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with PDILI must be assessed to determine if investigational medicinal product (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%).

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%).

Change #15

Section 7.2 Treatment(s) to be administered

Paragraph 2 has been updated

Tablets **must not be broken**. In rare cases where uneven dosing (e.g., 350mg/day, 450mg/day, 550mg/day, etc) is medically needed, although the interactive response technology (IRT) will not dispense the exact dose, please contact the medial monitor for additional instructions.

Has been changed to:

Tablets **must not be broken**. In rare cases where uneven dosing (e.g., 350mg/day, 450mg/day, 550mg/day, etc) is medically needed, although the interactive response technology (IRT) will not dispense the exact dose, please contact the Medical Monitor for additional instructions. 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 #16

Section 7.2.1 Treatment Period

Paragraph 1 and 3

At Visit 1, subjects who completed SP0982 will start on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

Has been changed to:

At Visit 1, subjects who completed SP0982 will start on a dose of LCM 10mg/kg/day for pediatric subjects weighing <30kg, LCM 8mg/kg/day for pediatric subjects weighing ≥30kg to <50kg, and LCM 400mg/day (200mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg. Subjects who are eligible Baseline failures from SP0982 will start at Visit 1 on a dose of LCM 2mg/kg/day for pediatric subjects weighing <50kg, and LCM 100mg/day (50mg bid) for adult subjects (≥18 years of age) or pediatric subjects weighing ≥50kg.

Subjects who tapered in SP0982 after the 125th event will enroll at Visit 1 and proceed directly to the Safety Follow-up Period without receiving LCM. At any time during the course of the study if it becomes apparent that a subject is unable to attain at least this minimum dose of 4mg/kg/day (oral solution) or 200mg/day (tablets), then the subject must enter the Taper Period and be withdrawn from the study.

Change #17

Section 8.1.1 Visit 1 (Week 0)

The following tasks and procedures are to be performed at this visit (for subjects who have completed SP0982, assessments marked [*] should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1; for eligible Baseline failures from SP0982, a full Visit 1 is required including all scheduled tasks and procedures).

Has been changed to:

The following tasks and procedures are to be performed at this visit (for subjects who have completed SP0982, assessments marked [*] should have already been completed during the last visit of the previous protocol and do not need to be repeated at Visit 1; for eligible Baseline failures from SP0982, a full Visit 1 is required including all scheduled tasks and procedures). Tapered subjects from SP0982 will enter EP0012 for the Safety Follow-Up only and will be withdrawn at Visit 1 once Visit 1 assessments have been performed. Details of the Safety Follow-Up are provided in Section 8.4.2 and Section 8.4.3.

Change #18

Section 8.1.2 Visits 2 to 8 (Weeks 2 to 46, Year 1)

Section 8.1.2 Visits 2 to 8 (Weeks 2 to 46, Year 1)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 2, 3, 4, 5, 6, and 7; complete, Visit 8)
- Neurological examination (brief, Visit 2, 3, 4, 5, 6, and 7; complete, Visit 8)
- ECG (12-lead) assessment (Visit 2, 4, 6, and 8 only)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight (Visit 4, 6, and 8 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 8 only)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) [Visit 2, 5, and 8 only], and a urine pregnancy test [for women of childbearing potential])

Has been changed to:

8.1.2 Visits 2 to 8 (Weeks 2 to 46, Year 1, excluding Visit 6 and Visit 7)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 2, 3, 4, and 5; complete, Visit 8)

- Neurological examination (brief, Visit 2, 3, 4, and 5; complete, Visit 8)
- ECG (12-lead) assessment (Visit 2, 4, and 8 only)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight (Visit 4,and 8 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 8 only)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) [Visit 2, 5, and 8 only], and a urine pregnancy test [for women of childbearing potential])

Change #19

Section 8.1.3 Visits 9 to 11 (Weeks 62 and 94, Year 2)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 9 and 10; complete, Visit 11)
- Neurological examination (brief, Visit 9 and 10; complete, Visit 11)
- ECG (12-lead) assessment (Visit 9, 10, and 11)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 9 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 11 only)
- 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])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 9 and 11) (for subjects ≥12 years of age)

- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age) (Visit 9 and 11 only)
- Achenbach CBCL for subjects <18 years of age (Visit 9 and 11 only)
- BRIEF for subjects <18 years of age (Visit 9 and 11 only)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Has been changed to:

8.1.3 Visits 9 and 11 (Weeks 62 and 94, Year 2, excluding Visit 10)

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (brief, Visit 9; complete, Visit 11)
- Neurological examination (brief, Visit 9; complete, Visit 11)
- ECG (12-lead) assessment (Visit 9, and 11)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 9 only)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 11 only)
- 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])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- EQ-5D-3L (Visit 9 and 11) (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age) (Visit 9 and 11 only)
- Achenbach CBCL for subjects <18 years of age (Visit 9 and 11 only)

- BRIEF for subjects <18 years of age (Visit 9 and 11 only)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #20

Section 8.1.4 Visits 12, 13, 14, 15, 16, and 17 (Weeks 118, 142, 166, 190, 214, and 238, Years 3 to 5)

This section has been split into two - 8.1.4.1 and 8.1.4.2

8.1.4.1 Subjects <18 years

The following tasks and procedures are to be performed at these visits:

- Concomitant medications and AEDs
- Physical examination (complete, Visit 13, 15, and 17)
- Neurological examination (brief, Visit 12, 14, and 16)
- ECG (12-lead) assessment (Visit 13, 15, and 17)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 12, 14, and 16)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 13, 15, and 17)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required). Laboratory tests are not performed at Visit 13 and Visit 15 according to Protocol Amendment 3.
- Urine pregnancy test (for women of childbearing potential)
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects ≥6 years to <18 years of age (Visit 13, 15, and 17)
- BRIEF for subjects ≥5 to <18 years of age (Visit 13, 15, and 17)

8.1.4.2 Subjects ≥18 years

- The following tasks and procedures are to be performed at these visits:
- Concomitant medications and AEDs
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required. Laboratory tests are not performed at Visit 13 and Visit 15 according to Protocol Amendment 3.
- Urine pregnancy test (for women of childbearing potential)
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting

Change #21

Section 8.1.5 Telephone contact

Telephone contacts are required every 8 weeks during Year 2 to Year 5, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, and Week 86. Telephone contacts in Years 3 to 5 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, and Week 230.

Has been changed to:

Telephone contacts are required at Week 30 and Week 38 and every 8 weeks during Year 2 to Year 5, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, and Week 86. Telephone contacts in Years 3 to 5 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, and Week 230.

Change #22

Section 8.2 Early Termination Visit

This section has been updated to indicate the tasks and procedures which exclude subjects ≥18 years.

The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs

- Physical examination (complete)
- Neurological examination (brief)
- ECG (12-lead) assessment
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age

The following assessments are only applicable at the ET Visit for subjects early terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Has been changed to:

The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs
- Physical examination (complete) excluding subjects ≥18 years after the first 2 years
- Neurological examination (brief) excluding subjects ≥18 years after the first 2 years

- ECG (12-lead) assessment excluding subjects ≥18 years after the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments excluding subjects ≥18 years after the first 2 years
- Body weight and height excluding subjects ≥18 years after the first 2 years
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) excluding subjects ≥18 years after the first 2 years
- C-SSRS assessment (for subjects ≥6 years of age) excluding subjects ≥18 years after the first 2 years
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age

The following assessments are only applicable at the ET Visit for subjects early terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #23

Section 8.3 Termination Visit

This section has been updated to indicate the tasks and procedures which exclude subjects ≥18 years.

The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs

- Physical examination (complete)
- Neurological examination (complete) Note: Complete neurological exam to be performed for patients terminating the study during Years 1-2, brief exam for patients terminating during Years 3-5.
- ECG (12-lead) assessment
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (excluding subjects ≥18 years)
- C-SSRS assessment (for subjects ≥6 years of age) (excluding subjects ≥18 years)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary for subjects undergoing taper
- Subject diary return/review
- Dispense LCM for subjects undergoing taper
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age

The following assessments are only applicable at the Termination Visit for subjects terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy

Days with help from a caregiver due to epilepsy

Has been changed to:

The following tasks and procedures are to be performed at this visit:

- Concomitant medications and AEDs
- Physical examination (complete) excluding subjects ≥18 years after the first 2 years

- Neurological examination (complete) Note: Complete neurological exam to be performed for patients terminating the study during Years 1-2 for all subjects and brief exam for subjects <18 years terminating during Years 3-5 (excluding subjects ≥18 years). Neurological exam is excluded for subjects ≥18 years after the first 2 years.
- ECG (12-lead) assessment excluding subjects ≥18 years after the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments excluding subjects ≥18 years after the first 2 years
- Body weight and height excluding subjects ≥18 years after the first 2 years
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) excluding subjects ≥18 years after the first 2 years
- C-SSRS assessment (for subjects ≥6 years of age) excluding subjects ≥18 years after the first 2 years
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, endocrinology for subjects <18 years of age at Visit 1, urinalysis, and a serum pregnancy test [for women of childbearing potential])
- Contact IRT
- Dispense subject diary for subjects undergoing taper
- Subject diary return/review
- Dispense LCM for subjects undergoing taper
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects <18 years of age
- BRIEF for subjects <18 years of age

The following assessments are only applicable at the Termination Visit for subjects terminating the study within the first 2 years (see Section 4.2.3):

- EQ-5D-3L (for subjects ≥12 years of age)
- QOLIE-31-P (for subjects ≥18 years of age)/PedsQL (for subjects <18 years of age)
- Healthcare resource use
- Work/school days lost due to epilepsy
- Days with help from a caregiver due to epilepsy

Change #24

Section 8.4.1

The following sentence has been added at the end of the section:

Subjects who were already tapered in SP0982 after the 125th event occurred do not need to undergo the End of Taper Visit assessments in EP0012 as the assessments were performed in SP0982.

Change #25

Section 8.4.2 Safety Follow-Up Visit

Following the End of Taper Visit, the subject will return 2 weeks 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:

Has been changed to:

Following the End of Taper Visit, the subject will return 2 weeks after the last dose of study drug for a Safety Follow-Up Visit (including subjects tapered in SP0982 after the 125th event occurs who enter EP0012 only for a Safety Follow-Up Visit). During the Safety Follow-Up Visit, the following assessments will be performed:

Change #26

Section 8.5 Unscheduled Visit

This section has been updated to indicate the tasks and procedures which exclude subjects ≥18 years.

During an Unscheduled Visit the following assessments are required:

- Concomitant medications and AEDs
- Physical examination (brief) during the first 2 years
- Neurological examination (brief) during the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments
- Contact IRT
- Subject diary return/review
- Assess withdrawal criteria
- AE reporting

Has been changed to:

During an Unscheduled Visit the following assessments are required:

- Concomitant medications and AEDs
- Physical examination (brief) during the first 2 years ≥18 years after the first 2 years
- Neurological examination (brief) during the first 2 years ≥18 years after the first 2 years
- Vital signs (pulse rate, BP) including orthostatic assessments ≥18 years after the first 2 years
- Contact IRT

- Subject diary return/review
- Assess withdrawal criteria
- AE reporting

Change #27

Section 10.3.1 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.

16.7 Appendix 7: Protocol Amendment 4

Rationale for the amendment

The primary purpose of this amendment is to extend the treatment of the subjects and have LCM available for the subjects till the main approvals for an extended PGTCS indication are obtained. UCB seeks to obtain the approvals in first instance in US, EU, and Japan.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Globally changed PGTC seizures to PGTCS.

Specific changes

Change #1

Title page:

The title was updated from "Protocol EP0012 Amendment 3" to "Protocol EP0012 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	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial
Protocol Amendment 3	29 Nov 2017	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial
Protocol Amendment 3	29 Nov 2017	Substantial
Protocol Amendment 4	13 Dec 2019	Substantial

Change #2

Section 1 Summary

Paragraph 6

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. During the Treatment Period, Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinical visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur every 24 weeks thereafter until the end of the study. From Year 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

Has been changed to:

EP0012 will consist of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. During the Treatment Period, Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinical visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur every 24 weeks thereafter until the end of the study. From Year 2 (Visit 11) to 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed, and empty LCM bottles will be returned.

Change #3

Section 4.1.1 Primary safety variables

The primary safety variables are:

- Adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- 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 days with absence seizures per 28 days during the Treatment Period as compared to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days during the Treatment Period as compared to the Prospective Baseline

Has been changed to:

The primary safety variables are:

- Adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- Incidence of new appearance of absence and/or myoclonic seizures during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days compared to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days compared to the Prospective Baseline
- Percentage of subjects with at least 50% worsening in days with absence seizures
- Percentage of subjects with at least 50% worsening in days with myoclonic seizures

Change #4

Section 5.1 Study description

Paragraph 2
For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, and study completers from SP0982 who are eligible for inclusion in EP0012 are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTC seizure criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTC seizures during that time or

Subjects who experience a second PGTC seizure after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTC seizures within the 24-week Treatment Period of SP0982

- Subjects who were ongoing in SP0982 when the 125th event occurred

SP0982 Safety Follow-Up subjects

- Subjects tapered in SP0982 after the 125th event occurs will enter EP0012 for the Safety Follow-Up Visit only.

Has been changed to:

For the purposes of this study, Baseline failures, randomized subjects who meet SP0982 exit criteria, study completers from SP0982 who are eligible for inclusion in EP0012, SP0982 Safety Follow-Up subjects, and Other are defined as:

SP0982 Baseline failures

- Subjects who complete the Prospective Baseline Period of SP0982 and meet all entry criteria except the minimum PGTCS criteria required for randomization (Baseline failures)

Randomized subjects meeting SP0982 exit criteria

- Subjects who completed the first 6 weeks of the Treatment Period (after randomization) of SP0982 and experienced ≥2 PGTCS during that time or

Subjects who experience a second PGTCS after the first 6 weeks of the Treatment Period of SP0982

SP0982 completers

- Subjects who experience <2 PGTCS within the 24-week Treatment Period of SP0982
- Subjects who were ongoing in SP0982 when the 125th event occurred

SP0982 Safety Follow-Up subjects

- Subjects tapered in SP0982 after the 125th event occurs will enter EP0012 for the Safety Follow-Up Visit only

Other

- Subjects that enrolled in EP0012 that did not fall into the above categories

Change #5

Section 5.1 Study description

Paragraphs 9 and 10

EP0012 will last at least 2 years and consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1. Visit 2 will occur 2 weeks after Visit 1, and Visit 3 will occur 4 weeks later (Week 6). Clinic visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur every 24 weeks thereafter until the end of the study. From Year 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed and empty LCM bottles will be returned.

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs, as well as to ensure subjects are compliant with LCM administration and diary completion. The study duration and the total number of clinic visits will vary for each subject. Treatment will continue until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until UCB decides to close the study.

Have been changed to:

EP0012 will last at least 2 years and consist of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. Visit 1 of EP0012 is the same as the Final Clinic Visit of SP0982 for completers and subjects who meet the SP0982 exit criteria. Eligible Baseline failures from SP0982 who choose to enter this study will undergo a complete Visit 1. Visit 2 will occur 2 weeks after Visit 1 and Visit 3 will occur 4 weeks later (Week 6). Clinic visits will then occur every 8 weeks for the first year, and every 16 weeks in the second year. For subjects who continue in the study after Year 2, visits will occur every 24 weeks thereafter until the end of the study. From Year 2 (Visit 11) to 3 onwards, pediatric subjects weighing <50kg will return to the clinic for an additional Dispensation Visit 12 weeks after each 24-weekly visit, for the dispensation of LCM solution; LCM usage will be reviewed, and empty LCM bottles will be returned.

A telephone contact will occur every 8 weeks if no clinic visit is scheduled. Telephone contacts will be used to obtain information regarding concomitant medication use, and assess withdrawal criteria and AEs, as well as to ensure subjects are compliant with LCM administration and diary completion.

Change #6

Section 5.1 Study description

Paragraph 13

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or their parent(s)/legal representative(s).

Has been changed to:

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM (Taper Visit and SFU) may not be required for some subjects who leave the study depending on the treatment option selected by the investigator in consultation with the subject and/or their parent(s)/legal representative(s).

Change #7

Section 5.1.1 Study duration per subject

For each subject, the study will last from study entry until LCM is approved for use in the subject's country for the treatment of PGTC seizures in subjects with IGE, or until UCB has determined that the clinical development program for the indication will be formally discontinued, or until the sponsor decides to close the study. It is anticipated that at least 2 years of treatment will be performed to allow for the collection of long-term safety data. If LCM is not approved for use in the subject's country at the time the sponsor closes the study, access to LCM will be provided according to local laws.

The following study periods are defined:

- A Treatment Period lasting at least 2 years.
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator.
  - Subjects tapering off LCM will do so over a period of up to 4 weeks (see taper schedule, Table 7–2).
  - An End of Taper Visit will occur after the final LCM dose for subjects who taper off LCM. 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 same design will apply to some of the subjects tapered in SP0982 at the time of the 125th event and who entered EP0012 for the Safety Follow-Up Visit only and to subjects who entered EP0012 for a Safety Follow-up Visit after discontinuing SP0982 due to the study stopping.

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

Depending on the local regulations, after 2 years, subjects may continue to receive LCM in a managed access program (MAP).

Has been changed to:

For adult subjects, treatment will continue for at least 2 years. Once 2 years of participation are reached, adult subjects will continue to participate until 1 of the 2 following conditions are met.

- LCM is approved for use for the treatment of PGTCS in subjects with IGE in the subject's country for or until the latest approval is granted either by EMA, FDA, or PMDA.
- For pediatric subjects, treatment will continue until the latest of 1 of the following 2 conditions are met:
  - up to 5 years of participation or
  - until the latest approval is granted either by EMA, FDA, or PMDA

Adult and pediatric subjects are completers if they continue in the study for the maximum duration in their respective region.

The following study periods are defined:

- A Treatment Period lasting for at least 5 years (238 weeks) for the population less than 18 years old at enrollment and will be shorter for adults leaving the study when the PGTCS indication approvals are being obtained during the course of the study.
- An up to 4-week Taper Period and a 30-day Safety Follow-Up Period.
  - Subjects continuing LCM treatment with commercially available LCM will transition to a dose determined by the investigator and do not have to perform the tapering (Taper Visit and SFU).
  - Subjects tapering off LCM will do so over a period of up to 4 weeks (see taper schedule, Table 7–2).
  - An End of Taper Visit (latest 3 days after the final dose) will occur after the final LCM dose for subjects who taper off LCM. 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 same design will apply to some of the subjects tapered in SP0982 at the time of the 125th event and who entered EP0012 for the Safety Follow-Up Visit only and to subjects who entered EP0012 for a Safety Follow-up Visit after discontinuing SP0982 due to the study stopping.

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

Subjects who entered EP0012 as <18 years and become adults (≥18 years) during the study, will remain in the study for at least 5 years (238 weeks).

Change #8

Section 5.2 Schedule of study assessments

Table 5-1 Schedule of study assessments for Years 1 and 2 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit)

Footnote ‘a’

The Treatment Period will continue for at least 2 years.

Footnote ‘e’

An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4.

Has been changed to:

Footnote ‘a’

The duration of the Treatment Period will continue for at least 2 years and vary by subject age group and is defined in Section 5.1.1.

Footnote ‘e’

An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the early Termination Visit is the last visit in the study.

Change #9

Section 5.2 Schedule of study assessments

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit[h]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X		X
Physical exam (complete)[i]			X		X		X	X	X		
Neurological exam (brief)[j]		X		X		X			X		
12-lead ECG[k]			X		X		X	X	X		
Vital signs (BP and pulse) including orthostatic assessments[l]		X	X	X	X	X	X	X	X		X
Body weight and height[m]		X	X	X	X	X	X	X	X		
Tanner Stage[n]			X		X		X	X	X		
Laboratory tests		X		X		X	X[o]	X	X		
Endocrinology[p]								X	X		
Pregnancy test[q]		X	X	X	X	X	X	X	X		
Call IRT		X	X	X	X	X	X	X	X		X
C-SSRS[r]		X	X	X	X	X	X	X	X		X
Dispense subject diary		X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X		X

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit[h]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**
Dispense LCM		X	X	X	X	X	X	X	X	X	
LCM review/return		X	X	X	X	X	X	X	X	X	
Withdrawal criteria	X	X	X	X	X	X	X	X	X		X
AE reporting	X	X	X	X	X	X	X	X	X		X
Achenbach CBCL[s]			X		X		X	X	X		
BRIEF[t]			X		X		X	X	X		

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; exam=examination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit

Note: Subjects who turn 18 years during the course of this study will be considered as pediatrics, however these subjects will not need to complete the Achenbach CBCL and BRIEF assessments.

[a] The Treatment Period will continue for at least 2 years.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230.

[e] At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4.

[g] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 17 if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[h] Dispensation Visit will occur 12 weeks after each 24-weekly visit from Year 2 (Visit 11) to Year 3 onwards and will be for the purpose of dispensing LCM solution for pediatric subjects <50kg.

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

[j] The brief neurological examination will include selected assessment 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) a 12-lead ECG (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] Height will be recorded at Visits 12, 14, and 16, and at the ET and Termination Visit.

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

[o] Laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required.

[p] If the patient was treated in SP0982, endocrinology should be done if age was <18 years at SP0982 Visit 1. If the patient was a Baseline failure in SP0982, endocrinology should be done if age is <18 years at EP0012 Visit 1.

[q] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

[r] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[s] The Achenbach CBCL: CBCL/6-18 for children ≥6 years to <18 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range. The Achenbach CBCL should be completed by the same parent/legal representative, if possible (see Section 10.4.6).

[t] The BRIEF should be used for subjects who are ≥5 years of age. For each developmentally appropriate version of the BRIEF, subjects must have at least 1 year of data before transitioning to the next age range (see Section 10.4.7).

Has been changed to:

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years at enrollment)

	Treatment period[a]								End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years								Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5 + Extended Period						
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**Vx[f]**	**ET Visit[g]**	**Term Visit[h]**	**LCM Solution Dispensation Visit[i]**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**X**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X		X
Physical exam (complete)[j]			X		X		X	X (odd visits only)	X	X		
Neurological exam (brief)[k]		X		X		X	X	X (even visit only)		X		
12-lead ECG[l]			X		X		X	X (odd visits only)	X	X		
Vital signs (BP and pulse) including orthostatic assessments[m]		X	X	X	X	X	X	X	X	X		X
Body weight and height[n]		X	X	X	X	X	X	X (even visits only)	X	X		
Tanner Stage[o]			X		X		X	X (odd visits only)	X	X		
Laboratory tests		X		X		X	X[p]	X[p]	X	X		
Endocrinology[q]									X	X		
Pregnancy test[r]		X	X	X	X	X	X	X	X	X		
Call IRT		X	X	X	X	X	X	X	X	X		X
C-SSRS[s]		X	X	X	X	X	X	X	X	X		X

Dispense subject diary		X	X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	X	
LCM 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
AE reporting	X	X	X	X	X	X	X	X	X	X		X
Achenbach CBCL[t]			X		X		X	X (odd visits only)	X	X		
BRIEF[u]			X		X		X	X (odd visits only)	X	X		

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRIEF=Behavior Rating Inventory of Executive Function; BRIEF-P=Behavior Rating Inventory of Executive Function-Preschool Version; CBCL=Child Behavior Checklist; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; exam=examination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit; Vx=Visit X

Note: Subjects who turn 18 years during the course of this study will be considered as pediatrics, however these subjects will not need to complete the Achenbach CBCL and BRIEF assessments.

[a] The duration of the Treatment Period will vary by subject age group and is defined in Section 5.1.1.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230. If the subject remains in the study beyond Week 238, telephone contacts will continue at 8-week intervals.

[e] At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] Subjects may require additional routine visits (Visit X) if the study is still ongoing at Week 238 for the respective subject. Vx visits are to be performed every 24 weeks. Additional routine visits should be scheduled and performed in accordance with footnote 'b' to avoid visit window deviations. Assessments must be performed in accordance with Table 5–3.

[g] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the early Termination Visit is the last visit in the study.

[h] A Termination Visit must be completed for all subjects who complete the study. This can be performed in alignment of the date of the last scheduled visit if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[i] Dispensation Visit will occur 12 weeks after each 24-weekly visit from Year 2 (Visit 11) to Year 3 onwards and will be for the purpose of dispensing LCM solution for pediatric subjects <50kg.

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

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

[l] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[n] Height will be recorded at Visits 12, 14, 16, Visit X (even visits), and at the ET and Termination Visit.

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

[p] Laboratory tests are applicable for combined the last scheduled visit/Termination Visit. If the last scheduled visit is not the Termination Visit, laboratory tests are not required.

[q] If the patient was treated in SP0982, endocrinology should be done if age was <18 years at SP0982 Visit 1. If the patient was a Baseline failure in SP0982, endocrinology should be done if age is <18 years at EP0012 Visit 1.

[r] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

[s] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[t] The Achenbach CBCL: CBCL/6-18 for children ≥6 years to <18 years of age; to be completed by the parent(s)/legal representative(s) (estimated completion time 45 minutes). For each version of the CBCL, subjects must have at least 1 year of data before transitioning to the next age range. The Achenbach CBCL should be completed by the same parent/legal representative, if possible (see Section 10.4.6).

[u] The BRIEF should be used for subjects who are ≥5 years of age. For each developmentally appropriate version of the BRIEF, subjects must have at least 1 year of data before transitioning to the next age range (see Section 10.4.7).

Table 5-3: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects ≥18 years)

	Treatment period[a]							End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years							Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5					
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17/ Term[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X		X
Laboratory tests[h]		X		X		X	X	X	X		
Pregnancy test[i]		X	X	X	X	X	X	X	X		
Dispense subject diary		X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X		X
Call IRT		X	X	X	X	X	X	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	
LCM review/return		X	X	X	X	X	X	X	X	X	
Withdrawal criteria	X	X	X	X	X	X	X	X	X		X
AE reporting	X	X	X	X	X	X	X	X	X		X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit

[a] The Treatment Period will continue for at least 2 years.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230.

[e] At the completion of the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. This will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4.

[g] A Termination Visit must be completed for all subjects who complete the study. This can be combined with Visit 17 if appropriate. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study.

[h] Laboratory tests include chemistry, hematology and, urinalysis.

[i] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

Has been changed to:

Table 5-3: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects ≥18 years)

	Treatment period[a]								End of Study period			Unscheduled[b]
Duration	Open-label: up to approximately 5 years								Up to 5 weeks			
Year of study	Year 3			Year 4		Year 5 +Extended Period						
Visit[c]	**TC[d]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[e]**	**Vx[e]**	**ET Visit[f]**	**Term Visit[g]**	**LCM Solution Dispensation Visit**	**Unscheduled Visit**
Week		**118**	**142**	**166**	**190**	**214**	**238**	**X**				**NA**
Concomitant medications and AED(s)	X	X	X	X	X	X	X	X	X	X		X
Laboratory tests[h]		X		X		X	X	X	X	X		
Pregnancy test[i]		X	X	X	X	X	X	X	X	X		
Dispense subject diary		X	X	X	X	X	X	X	X	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X		X
Call IRT		X	X	X	X	X	X	Xe	X	X		X
Dispense LCM		X	X	X	X	X	X	X	X	X	X	
LCM 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
AE reporting	X	X	X	X	X	X	X	X	X	X		X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IRT=interactive response technology; LCM=lacosamide; NA=not applicable; Term=Termination; V=Visit; Vx=Visit X

[a] The duration of the Treatment Period will vary by patient age group and is defined in Section 5.1.1.

[b] Unscheduled Visits may be performed at any time after Visit 1 as clinic visits or telephone contacts, at the discretion of the investigator. 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 physical or neurological examination, ECG, vital signs, laboratory tests, etc. The C-SSRS must be performed if the Unscheduled Visit is due to a psychiatric AE.

[c] A window of ±7 days relative to Visit 1 is applicable for all visits and telephone contacts. Subjects will have a Telephone Contact every 8 weeks if no clinic visit is scheduled.

[d] Telephone contacts are required every 8 weeks during the study. Telephone contacts are not required during weeks in which a clinic visit is planned (eg, Week 118). Therefore, telephone contacts are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, Week 230. If the subject remains in the study beyond Week 238, telephone contacts will continue at 8-week intervals.

[e] Vx visits are to be performed every 24 weeks. When subjects leave the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[f] An ET Visit must be completed for all subjects who prematurely discontinue from the study. For subjects who will not continue on LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the early Termination Visit is the last visit in the study. Investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[g] A Termination Visit must be completed for all subjects who complete the Treatment Period (Week 238 or extended treatment period). This can be performed in alignment of the date of the last scheduled visit if applicable. For subjects who will not continue on commercial LCM, this visit will be followed by LCM taper, an End of Taper Visit, and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on LCM, the Termination Visit is the last visit in the study. A Termination Visit is to be done if the subject is leaving the study prior to Week 238 following the approval of the PGTCS indication in their respective region/country as follows: for US subjects, when the US approval is obtained; for EU subjects, if the EU approval is obtained; and for all other adults at the approval of the PGTCS indication in Japan (last targeted approval). When subjects leave the study, investigators should discuss treatment options with the subject and/or legal representative to best manage the subject's epilepsy.

[h] Laboratory tests include chemistry, hematology and, urinalysis.

[i] Pregnancy tests will be performed for female subjects of childbearing potential only. Serum pregnancy tests will be conducted at the following visits: Visit 1 (W0), ET, and Termination Visit. All other pregnancy tests will be urine dipstick. Baseline failures from SP0982 may have an additional urine pregnancy test at V1 of EP0012, at the investigator's discretion.

Table 5-4: Schedule of study assessments (Taper Period and Safety Follow-Up Period)

Assessment	Taper Period[a] (up to 4 weeks)	Safety Follow-Up Period[b]	
	End of Taper Visit[c]	Safety Follow-Up Visit	Safety Follow-Up TC
		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)	X	X	
Neurological exam (brief)	X	X	
12-lead ECG[d]	X	X[e]	
Vital signs (BP and pulse) including orthostatic assessments	X	X	
Body weight	X	X	
Laboratory tests:			
Chemistry/hematology	X	X[e]	
Endocrinology		X[e]	
Urine pregnancy test[f]	X	X	
Contact IRT	X		
Subject diary return/review[g]	X		
LCM review/return	X		
Withdrawal criteria	X		
AE reporting	X	X	X
C-SSRS[h]	X	X	
Healthcare resource use[i]	X	X	
Work/school days lost due to epilepsy[i]	X	X	
Days with help from a caregiver due to epilepsy[i]	X	X	

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

Note: The schedule of study assessments for the Taper Period and Safety Follow-Up Visit includes some of the subjects who tapered in SP0982 after the 125th event who consented to enter EP0012 for the Safety Follow-Up only.

[a] All subjects who discontinue LCM must complete the End of Taper Visit.

[b] 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 Visit.

[c] 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 7–2. 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 place at the ET or Termination Visit.

[d] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[f] Pregnancy tests will be performed for female subjects of childbearing potential only. A urine pregnancy test will be performed.

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

[h] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[i] Healthcare resource use, work/schools days lost due to epilepsy, and days with help from a caregiver due to epilepsy will be assessed only for patients completing the study after ≤2 years. These assessments are not applicable for patients tapering down or performing the SFU-visits during Years 3, 4 or 5).

Has been changed to:

Assessment	Taper Period[a] (up to 4 weeks)	Safety Follow-Up Period[b]	
	End of Taper Visit (maximum 3 days after visit)[c]	Safety Follow-Up Visit	Safety Follow-Up TC
		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)	X	X	
Neurological exam (brief)	X	X	
12-lead ECG[d]	X	X[e]	
Vital signs (BP and pulse) including orthostatic assessments	X	X	
Body weight	X	X	
Laboratory tests:			
Chemistry/hematology	X	X[e]	
Endocrinology		X[e]	
Urine pregnancy test[f]	X	X	
Contact IRT	X		
Subject diary return/review[g]	X		
LCM review/return	X		
Withdrawal criteria	X		
AE reporting	X	X	X
C-SSRS[h]	X	X	
Healthcare resource use[i]	X	X	
Work/school days lost due to epilepsy[i]	X	X	
Days with help from a caregiver due to epilepsy[i]	X	X	

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

Note: The schedule of study assessments for the Taper Period and Safety Follow-Up Visit includes some of the subjects who tapered in SP0982 after the 125th event who consented to enter EP0012 for the Safety Follow-Up only.

[j] Subjects who will not continue on LCM must complete an End of Taper Visit and a Safety Follow-Up Period; see Table 5-4. For subjects who continue on commercial LCM, the (Early) Termination Visit is the last visit in the study.

[k] 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 Visit.

[l] 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 7–2. 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 place at the ET or Termination Visit.

[m] 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) a 12-lead ECG (2 interpretable recordings) approximately 20 to 30 minutes apart must be performed.

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

[o] Pregnancy tests will be performed for female subjects of childbearing potential only. A urine pregnancy test will be performed.

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

[q] The C-SSRS will be completed for all subjects ≥6 years of age (see Section 10.4.3).

[r] Healthcare resource use, work/schools days lost due to epilepsy, and days with help from a caregiver due to epilepsy will be assessed only for patients completing the study after ≤2 years. These assessments are not applicable for patients tapering down or performing the SFU-visits during Years 3, 4 or 5).

Change #10

Section 6.2 Exclusion criterion #4

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.

Has been changed to:

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 all subjects who entered EP0012 directly 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.

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

Change #11

Section 7.2.1 Treatment Period

Paragraphs 7 and 8

Subjects withdrawing from the study must complete the ET Visit and an up to 4-week taper followed by an End of Taper Visit (see taper schedule, Table 7–2). 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. A slow taper is permitted if medically necessary. Whenever possible, these cases should be discussed with the Medical Monitor prior to withdrawing the subject from the study. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

At the completion of the study, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent(s)/legal representative(s).

Have been changed to:

Subjects withdrawing from the study must complete the ET Visit and (if they do not proceed with commercially available LCM) an up to 4-week taper followed by an End of Taper Visit (see taper schedule, Table 7–2). 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. A slow taper is permitted if medically necessary. Whenever possible, these cases should be discussed with the Medical Monitor prior to withdrawing the subject from the study. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

At the completion of the Treatment Period, investigators should discuss treatment options with the subject and/or their parent(s)/legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects who complete the study depending on the treatment option selected by the investigator in consultation with the subject and/or parent(s)/legal representative(s).

Change #12

Section 7.2.1 Treatment period

Table 7-2 Lacosamide dosing for subjects requiring taper

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	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
800mg/day	600mg/day	400mg/day	200mg/day	100mg/day
700mg/day	500mg/day	300mg/day	200mg/day	100mg/day
600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
400mg/day	300mg/day	200mg/day	100mg/day	NA
300mg/day	200mg/day	100mg/day	NA	NA

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	Week 1	Week 2	Week 3	Week 4
200mg/day	100mg/day	NA	NA	NA

ET=early termination; LCM=lacosamide
Note: The oral solution is dosed as mg/kg/day and tablets are dosed as mg/day.
[a]Subjects will begin taper on ET/Termination Visit.

Has been changed to:

Dose of LCM at ET/Termination Visit[a]	LCM taper schedule			
	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
4mg/kg/day	2mg/kg/day	NA	NA	NA
800mg/day	600mg/day	400mg/day	200mg/day	100mg/day
700mg/day	500mg/day	300mg/day	200mg/day	100mg/day
600mg/day	500mg/day	300mg/day	200mg/day	100mg/day
500mg/day	400mg/day	300mg/day	200mg/day	100mg/day
400mg/day	300mg/day	200mg/day	100mg/day	NA
300mg/day	200mg/day	100mg/day	NA	NA
200mg/day	100mg/day	NA	NA	NA

ET=early termination; LCM=lacosamide
Note: The oral solution is dosed as mg/kg/day and tablets are dosed as mg/day.
[a]Subjects will begin taper on ET/Termination Visit.

Change #13

Section 8.1.4 Visits 12, 13, 14, 15, 16, and 17 (Weeks 118, 142, 166, 190, 214, and 238, Years 3 to 5)

8.1.4.1 Subjects <18years

The following tasks and procedures are to be performed at these visits :

- Concomitant medications and AEDs
- Physical examination (complete, Visit 13, 15, and 17)
- Neurological examination (brief, Visit 12, 14, and 16)
- ECG (12-lead) assessment (Visit 13, 15, and 17)
- Vital signs (pulse rate, BP) including orthostatic assessments

- Body weight and height (height at Visit 12, 14, and 16)
- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 13, 15, and 17)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required. Laboratory tests are not performed at Visit 13 and 15 according to Protocol Amendment 3.
- Urine pregnancy test (for women of childbearing potential)
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects ≥6 years to <18 years of age (Visit 13, 15, and 17)
- BRIEF for subjects ≥5 to <18 years of age (Visit 13, 15, and 17)

Has been changed to:

8.1.4 Visits 12, 13, 14, 15, 16, 17 and 17X (Weeks 118, 142, 166, 190, 214, and 238, and X, Years 3 to 5 + Extended Period)

8.1.4.1 Subjects <18years

The following tasks and procedures are to be performed at these visits (Visit X [Vx] visits are to be performed every 24 weeks):

- Concomitant medications and AEDs
- Physical examination (complete, Visit 13, 15, 17, and odd numbered visits thereafter)
- Neurological examination (brief, Visit 12, 14, 16, and even numbered visits thereafter)
- ECG (12-lead) assessment (Visit 13, 15, 17, and odd numbered visits thereafter)
- Vital signs (pulse rate, BP) including orthostatic assessments
- Body weight and height (height at Visit 12, 14, 16, and even numbered visits thereafter)

- Tanner staging (will be performed only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study) (Visit 13, 15, 17, and odd numbered visits thereafter)
- C-SSRS assessment (for subjects ≥6 years of age)
- Blood and urine samples for clinical laboratory assessments (includes hematology, chemistry, and urinalysis) (laboratory tests are applicable for combined Visit 17/Termination Visit. If Visit 17 is not the Termination Visit, laboratory tests are not required. Laboratory tests are not performed at Visit 13 and 15 according to Protocol Amendment 3.
- Urine pregnancy test (for women of childbearing potential)
- Contact IRT
- Dispense subject diary
- Subject diary return/review
- Dispense LCM
- LCM review/return
- Assess withdrawal criteria
- AE reporting
- Achenbach CBCL for subjects ≥6 years to <18 years of age (Visit 13, 15, 17, and odd numbered visits thereafter)
- BRIEF for subjects ≥5 to <18 years of age (Visit 13, 15, 17, and odd numbered visits thereafter)

Change #14

Section 8.1.4.2 Subjects ≥18 years

First paragraph

The following tasks and procedures are to be performed at these visits.

Has been changed to:

The following tasks and procedures are to be performed at these visits, additional routine visits (Visit X) can be done after Visit 17 (Vx visits are to be performed every 24 weeks) with assessments described in Table 5–3.

Change #15

Section 8.1.5 Telephone contact

First paragraph

Telephone contacts are required at Week 30 and Week 38 and every 8 weeks during Year 2 to Year 5, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore,

telephone contacts in Year 2 are scheduled for Week 54, Week 70 and Week 86. Telephone contacts in Years 3 to 5 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 222, and Week 230.

Has been changed to:

Telephone contacts are required at Week 30 and Week 38 and every 8 weeks during Year 2 to Year 5, except during weeks in which a clinic visit is planned (eg, Week 62). Therefore, telephone contacts in Year 2 are scheduled for Week 54, Week 70, Week 78 and Week 86. Telephone contacts in Years 3 to 5 are scheduled for: Year 3 - Week 102, Week 110, Week 126, Week 134; Year 4 - Week 150, Week 158, Week 174, Week 182; Year 5 - Week 198, Week 206, Week 214, Week 222, Week 230, Week 238, and every 8 weeks during the Extended Period.

Change #16

Section 8.2 Early termination visit

First paragraph

Subjects withdrawing from the study will complete the ET Visit, and LCM will be tapered over a period of up to 4 weeks (see taper schedule, Table 7–2).

Has been changed to:

Subjects withdrawing from the study will complete the ET Visit, and LCM will be tapered over a period of up to 4 weeks if not continuing with commercially available LCM (see taper schedule, Table 7–2).

Change #17

Section 8.3 Termination visit

Paragraphs 1, 2, and 3

Subjects completing the Treatment Period and not continuing with commercially available LCM will complete the Termination Visit, and LCM will be tapered over a period of up to 4 weeks (see taper schedule, Table 7–2). Once LCM becomes commercially available and the subject elects to continue treatment, they must also complete the Termination Visit and transition to commercially available LCM.

Patients transitioning to the MAP will complete the Treatment Period after 2 years but continue their treatment with MAP LCM.

Taper of LCM is not required for subjects who complete the study and continue on MAP LCM or commercially available LCM. Subjects transitioning to MAP LCM or commercially available LCM will do so immediately and will continue at a dose determined by the investigator. Note: this visit can be combined with Visit 17 if appropriate.

Have been changed to:

A Termination Visit will be completed by subjects who complete the Treatment Period and meet 1 of the following conditions:

8. The subject chooses to transition to commercial LCM.
9. The subject chooses not to continue treatment with LCM.

Subjects not continuing treatment with LCM will complete the Termination Visit, and LCM will be tapered over a period of up to 4 weeks (see taper schedule, Table 7–2). Subjects who continue treatment with commercial LCM must also complete the Termination Visit.

Taper of LCM is not required for subjects who leave the Termination Visit and transition to commercial LCM. Subjects transitioning to commercial LCM will do so immediately and will continue at a dose determined by the investigator. In this instance, the Termination Visit will serve as the subject's last visit in the study.

Change #18

Section 9.1 Seizure variables

Subjects will keep a diary to record seizure activity from Visit 1 until the end of study participation. Efficacy variables will be assessed using the seizure count information recorded on the subject diaries. The subject should be reminded to bring the diary to each clinic visit.

Has been changed to:

Subjects will keep a diary to record all seizure activity from Visit 1 until the end of study participation. Efficacy variables will be assessed using the seizure count information recorded on the subject diaries. The subject should be reminded to bring the diary to each clinic visit. Should an adverse event involving a seizure be reported, it must be consistent with the seizure information (including specific type of seizure) reported in the seizure diary.

Change #19

Section 10.1.1.1 Adverse events

Added fourth paragraph:

Should an AE involving a seizure be reported, it must be consistent with the seizure information (including specific type of seizure) reported in the seizure diary.

Change #20

Section 10.1.1.2 Serious adverse events

Added second paragraph:

If commercial LCM is given during hospitalization, this needs to be recorded on the CRF.

Change #21

Section 10.2 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 9.1).

Has been changed to:

Section 10.2 New seizure types, increase in days with and worsening of days with absence or myoclonic seizures

Incidence of new seizure types, increase in absence seizure days or myoclonic seizure days per 28 days during the Treatment Period, and 50% worsening in days with absence seizures or myoclonic seizures per 28 days during the Treatment Period will be assessed using the seizure count information recorded on the subject diaries (see Section 9.1).

Change #22

Section 10.3.1.3 Testing: identification/exclusion of alternative etiology

Table 10-4 (laboratory measurements):

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

Table 10-4: PDILI laboratory measurements

	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).

Has been changed to:

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	Differential count, hematocrit, hemoglobin, platelet count, RBC and WBC
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Albumin, AST, ALT, ALP, GGT, serum CPK, and LDH to evaluate possible muscle injury causing transaminase elevation

Table 10-4: PDILI laboratory measurements

Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

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

[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).

Change #23

Section 12.3.1 Safety analysis

Second 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. Laboratory measurements as described in Section 10.3 and other safety measurements as described in Section 10.4 will be presented.

Has been changed to:

Incidence of new seizure types, increase in days with absence seizure or myoclonic seizures per 28 days during the Treatment Period, and 50% worsening in days with absence seizures or myoclonic seizures per 28 days during the Treatment Period will be summarized. Laboratory measurements as described in Section 10.3 and other safety measurements as described in Section 10.4 will be presented.

Change #24

Section 12.4 Planned efficacy analysis

Second paragraph

Days with myoclonic or absence seizures are more clinically relevant endpoints; therefore, change in and percent change in days with myoclonus and absence will be summarized. The percentage of subjects with 50% reduction in days with absence and myoclonic seizures per 28 days compared to the Prospective Baseline will be presented. Subjects who were seizure-free from all generalized seizures will also be tabulated.

Has been changed to:

Days with myoclonic or absence seizures are more clinically relevant endpoints; therefore, change in and percent change in days with myoclonic and/or absence seizures will be summarized. The percentage of subjects with 50% reduction in days with absence and/or myoclonic seizures per 28 days compared to the Prospective Baseline will be presented. Subjects who were seizure-free from all generalized seizures will also be tabulated.

Change #25

Section 12.5 Handling of protocol deviations

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

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

Has been changed to:

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

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

Change #26

Added Section 13.4.1 Processing of subject health data

The processing of the subject personal health data in this study is allowed for the purpose of scientific research to evaluate the efficacy and the safety of the tested drug, in accordance with legal requirements from:

- the laws governing the conduct of clinical studies (ie, the provisions of the French Public Health Code and the EU clinical trial regulation 536/2014 which requires sponsors to collect and analyze such data before they are submitted to health authorities)
- the EU regulation 1235/2010 on pharmacovigilance which requires follow-up and reporting of adverse events of medicinal products to the health authorities, and any other applicable law

This means that after the end of the study the subject coded personal data will be retained for at least 25 years to ensure the validity of the research.

The subjects will be informed that the Sponsor is legally entitled and obliged to keep, retain, and use your medical data to ensure the quality of scientific results and to comply with legal or judicial retention periods.

16.8 Appendix 8: Protocol Amendment 5

Rationale for the amendment

The primary purpose of this amendment was to update the protocol based on comments received on the pediatric investigational plan as well as to clarify/solve inconsistencies between different sections of the protocol and to correct some minor errors.

Modifications and changes

Specific changes

Change #1

Title page:

The title was updated from "Protocol EP0012 Amendment 4" to "Protocol EP0012 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	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial
Protocol Amendment 3	29 Nov 2017	Substantial
Protocol Amendment 4	13 Dec 2019	Substantial

Has been changed to:

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	15 Oct 2012	Not applicable
Protocol Amendment 1	27 Jan 2015	Substantial
Protocol Amendment 2	09 Jun 2016	Substantial
Protocol Amendment 3	29 Nov 2017	Substantial
Protocol Amendment 4	13 Dec 2019	Substantial
Protocol Amendment 5	27 Aug 2020	Non-substantial

Change #2

4.1.1 Primary safety variables

The primary safety variables are:

- Adverse events as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- Incidence of new appearance of absence and/or myoclonic seizures during the Treatment Period
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days compared to the Prospective Baseline
- Subjects with an increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days compared to the Prospective Baseline
- Percentage of subjects with at least 50% worsening in days with absence seizures
- Percentage of subjects with at least 50% worsening in days with myoclonic seizures

Has been changed to:

The primary safety variables are:

- The incidence of TEAEs over the duration of the Treatment Period.
- Subject withdrawals due to TEAEs
- Incidence of new appearance of absence and/or myoclonic seizures during the Treatment Period
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with absence seizures per 28 days compared to the Prospective Baseline
- An increase of up to 25%, >25% to 50%, >50% to 75%, and >75% in days with myoclonic seizures per 28 days compared to the Prospective Baseline
- At least 50% worsening in days with absence seizures
- At least 50% worsening in days with myoclonic seizures

Change #3

4.2.3 Other efficacy variables

Bullets 5, 6 and 7

- Percentage of subjects with at least a 50% reduction in PGTCS frequency compared to the Combined Baseline

- Percentage of subjects with at least a 50% reduction in myoclonic seizure days compared to the Prospective Baseline
- Percentage of subjects with at least a 50% reduction in absence seizure days compared to the Prospective Baseline

Has been changed to:

- At least a 50% reduction in PGTCS frequency compared to the Combined Baseline
- At least a 50% reduction in myoclonic seizure days compared to the Prospective Baseline
- At least a 50% reduction in absence seizure days compared to the Prospective Baseline

Change #4

Section 5.1.1 Study duration per subject

Paragraph 1, bullet #2

- For pediatric subjects, treatment will continue until the latest of 1 of the following 2 conditions are met:
  - up to 5 years of participation or
  - until the latest approval is granted either by EMA, FDA, or PMDA

Has been changed to:

- For pediatric subjects, treatment will continue until 1 of the following 2 conditions are met:
  - up to 5 years of participation or
  - until the approval of the extension of indication to cover the target age group is granted

Change #5

5.2 Schedule of study assessments

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years at enrollment)

Neurological exam (brief): added 'X' to study ET Visit

Footnote 'p'

Laboratory tests are applicable for combined the last scheduled visit/Termination Visit. If the last scheduled visit is not the Termination Visit, laboratory tests are not required.

Table 5-3 Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects ≥18 years at enrollment)

Deleted footnote 'e' from V17.

Added footnote 'i':

i Laboratory tests are applicable for the combined last scheduled visit/Termination Visit. If the last scheduled visit is not the Termination Visit, laboratory tests are not required.

Table 16-6:Schedule of study assessments (Taper Period and Safety Follow-Up Period)

Table header column 2

End of Taper Visit (maximum 3 days after visit)

Has been changed to:

Table 5–2: Schedule of study assessments for Years 3 through 5 for EP0012 (Treatment Period, ET Visit, Termination Visit, and Unscheduled Visit for subjects <18 years at enrollment)

Footnote 'p'

Laboratory tests are applicable for combined the last scheduled visit/Termination Visit. If the last scheduled visit is not the Termination Visit, laboratory tests are not required.

Table 16-7:Schedule of study assessments (Taper Period and Safety Follow-Up Period)

Table header column 2

End of Taper Visit (maximum 3 days after the last dose)

Change #6

Section 8.1.4.1 Subjects <18 years

Bullet #3

- Neurological examination (brief, Visit 12, 14, 16, and even numbered visits thereafter)

Has been changed to:

- Neurological examination (brief, Visit 12, 14, 16, 17, and even numbered visits thereafter)

Change #7

12.3.1 Safety analyses

Paragraph 1

The incidence and frequency of TEAEs will be summarized. The incidence of SAEs and TEAEs leading to premature discontinuation from study drug will also be summarized. Additional summaries will be provided by maximum intensity and relationship to study drug. All tables of AEs will include Medical Dictionary for Regulatory Activities primary System Organ Class and Preferred Term. Further details on the analysis of each variable will be given in the SAP. Frequency tables for subject withdrawal due to AE will be presented giving absolute and relative frequencies for the course of the study. Additionally, per year frequencies will be provided, where the denominator will be adjusted for the number of subjects still at risk, ie, the number of subjects entering the respective year of the study. Relative years will be used for this type of analysis, not calendar years.

Has been changed to:

The incidence of all TEAEs, treatment emergent SAEs and TEAEs leading to premature discontinuation from study drug will also be summarized descriptively. Additional summaries will be provided by maximum intensity and relationship to study drug. All tables of TEAEs will include Medical Dictionary for Regulatory Activities primary System Organ Class and Preferred Term. Further details on the analysis of each variable will be given in the SAP.

16.9 Appendix 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

17 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

18 SPONSOR DECLARATION

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

Approval Signatures

Name: ep0012-protocol-amend-5

Version: 1.0

Document Number: CLIN-000158392

Title: EP0012 Protocol Amendment 5 - Open multicenter extension, evaluate long-term safety,efficacy of adjunctive LCM for uncontrolled PGTC seizures (IGE)

Approved Date: 31 Aug 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 28-Aug-2020 15:55:58 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 31-Aug-2020 08:01:31 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 31-Aug-2020 13:51:25 GMT+0000