# PROTOCOL EP0034 AMENDMENT 3

# A MULTICENTER, OPEN-LABEL, LONG-TERM EXTENSION STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN PEDIATRIC SUBJECTS WITH EPILEPSY WITH PARTIAL-ONSET SEIZURES

## PHASE 3

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**Confidential Material**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AED | antiepileptic drug |
| ALP | Alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AV | atrioventricular |
| Bayley-III® | Bayley Scales of Infant and Toddler Development, Third Edition |
| bid | twice daily |
| 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 |
| $C_{max}$ | maximum plasma concentration |
| COVID-19 | coronavirus disease 2019 |
| CRO | contract research organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DEM | data evaluation meeting |
| ECG | electrocardiogram |
| eCRF | electronic Case Report form |
| EI-AED | enzyme-inducing antiepileptic drug |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyltransferase |
| GMP | Good Manufacturing Practice |
| HRQoL | health-related quality of life |
| ICF | Informed Consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |
| IXRS | interactive voice/web response system |
| LCM | lacosamide |

| | |
|---|---|
| LFT | liver function test |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| PDILI | potential drug-induced liver injury |
| PedsQL™ | Pediatric Quality of Life Inventory |
| PK | pharmacokinetic(s) |
| QTc | corrected QT interval |
| RDC | remote data capture |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SOP | Standard Operating Procedure |
| SS | Safety Set |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| VNS | vagus nerve stimulation |

# 1 SUMMARY

EP0034 is a Phase 3, multicenter, open-label, extension study to obtain long-term safety and efficacy data in pediatric subjects with epilepsy with partial-onset seizures treated with lacosamide (LCM) oral solution or LCM tablets as adjunctive therapy. The study will provide continued availability of LCM to subjects who have completed SP0969 (pediatric subjects with epilepsy aged ≥4 to <17 years with partial-onset seizures). EP0034 will also be open to subjects who participate in SP0967 (pediatric subjects with epilepsy aged 1 month to <4 years with partial-onset seizures). Both SP0969 and SP0967 are Phase 3, double-blind, placebo-controlled studies for LCM as adjunctive therapy.

Approximately 500 subjects from SP0967 and SP0969 may be eligible to enroll in this open-label extension study, for a maximum duration per subject of approximately 2 years. The number of sites is dependent on the number of enrolling centers from SP0967 and SP0969. The study will be conducted in North America, Europe, Latin America, and the Asia/Pacific regions, with the possibility to expand the study to other countries and regions if deemed necessary. At selected sites, subjects may also be able to participate in a substudy without withdrawing from EP0034.

The study medication is LCM in either the oral solution formulation or tablet formulation. Subjects may take either oral solution or tablets during the Treatment Period, based on clinical judgment, regardless of their weight. Lacosamide will be administered twice daily (bid) at approximately 12-hour intervals, once in the morning and once in the evening, in divided doses. The oral solution formulation will be measured and administered via a dosing syringe.

After completion of the Transition Period in the primary study, subjects will have been transitioned to a dose of LCM according to their weight. Subjects will receive LCM 10mg/kg/day (oral solution) for subjects weighing <30kg, LCM 6mg/kg/day (oral solution) for subjects weighing ≥30kg to <50kg, and LCM 300mg/day (tablets) for subjects weighing ≥50kg during at least their first week in the Treatment Period of EP0034. After 1 week in EP0034, the investigator may adjust the LCM dose during the Treatment Period based on clinical judgment within a range of 2mg/kg/day to 12mg/kg/day for the oral solution and 100mg/day to 600mg/day for the tablets.

During the Treatment Period, study visits are scheduled at Weeks 0, 4, 8, 12, 20, 28, 36, 44, 52, 60, 72, 84, and 96. Telephone contacts are scheduled at Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56, 66, and 78. Subjects who withdraw from treatment during the study should taper off LCM if the following doses are achieved: LCM ≥3mg/kg/day (oral solution) for subjects receiving LCM oral solution, or LCM ≥150mg/day (tablet) for subjects taking tablets; lower doses will not require a taper. An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study. Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM. A Safety Follow-Up Telephone Contact will be made 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152. 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 or withdraw from the study

prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

Safety will be evaluated based on the occurrence of adverse events (AEs), the results of periodic clinical laboratory tests, electrocardiograms (ECGs), physical (Tanner Stage, if applicable, depending on subject's developmental status) and neurological examinations, vital signs (blood pressure and pulse rate) monitoring, and body weight and height.

The efficacy variables will be based on seizure diary data and will include the percentage of seizure-free days during the study. The following other efficacy variables based on seizure diary data will be computed for subjects from SP0969: the percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline) and the percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline, the percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline) and the percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline, absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline (Baseline is defined as the period before receiving study medication in the previous pediatric study), and partial-onset seizure frequency per 28 days. The following other efficacy variables will be computed for all subjects in EP0034: achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized), Clinical Global Impression of Change, and Caregiver's Global Impression of Change.

Other evaluations will include behavioral and cognition assessments (Achenbach Child Behavior Checklist [CBCL], Behavior Rating Inventory of Executive Function [BRIEF®]/BRIEF Preschool Version [BRIEF®-P], and Bayley Scales of Infant and Toddler Development, Third Edition [Bayley-III®] for subjects enrolled in English-speaking countries), quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]), health care resource use (concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol).

# 2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy worldwide (Ngugi et al, 2011). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). The Institute of Medicine of the National Academies recently provided a review of the burdens of epilepsy, global incidence and prevalence of epilepsy, and general recommendations (Institute of Medicine, 2012). Several newer options for the medical treatment of epilepsy have been introduced, including novel antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS). The classification of epilepsies in children was described in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (1989; Aicardi, 1994). Seizures are categorized based on whether the onset is focal or generalized and whether the disorder is idiopathic, symptomatic, or cryptogenic. Specific syndromes are further classified

according to a number of criteria, including seizure type, cause, anatomy, precipitating factors, age at onset, and sometimes prognosis.

The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and pharmacokinetic (PK) characteristics (Herman and Pedley, 1998). However, more than 30% of patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (CHMP/EWP/566/98, 2010). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander, 1998).

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

Lacosamide (VIMPAT®; SPM 927; previously referred to as harkoseride; [R] 2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) belongs to a novel class of functionalized amino acids. It has minimal protein binding and effect on cytochrome P450 enzyme system function (reducing the risk of drug-drug interactions), high oral bioavailability, and a half-life of approximately 13 hours (in adults), which allows a bid dose regimen. It also displays dose-proportional PK following administration over a range of doses up to 800mg in adults.

Lacosamide has been approved as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the United States (tablets, oral solution, and solution for intravenous [iv] infusion) and as monotherapy or adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (tablets, oral solution, and solution for iv infusion). The oral solution (also referred to as syrup) is a formulation suitable for administration to children. Bioequivalence has been shown between the tablet and oral solution formulations, comparing 2 tablets of LCM 100mg and the oral solution containing LCM 200mg, after single-dose administration in healthy subjects. The PK of LCM and SPM 12809 (major LCM metabolite in humans) in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution.

In the clinical development program for LCM, safety and tolerability of multiple doses of up to LCM 400mg bid (LCM 800mg/day) were evaluated in approximately 800 unique volunteers who received LCM in Phase 1 studies. The safety and efficacy of LCM has also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2400 adult subjects in other indications (neuropathic pain, osteoarthritis, fibromyalgia, and migraine prophylaxis). In addition, LCM solution for infusion was evaluated as short-term replacement therapy in a subset of subjects with partial-onset seizures (220 patients) who were receiving adjunctive LCM tablets.

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

randomized dose (LCM 200mg/day, LCM 400mg/day, or LCM 600mg/day) in 100mg/day per week increments.

When oral LCM was administered as adjunctive therapy at doses up to 600mg/day in the 3 double-blind, placebo-controlled, multicenter studies in subjects with partial-onset seizures, the most frequently reported treatment-emergent AEs (TEAEs) were central nervous system- and gastrointestinal-associated events. A dose relationship was seen for the most frequently reported common TEAEs, including dizziness, nausea, and diplopia. The nature and frequency of AEs were comparable to adjunctive therapy with other marketed AEDs. Safety evaluations support the further development of LCM as an AED.

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

EP0034 is a Phase 3, multicenter, open-label, extension study to obtain long-term safety and efficacy data in pediatric subjects with epilepsy with partial-onset seizures treated with LCM oral solution or LCM tablets as adjunctive therapy. The study will provide continued availability of LCM to subjects who have completed SP0969 (pediatric subjects with epilepsy aged ≥4 to <17 years with partial-onset seizures). EP0034 will also be open to subjects who participate in SP0967 (pediatric subjects with epilepsy aged 1 month to <4 years with partial-onset seizures).

# 3 STUDY OBJECTIVES

## 3.1 Primary objective

- To assess the long-term safety and tolerability of LCM in pediatric subjects

## 3.2 Secondary objective

- To assess the efficacy of LCM during long-term exposure in pediatric subjects

## 3.3 Other objectives

- To assess behavior, cognition, quality of life, and development during long-term LCM exposure in pediatric subjects

# 4 STUDY VARIABLES

## 4.1 Safety variables

### 4.1.1 Primary safety variables

The primary safety variables include the following:

- Incidence of TEAEs

- Incidence of serious TEAEs
- Incidence of TEAEs leading to study discontinuation

### 4.1.2 Other safety variables

The other safety variables include the following:

- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyltransferase [GGT]; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms
- Physical (Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations
- Vital signs (blood pressure and pulse rate)
- Body weight and height
- Change from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1.5 to 5 years of age and the Achenbach CBCL/6-18 for children ≥6 years of age
- Change from Baseline in the BRIEF-P score for subjects ≥2 and <5 years of age
- Change from Baseline in the BRIEF score for subjects ≥5 years of age
- Change from Baseline in the Bayley-III scales in subjects <18 months of age at study entry (applicable only to subjects enrolled in English-speaking countries)

## 4.2 Efficacy variables

### 4.2.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

### 4.2.2 Secondary efficacy variable

The secondary efficacy variable planned for analysis will be based on seizure diary data from EP0034 and will include the following for all subjects:

- Percentage of seizure-free days during the study (presented for the overall Treatment Period only)

### 4.2.3 Other efficacy variables

The following other efficacy variables will be computed for subjects from SP0969 and include the following:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline

- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034 and include the following:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in PedsQL
- Health care resource use: concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol

# 5 STUDY DESIGN

## 5.1 Study description

EP0034 is a Phase 3, multicenter, open-label, extension study to obtain long-term safety and efficacy data in pediatric subjects with epilepsy with partial-onset seizures treated with LCM oral solution or LCM tablets as adjunctive therapy.

Subjects who have participated in SP0967 or SP0969, meet the eligibility requirements of this open-label extension study, and who consent or whose legal representative consents to participation can enroll into EP0034 for a maximum duration of approximately 2 years.

During the study, LCM will be available in either the oral solution formulation or tablet formulation. Subjects who are able and willing to swallow tablets may be dispensed LCM tablets during the Treatment Period, based on clinical judgment, regardless of their weight.

Treatment Period

After completion of the Transition Period in the primary study, subjects will have been transitioned to a dose of LCM according to their weight. Subjects will receive LCM 10mg/kg/day (oral solution) for subjects weighing <30kg, LCM 6mg/kg/day (oral solution) for subjects weighing ≥30kg to <50kg, and LCM 300mg/day (tablets) for subjects weighing ≥50kg during at least their first week in the Treatment Period of EP0034. After 1 week in EP0034, the investigator may adjust the LCM dose during the Treatment Period according to Table 7-1 (refer to Section 7.2.1). Subjects may take either oral solution or tablets during the Treatment Period, based on clinical judgment, regardless of their weight.

During the Treatment Period, study visits are scheduled at Weeks 0, 4, 8, 12, 20, 28, 36, 44, 52, 60, 72, 84, and 96. Telephone contacts are scheduled at Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56, 66, and 78.

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 legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or legal representative) should taper LCM gradually as described in Section 7.2.2. These subjects should complete Visit 13/Termination Visit and enter the Taper Period.

Subjects who prematurely discontinue the study should complete an Early Termination Visit. At the time of withdrawal from 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 withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s). These subjects should complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Subjects who withdraw from the study prematurely and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or legal representative) should taper LCM gradually as described in Section 7.2.2. These subjects should enter the Taper Period.

Taper Period

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

End of study and Safety Follow-Up Period

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM. A Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit and the

Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

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

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

No formal interim analysis or Data Monitoring Committee is planned.

### 5.1.1 Study duration per subject

The maximum duration of LCM administration during EP0034 will be approximately 2 years.

The start of the study is defined as the first visit of the first subject entering the study. The end of the study is defined as the date of the last telephone contact (or last site visit if telephone contact does not happen) of the last subject in the study.

### 5.1.2 Planned number of subjects and site(s)

Approximately 500 subjects from SP0967 and SP0969 may be eligible to enroll in this open-label extension study. The number of sites is dependent on the number of enrolling centers from SP0967 and SP0969.

### 5.1.3 Anticipated regions and countries

The study will be conducted in North America, Europe, Latin America, and the Asia/Pacific regions, with the possibility to expand the study to other countries and regions if deemed necessary.

## 5.2 Schedule of study assessments

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

## Table 5-1: Schedule of study assessments: Treatment Period up to Week 28

| Assessments | Treatment Period[a] | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | TC1 | V2 | TC2 | V3 | TC3 | V4 | TC4 | V5 | TC5 | V6 | | |
| | W0 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W28 | | |
| Informed consent | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | | | |
| Medical history update | X | | | | | | | | | | | | |
| Concomitant medications | X[d] | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant AEDs | X[d] | X | X | X | X | X | X | X | X | X | X | X | X |
| VNS assessment[e] | X[d] | | X | | X | | X | | X | | X | X | X |
| Physical examination (complete) | X[d] | | | | | | | | X | | | X | |
| Physical examination (brief) | | | X | | X | | X | | | | X | | |
| Tanner Stage[f] | X[g] | | | | | | | | X | | | X | |
| Blood pressure and pulse rate (including orthostatic assessments in ambulatory subjects) | X[d] | | X | | X | | X | | X | | X | X | X |
| Body weight and height | X[d] | | X | | X | | X | | X | | X | X | X[h] |
| Head circumference | X[g] | | | | | | | | X | | | X | |
| Neurological examination (complete) | X[d] | | | | | | | | X | | | X | |
| Neurological examination (brief) | | | X | | X | | X | | | | X | | |
| 12-lead ECG[i] | X[g] | | X | | | | | | | | X | X | |
| Clinical chemistry and hematology blood sample | X[d] | | | | | | | | X | | | X | |
| Endocrinology blood sample | X[g] | | | | | | | | X | | | X | |
| Urinalysis (subjects aged ≥5 years)[j] | X[d] | | | | | | | | X | | | X | |

## Table 5-1: Schedule of study assessments: Treatment Period up to Week 28

| Assessments | Treatment Period[a] | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | TC1 | V2 | TC2 | V3 | TC3 | V4 | TC4 | V5 | TC5 | V6 | | |
| | W0 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W28 | | |
| Serum pregnancy test[k] | | | | | | | | | X | | | X | |
| Urine pregnancy test[k] | X[d] | | X | | X | | X | | | | X | | |
| C-SSRS[l] | X[d] | | X | | X | | X | | X | | X | X | X[m] |
| Clinical GIC | | | | | | | | | X | | | X | |
| Caregiver GIC | | | | | | | | | X | | | X | |
| Achenbach CBCL[n] | X | | | | | | | | X | | | X | |
| Bayley-III[o] | X[d] | | | | | | | | X | | | X | |
| BRIEF/BRIEF-P[p] | X | | | | | | | | X | | | X | |
| PedsQL[q] | X[g] | | | | | | | | X | | | X | |
| Contact IXRS | X | | X | | X | | X | | X | | X | X[r] | |
| LCM return/compliance | X[d] | | X | | X | | X | | X | | X | X | |
| Dispense LCM | X | | X | | X | | X | | X | | X | X[s] | |
| Subject diary[t] | X[d] | 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 |
| AE reporting[u] | X[d] | X | X | X | X | X | X | X | X | X | X | X | X |
| Health care resource use | X[d] | | X | | X | | X | | X | | X | X | |

AE=adverse event; AED=antiepileptic drug; Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition; BRIEF-P/BRIEF=Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; $C_{max}$=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; TC=telephone contact; Unsch=Unscheduled; V=Visit; VNS=vagus nerve stimulation; W=week

## Table 5-1: Schedule of study assessments: Treatment Period up to Week 28

| Assessments | Treatment Period[a] | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | TC1 | V2 | TC2 | V3 | TC3 | V4 | TC4 | V5 | TC5 | V6 | | |
| | W0 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W28 | | |

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts after Visit 1 during the Treatment Period.

[b] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.

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

[d] Assessments may have already been completed during the final Transition Visit of the primary study (SP0969 or SP0967) and should not be repeated at Visit 1 of EP0034.

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

[f] The Tanner Stage will be performed only for subjects who are pubescent at V1 or who enter puberty during the course of the study.

[g] Assessments may have already been completed during the final Maintenance Visit of the primary study (SP0969 or SP0967) and should not be repeated at Visit 1 of EP0034.

[h] Height will not be recorded at an Unscheduled Visit.

[i] A 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) will be performed prior to any blood draws and vital signs and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording. All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added, will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

[j] For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container).

[k] For female subjects of childbearing potential.

[l] For all subjects ≥6 years of age, the "Since Last Visit" version of the C-SSRS should be completed. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits.

[m] The C-SSRS assessment should be completed if the Unscheduled Visit is due to a safety or efficacy reason.

[n] 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 primary 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.

[o] The Bayley-III scales should be completed for subjects <18 months of age at study entry if enrolled in English-speaking countries. The same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period.

[p] 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

## Table 5-1: Schedule of study assessments: Treatment Period up to Week 28

| Assessments | Treatment Period[a] | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | TC1 | V2 | TC2 | V3 | TC3 | V4 | TC4 | V5 | TC5 | V6 | | |
| | W0 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W28 | | |

Baseline assessment of the primary 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 only be administered in countries where a validated translated version is available.

[q] 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 of the primary study, and subsequently the form consistent with his/her age at the time of assessment should be completed. The PedsQL will only be administered in countries where a validated translated version is available.

[r] Only if LCM will be dispensed for taper.

[s] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥3mg/kg/day (oral solution) or LCM ≥150mg/day (tablet). It is recommended that the dose be tapered gradually in weekly decrements. A slower taper is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

[t] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis.

[u] Ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study.

## Table 5-2: Schedule of study assessments: Treatment Period from Week 32 to Week 96/Termination Visit

| Assessments | Treatment Period[a] | | | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC6 | V7 | TC7 | V8 | TC8 | V9 | TC9 | V10 | TC10 | V11 | TC11 | V12 | V13 / TermV[d] | | |
| | W32 | W36 | W40 | W44 | W48 | W52 | W56 | W60 | W66 | W72 | W78 | W84 | W96 | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant AEDs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| VNS assessment[e] | | X | | X | | X | | X | | X | | X | X | X | X |
| Physical exam (complete) | | | | | | X | | | | | | | X | X | |
| Physical exam (brief) | | X | | X | | | | X | | X | | X | | | |
| Tanner Stage[f] | | | | | | X | | | | | | | X | X | |
| Blood pressure and pulse rate (including orthostatic assessments in ambulatory subjects) | | X | | X | | X | | X | | X | | X | X | X | X |
| Body weight and height | | X | | X | | X | | X | | X | | X | X | X | X[g] |
| Head circumference | | | | | | X | | | | X | | | X | X | |
| Neurological exam (complete) | | | | | | X | | | | | | | X | X | |
| Neurological exam (brief) | | X | | X | | | | X | | X | | X | | | |
| 12-lead ECG[h] | | | | | | X | | | | X | | | X | X | |
| Clinical chemistry and hematology blood sample | | | | | | X | | | | X | | | X | X | |

## Table 5-2: Schedule of study assessments: Treatment Period from Week 32 to Week 96/Termination Visit

| Assessments | Treatment Period[a] | | | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC6 | V7 | TC7 | V8 | TC8 | V9 | TC9 | V10 | TC10 | V11 | TC11 | V12 | V13 / TermV[d] | | |
| | W32 | W36 | W40 | W44 | W48 | W52 | W56 | W60 | W66 | W72 | W78 | W84 | W96 | | |
| Endocrinology blood sample | | | | | | X | | | | X | | | X | X | |
| Urinalysis (subjects aged ≥5 years)[i] | | | | | | X | | | | X | | | X | X | |
| Serum pregnancy test[j] | | | | | | X | | | | X | | | X | X | |
| Urine pregnancy test[j] | | X | | X | | | | X | | | | X | | | |
| C-SSRS[k] | | X | | X | | X | | X | | X | | X | X | X | X[l] |
| Clinical GIC | | | | | | X | | | | X | | | X | X | |
| Caregiver GIC | | | | | | X | | | | X | | | X | X | |
| Achenbach CBCL[m] | | | | | | X | | | | X | | | X | X | |
| Bayley-III[n] | | | | | | X | | | | X | | | | X | |
| BRIEF/BRIEF-P[o] | | | | | | X | | | | X | | | X | X | |
| PedsQL[p] | | | | | | X | | | | X | | | X | X | |
| Contact IXRS | | X | | X | | X | | X | | X | | X | X[q] | X[p] | |
| LCM return/ compliance | | X | | X | | X | | X | | X | | X | X | X | |
| Dispense LCM | | X | | X | | X | | X | | X | | X | X[r] | X[q] | |
| Subject diary[s] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Withdrawal criteria | X | X | X | X | X | X | X | X | X | X | X | X | | | X |
| AE reporting | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Table 5-2: Schedule of study assessments: Treatment Period from Week 32 to Week 96/Termination Visit

| Assessments | Treatment Period[a] | | | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC6 | V7 | TC7 | V8 | TC8 | V9 | TC9 | V10 | TC10 | V11 | TC11 | V12 | V13 / TermV[d] | | |
| | W32 | W36 | W40 | W44 | W48 | W52 | W56 | W60 | W66 | W72 | W78 | W84 | W96 | | |
| Health care resource use | | X | | X | | X | | X | | X | | X | X | X | |

AE=adverse event; AED=antiepileptic drug; Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition; BRIEF-P/BRIEF=Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; $C_{max}$=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; TC=telephone contact; TermV=Termination Visit; Unsch=Unscheduled; V=Visit; VNS=vagus nerve stimulation; W=week

[a] A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts after Visit 1 during the Treatment Period.
[b] An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study.
[c] If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion.
[d] Visit 13 will be the treatment Termination Visit for subjects who complete up to 2 years of treatment.
[e] Only applicable for subjects with an implanted VNS device.
[f] The Tanner Stage will be performed only for subjects who are pubescent at V1 or who enter puberty during the course of the study.
[g] Height will not be recorded at an Unscheduled Visit.
[h] A 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) will be performed prior to any blood draws and vital signs and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording. All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.
[i] For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container).
[j] For female subjects of childbearing potential.
[k] For all subjects ≥6 years of age, the "Since Last Visit" version of the C-SSRS should be completed. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits.
[l] The C-SSRS assessment should be completed if the Unscheduled Visit is due to a safety or efficacy reason.

## Table 5-2: Schedule of study assessments: Treatment Period from Week 32 to Week 96/Termination Visit

| Assessments | Treatment Period[a] | | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC6 | V7 | TC7 | V8 | TC8 | V9 | TC9 | V10 | TC10 | V11 | TC11 | V12 | V13 / TermV[d] | |
| | W32 | W36 | W40 | W44 | W48 | W52 | W56 | W60 | W66 | W72 | W78 | W84 | W96 | |

[m] 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 primary 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.

[n] The Bayley-III scales should be completed for subjects <18 months of age at study entry if enrolled in English-speaking countries. The same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period.

[o] 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 primary study and turn 5 years of age within 1 year after the Baseline assessment of the primary study, the BRIEF-P should be completed 1 year after the Baseline assessment of the primary study, and subsequently the BRIEF should be completed. The BRIEF-P and BRIEF will only be administered in countries where a validated translated version is available.

[p] 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 of the primary study, and subsequently the form consistent with his/her age at the time of assessment should be completed. The PedsQL will only be administered in countries where a validated translated version is available.

[q] Only if LCM will be dispensed for taper.

[r] Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥3mg/kg/day (oral solution) or LCM ≥150mg/day (tablet). It is recommended that the dose be tapered gradually in weekly decrements. A slower taper is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible. Taper of LCM may not be required for some subjects who withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

[s] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis. For subjects who enter the Safety Follow-Up Period, the subject diary will be returned at the Safety Follow-Up Visit. Subjects who do not enter the Safety Follow-Up Period will return the diary at V13/TermV.

## Table 5-3: Schedule of study assessments: Taper Period and Safety Follow-Up Period

| Assessments | Taper Period | Safety Follow-Up Period | |
|---|---|---|---|
| | Taper Visit[a] | Safety Follow-Up Visit[b] | Safety Follow-Up Telephone Call[c] |
| Concomitant medications | X | X | X |
| Concomitant AEDs | X | X | X |
| VNS assessment[d] | X | X | |
| Physical exam (complete) | | X | |
| Physical exam (brief) | X | | |
| Tanner Stage[e] | | X | |
| Blood pressure and pulse rate (including orthostatic assessments in ambulatory subjects) | X | X | |
| Body weight and height | X | X | |
| Neurological exam (complete) | | X | |
| Neurological exam (brief) | X | | |
| 12-lead ECG[f] | X | X | |
| Clinical chemistry and hematology blood sample | X | X | |
| Endocrinology blood sample | X | X | |
| Urinalysis (subjects aged ≥5 years)[g] | X | X | |
| Serum pregnancy test[h] | X | X | |
| C-SSRS[i] | X | X | |
| LCM return/compliance | X | | |
| Subject diary[j] | X | X | |
| AE reporting | X | X | X[k] |
| Health care resource use | X | X | |

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

[a] The Taper Period (up to 4 weeks, depending on dose level achieved, see Section 7.2.2 for details) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets. The Taper Visit will be performed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

[b] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM (including that from LCM taper). The Safety Follow-Up Visit is not required for subjects who complete the study and do not undergo taper of LCM. The Safety Follow-Up Visit is not required for subjects who participate in EP0151 or EP0152.

## Table 5-3: Schedule of study assessments: Taper Period and Safety Follow-Up Period

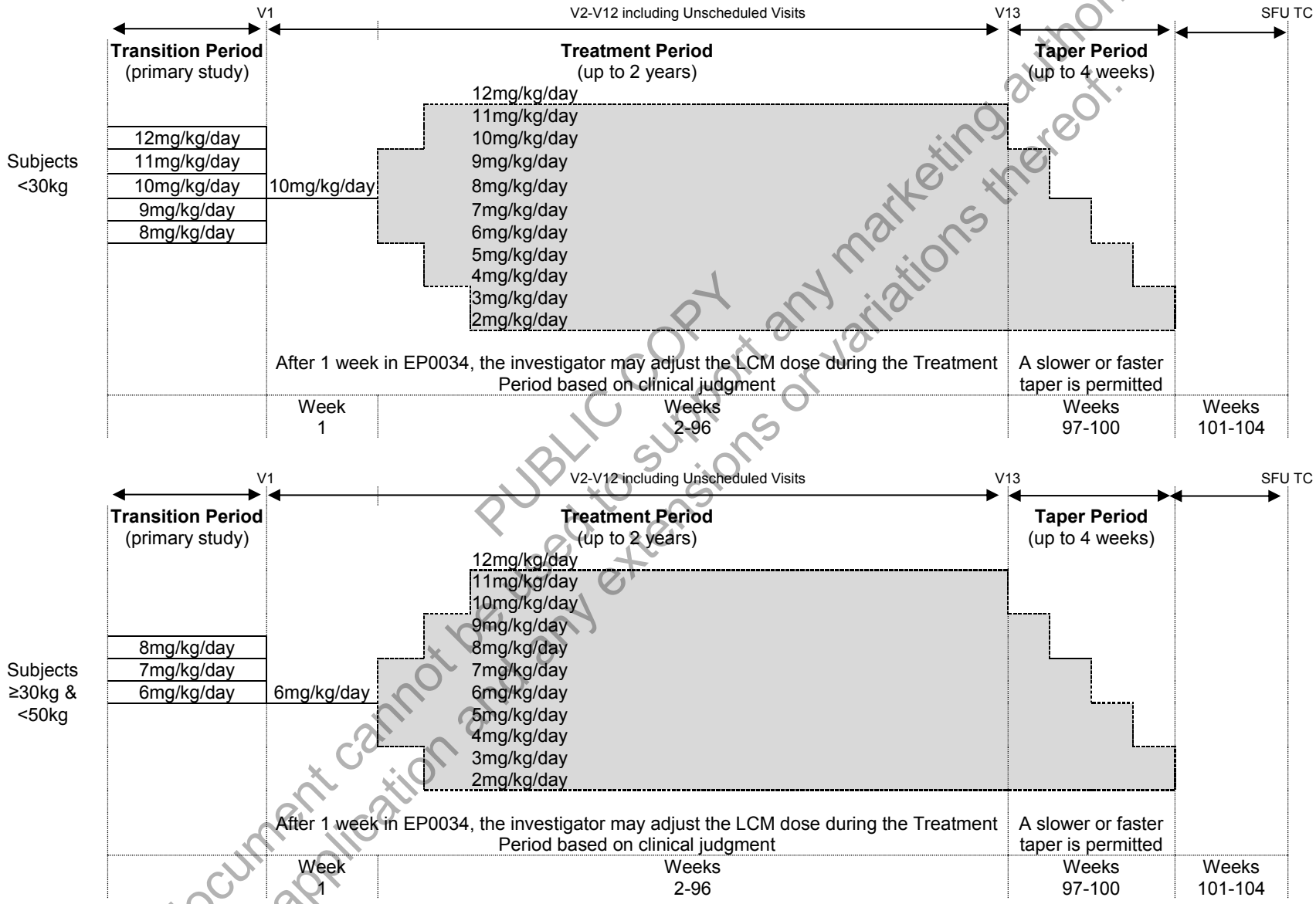
| Assessments | Taper Period | Safety Follow-Up Period | |
|---|---|---|---|
| | Taper Visit[a] | Safety Follow-Up Visit[b] | Safety Follow-Up Telephone Call[c] |

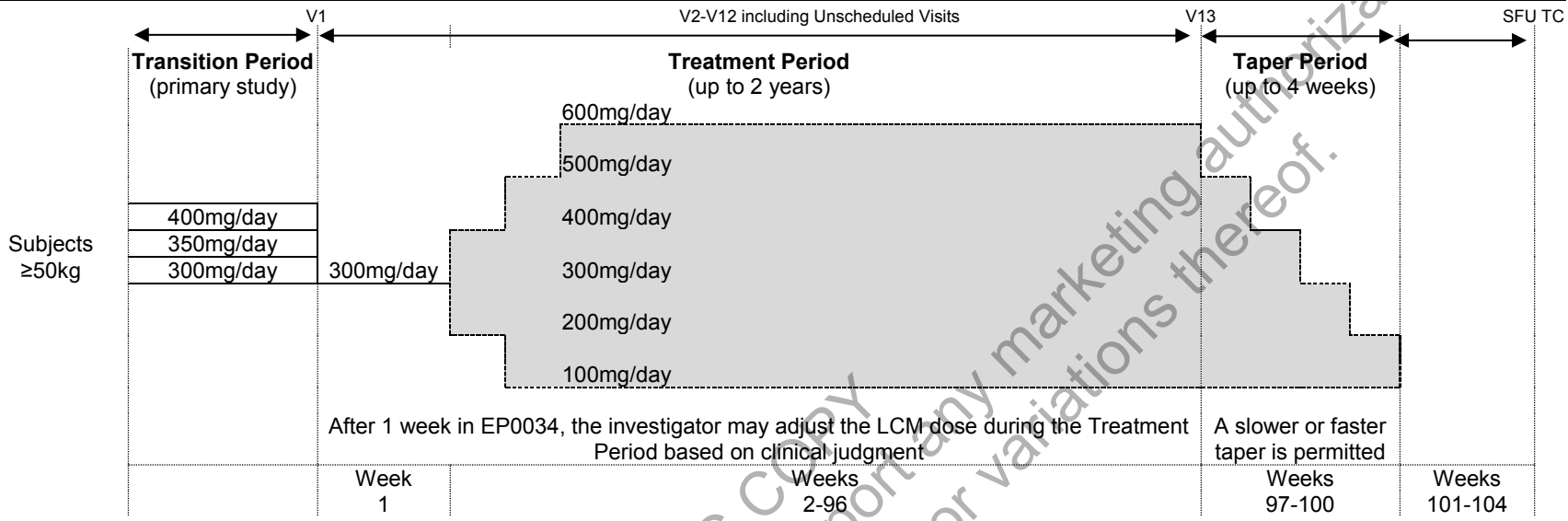
[c] The Safety Follow-Up Telephone Call occurs 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Telephone Call is not required for subjects who participate in EP0151 or EP0152.
[d] Only applicable for subjects with an implanted VNS device.
[e] The Tanner Stage will be performed only for subjects who are pubescent at V1 or who enter puberty during the course of the study.
[f] A 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) will be performed prior to any blood draws and vital signs and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording.
[g] For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container).
[h] For female subjects of childbearing potential.
[i] For all subjects ≥6 years of age, the "Since Last Visit" version of the C-SSRS should be completed. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits.
[j] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis. For subjects who enter the Safety Follow-Up Period, the subject diary will be returned at the Safety Follow-Up Visit. Subjects who do not enter the Safety Follow-Up Period will return the diary at V13/TermV.
[k] If an AE is reported at this telephone contact, the investigator will follow the AE 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.

## 5.3 Schematic diagram

Figure 5-1 presents schematic diagrams of dosing for EP0034.

## Figure 5-1: Schematic diagram






LCM=lacosamide; SFU=Safety Follow-Up; TC=telephone contact; V=visit
Note: Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

## 5.4 Rationale for study design and selection of dose

Epilepsy is a condition for which an improved benefit/risk ratio for medicinal products remains a challenge; this is especially true for pediatric patients.

EP0034 will provide continued availability of LCM to subjects who have completed SP0969, which is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM as adjunctive therapy in pediatric subjects with epilepsy ≥4 years to <17 years of age with partial-onset seizures. EP0034 will also be open to subjects who complete SP0967, which is the planned confirmatory study for LCM as adjunctive therapy in pediatric subjects with epilepsy aged ≥1 month to <4 years with partial-onset seizures.

Dose selection in EP0034 is based on the primary studies (ie, SP0969 and SP0967). During EP0034, 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 600mg/day or 12mg/kg/day, whichever is lower based on body weight.

# 6 SELECTION AND WITHDRAWAL OF SUBJECTS

## 6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form (ICF) is signed and dated by the subject or legal representative. The ICF or a specific Assent form, where required, will be signed and dated by minors.
2. Subject has completed the Transition Period of SP0967 or SP0969 for the treatment of uncontrolled partial-onset seizures in pediatric epilepsy.
3. Subject is expected to benefit from participation, in the opinion of the investigator.
4. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.
5. Subject is male or female aged 1 month to ≤17 years.
6. Subject has a diagnosis of epilepsy with partial-onset seizures.

## 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 a mandatory withdrawal criterion (ie, MUST withdraw criterion) for SP0967 or SP0969, or is experiencing an ongoing serious AE (SAE).
3. For subjects ≥6 years of age, 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 Visit 1.

5. Female subject who is pregnant or nursing, and/or a female subject of childbearing potential who is not surgically sterile or does not practice 1 highly effective method of contraception (according to the International Council for Harmonisation [ICH] guidance defined as those that result in a failure rate <1% per year when used consistently and correctly), unless sexually abstinent, for the duration of the study. Female subject of childbearing potential taking enzyme-inducing antiepileptic drugs (EI-AEDs: carbamazepine, phenytoin, barbiturates, primidone, topiramate, oxcarbazepine) who is not surgically sterile or does not practice 1 highly effective method of contraception according to the World Health Organization recommendation (ie, depot medroxyprogesterone acetate, norethisterone enantate, intrauterine devices, combined injectables, and progestogen implants) with administration of EI-AEDs OR does not practice 2 combined methods of contraception (ie, combined hormonal contraception plus barrier method with spermicidal agent), unless sexually abstinent, for the duration of the study.
6. Subject has >2x the upper limit of normal (ULN) of any of the following: ALT, AST, 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 enrolled subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

## 6.3 Withdrawal criteria

Subjects are free to withdraw or the subject's legal representatives are free to withdraw the subject from the study at any time, without prejudice to their continued care.

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

1. Subject experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject has a QTc interval ≥500ms that is confirmed by a cardiologist over read on any ECG.
4. Subject develops a second-degree atrioventricular (AV) block while awake or develops a third-degree AV block.
5. For subjects ≥6 years of age, subject has actual suicidal ideation since last visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
6. Subject is unwilling or unable to continue or legal representative is unwilling or unable to allow the subject to continue in the study.
7. Investigator decides that withdrawal from further participation would be in the subject's best interest.
9. Female subject who achieves menarche during the study and does not practice contraception as provided in Exclusion Criteria 5 unless sexually abstinent.

10. Subject becomes pregnant, as evidenced by a positive pregnancy test.

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

1. Any clinically relevant change in medical or psychiatric condition (if, in the opinion of the investigator, the condition warrants discontinuation from the study).
2. Subject requires a medication that is not permitted by the protocol (see Section 7.8.1).
3. Subject and/or legal representative is noncompliant with study procedures or medication, in the opinion of the investigator.

Subjects discontinuing LCM for any reason should taper off medication as described in Section 7.2.2. Whenever possible, these cases should be discussed with the Medical Monitor prior to withdrawing the subject from the study.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow-up, the investigator should make an effort (at least 1 phone call and 1 written message to the subject and/or legal representative), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable. The eCRF must document the primary reason for withdrawal or discontinuation.

### 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if 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:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

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

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

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

Evaluation of PDILI must be initiated as described in Section 10.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

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

# 7 STUDY TREATMENT(S)

## 7.1 Description of investigational medicinal product

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 one side and "50" on the other. The 100mg tablets are dark yellow, oval, film-coated tablets debossed with "SP" on one side and "100" on the other.

## 7.2 Treatment(s) to be administered

Lacosamide will be administered bid (at approximately 12-hour intervals, once in the morning and once in the evening) in divided doses. The oral solution formulation will be measured and administered via a dosing syringe.

Oral administration is the preferred route in this study. Feeding tube administration is an alternative route in case a subject is unable to swallow the study medication.

Each subject's weight will be monitored at every visit, and the LCM dose will be adjusted accordingly.

### 7.2.1 Treatment Period

After completion of the Transition Period in the primary study, all subjects will have been transitioned to a dose of LCM according to their weight. Subjects will receive LCM 10mg/kg/day (oral solution) for subjects weighing <30kg, LCM 6mg/kg/day (oral solution) for subjects weighing ≥30kg to <50kg, and LCM 300mg/day (tablets) for subjects weighing ≥50kg during at least their first week in the Treatment Period of EP0034. After 1 week in EP0034, the investigator may adjust the LCM dose during the Treatment Period based on clinical judgment according to Table 7-1. If the investigator wants to adjust the LCM dosage after 1 week in EP0034, the subject should return to the clinic for an Unscheduled Visit, at the discretion of the investigator. Subjects who are able and willing to swallow tablets may be dispensed LCM tablets during the Treatment Period, based on clinical judgment, regardless of weight. Lacosamide doses may be increased up to a maximum of LCM 600mg/day or 12mg/kg/day, whichever is lower based on body weight.

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

| Formulation | Minimum LCM dose | Maximum LCM dose |
|---|---|---|
| Oral solution | 2mg/kg/day | 12mg/kg/day |
| Tablets | 100mg/day | 600mg/day |

LCM=lacosamide

Subjects may be allowed to switch from one formulation to the other formulation during the Treatment Period based on clinical judgment. Consideration of the current LCM milligram dose in the oral solution should occur if/when transitioning to the tablet formulation. In cases where the LCM dose received with the oral solution is not supported by the tablet strengths available in EP0034 (50mg and 100mg), a clinical decision must be made by the investigator or other study physician to either increase or decrease the LCM dose to the next multiple of 50mg with a maximum permitted dose of 600mg/day.

### 7.2.2 Taper Period

Subjects who withdraw during the study should taper off LCM if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving LCM oral solution or LCM ≥150mg/day for subjects taking tablets. It is recommended that the dose be tapered gradually in weekly decrements (see Table 7-2 and Table 7-3). A slower taper is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

**Table 7-2: Dose taper steps for subjects receiving oral solution**

| LCM dose achieved | LCM doses for the Taper Period | | | | |
|---|---|---|---|---|---|
| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 |
| 11 to 12mg/kg/day | 9mg/kg/day | 6mg/kg/day | 4mg/kg/day | 2mg/kg/day | – |
| 9 to 10mg/kg/day | 8mg/kg/day | 6mg/kg/day | 4mg/kg/day | 2mg/kg/day | – |
| 7 to 8mg/kg/day | 6mg/kg/day | 4mg/kg/day | 2mg/kg/day | 2mg/kg/day | – |
| 5 to 6mg/kg/day | 4mg/kg/day | 2mg/kg/day | 2mg/kg/day | – | – |
| 3 to 4mg/kg/day | 2mg/kg/day | 2mg/kg/day | – | – | – |

LCM=lacosamide

**Table 7-3: Dose taper steps for subjects taking tablets**

| LCM dose achieved | LCM doses for the Taper Period | | | | |
|---|---|---|---|---|---|
| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 |
| >500 to 600mg/day | 500mg/day | 300mg/day | 200mg/day | 100mg/day | – |
| >400 to 500mg/day | 400mg/day | 300mg/day | 200mg/day | 100mg/day | – |
| >300 to 400mg/day | 300mg/day | 200mg/day | 100mg/day | 100mg/day | – |
| >200 to 300mg/day | 200mg/day | 100mg/day | 100mg/day | – | – |
| ≥150 to 200mg/day | 100mg/day | 100mg/day | – | – | – |

LCM=lacosamide

Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

### 7.2.3 Alternative study treatment supply due to coronavirus disease 2019 pandemic

When a subject can no longer return to the study site due to general circumstances but will continue in the study, the following methods may be used to provide study treatment:

- Site to subject: In instances where site staff can ship study treatment dispensed from the site pharmacy supply directly to the subject.
- Depot to subject: In instances where it is not possible for the site staff to access study treatment in the site pharmacy and/or ship study treatment dispensed from the site pharmacy supply directly to the subject.

## 7.3 Packaging

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

Lacosamide 10mg/mL oral solution will be packaged in amber polyethylene terephthalate bottles with a white, child-proof, polypropylene screw cap. The LCM dose will be measured and administered via a dosing syringe.

Lacosamide tablets will be packaged in high-density polyethylene bottles with a child-proof, polypropylene screw cap.

## 7.4 Labeling

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

## 7.5 Handling and storage requirements

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

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

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

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

## 7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the sponsor's designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned.

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB's designee, preferably in their original package. The IMP intended for the study cannot be used for any other purpose than that described in this protocol.

## 7.7 Procedures for monitoring subject compliance

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

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

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

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

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

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

The following concomitant medications are prohibited during the study:

- Clozapine
- Monoamine oxidase-A inhibitors
- Barbiturates (except as AEDs)
- Cannabidiols (not approved or indicated for epilepsy by local health authority)
  - Long-term use of narcotic analgesics (the use of short-term [2 to 3 weeks] narcotic analgesics may be allowed for management of acute pain (eg, fractures or during the perioperative period for subjects requiring surgery).

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

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

If needed to optimize tolerability and seizure reduction in selected subjects, concomitant AEDs may be carefully tapered and discontinued to achieve LCM monotherapy. New concomitant AEDs may be introduced as treatment if the medication has been approved by the regulatory authorities in the country in which the subject lives. New concomitant AEDs should be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM.

Implantation of and changes in vagal nerve stimulation settings are permitted.

The investigator must contact the Medical Monitor if surgery is planned for any subject. In general, it is not necessary to discontinue LCM for subjects undergoing surgery, although each case must be discussed on a case-by-case basis. The investigator must contact the Medical Monitor before re-starting LCM after a surgery.

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 the frame of this study. The subject's participation in this study may be discontinued in such a case.

## 7.9 Blinding

EP0034 is an open-label study; thus, there will be no blinding.

## 7.10 Randomization and numbering of subjects

Subjects will not be randomized in this study. The same unique 5-digit identification number used in the primary study (ie, SP0967 or SP0969) will be used in EP0034. This subject number will be used to identify the subject throughout the study and to maintain subject confidentiality.

At study visits, an interactive voice/web response system (IXRS) will assign the applicable LCM bottle number. Further instructions will be provided in the IXRS manual.

# 8 STUDY PROCEDURES BY VISIT

Detailed tabular schedules of study procedures are provided in Section 5.2.

A time window of ±7 days relative to Visit 1 is applicable for all scheduled visits and telephone contacts after Visit 1 during the Treatment Period. On the mornings of the clinic visits, the subject should take the morning LCM dose at the usual time.

At all visits and telephone contacts, subjects will be instructed to call the investigator if any intolerable and/or serious AEs occur before the next visit or contact.

Subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM maximum plasma concentration ($C_{max}$) 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit (Section 8.5), if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

The PedsQL, the Achenbach CBCL, and the BRIEF-P and BRIEF will only be administered in countries where a validated translated version is available. The Bayley-III scales should be completed only for subjects enrolled in English-speaking countries.

## 8.1 Treatment Period

### 8.1.1 Visit 1 (Week 0)

For subjects completing the Transition Period of the primary studies and choosing to enroll in EP0034, the final Transition Visit (Transition Visit 4 in SP0969 and Final Transition Visit in SP0967) will serve as Visit 1 of EP0034. At Visit 1 (Week 0), prior to the conduct of any study-related procedures, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's legal representative(s) by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved ICF. When possible, or as required by the local IRB/IEC, the subject will be requested to give assent to participate in the study.

The subject's eligibility for the study will be determined at Visit 1 on the basis of the inclusion/exclusion criteria, signature of an ICF prior to any study-related procedures or evaluations, and the results of the assessments listed below (for further details of the assessments and the required procedures and methods, please refer to Section 9 and Section 10 of this protocol).

At Visit 1 (Week 0), all subjects will have been transitioned to a dose of LCM according to their weight and will receive a dose of LCM 10mg/kg/day (oral solution) for subjects weighing <30kg, LCM 6mg/kg/day (oral solution) for subjects weighing ≥30kg to <50kg, and LCM 300mg/day (tablets) for subjects weighing ≥50kg during at least their first week in the Treatment Period of EP0034. After 1 week in EP0034, the investigator may adjust the LCM dose according to Table 7-1. During the Treatment Period, subjects may take either oral solution or tablets, based on clinical judgment, regardless of their weight.

During Visit 1 (Week 0), the following assessments will be performed (assessments marked [T] may have already been completed during the final Transition Visit of the primary study and should not be repeated at Visit 1 of EP0034; assessments marked [M] may have already been completed during the final Maintenance Visit of the primary study and should not be repeated at Visit 1 of EP0034):

- Medical history update
- Concomitant medications assessment (T)
- Concomitant AEDs assessment (T)
- VNS assessments (T) (if applicable)
- Physical examination (complete) (T)
- Tanner Stage (M) (only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects (T)
- Body weight and height assessments (T)
- Head circumference (M)
- Neurological examination (complete) (T)
- 12-lead ECG (M) (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry and hematology (T)
- Blood sample for endocrinology (M)
- Urine sample for urinalysis (T) (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Urine pregnancy test (T) (for female subjects of childbearing potential)
- C-SSRS (T) (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)

- Achenbach CBCL ([M]) (the CBCL/1½-5 for children from 1.5 to 5 years old and the CBCL/6-18 for children 6 years and older; however, the version used in the primary study must be used for 1 year after the Baseline assessment of the primary study, as described in Section 10.8.7)
- Bayley-III scales ([T]) (in subjects <18 months of age at study entry; the same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) assessment ([M]) (version consistent with age at the visit; however, the version used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 10.8.8)
- PedsQL assessment ([M]) (form consistent with age at the visit; however, the form used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 9.3)
- Contact IXRS
- Review LCM return and compliance ([T])
- Dispense LCM
- Reminder to complete subject diary on a daily basis ([T])
- Adverse event reporting ([T]) (ongoing AEs from the primary study will be followed, as well as recording of new AEs during the current study)
- Health care resource use ([T])

A telephone contact will be made approximately 2 weeks after Visit 1 (end of Week 2, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 4 weeks after Visit 1. If the investigator wants to adjust the LCM dosage after 1 week in EP0034, the subject should return to the clinic for an Unscheduled Visit, at the discretion of the investigator.

### 8.1.2 Telephone contact (Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56, 66, and 78)

At the end of Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56, 66, and 78, between scheduled visits, the investigator or designee should contact the subject and/or caregiver (including legal representative) by telephone (a time window of ±7 days relative to Visit 1 is allowed). The investigator (or designee) should remind the subject and caregiver (including legal representative) to bring used and unused LCM to the next clinic visit. The following should be performed via telephone:

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

If an AE necessitates the subject's withdrawal from the study, the subject should return for an Early Termination Visit (Section 8.1.13) as soon as possible.

Lacosamide is supplied so that the subject or caregiver (including legal representative) can immediately decrease their dose, if needed, in consultation over the telephone with the investigator or subinvestigator. Thus, LCM can be continued at a decreased dose until a clinic visit can be scheduled.

### 8.1.3 Visit 2 (Week 4)

At Visit 2 (end of Week 4 ±7 days relative to Visit 1), subjects will return for a clinic visit and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Urine pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 2 weeks after Visit 2 (end of Week 6, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 4 weeks.

### 8.1.4 Visit 3 (Week 8) and Visit 4 (Week 12)

Subjects will return to the clinic at Visit 3 (end of Week 8 ±7 days relative to Visit 1) and Visit 4 (end of Week 12 ±7 days relative to Visit 1), and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- Urine pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 2 weeks after Visit 3 and approximately 4 weeks after Visit 4 (end of Weeks 10 and 16, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit approximately 8 weeks after Visit 4.

### 8.1.5 Visit 5 (Week 20)

At Visit 5 (end of Week 20 ±7 days relative to Visit 1), subjects will return for a clinic visit and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (complete)
- Tanner Stage (only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)

- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Head circumference
- Neurological examination (complete)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Clinical Global Impression of Change assessment
- Caregiver's Global Impression of Change assessment
- Achenbach CBCL (the CBCL/1½-5 for children from 1.5 to 5 years old and the CBCL/6-18 for children 6 years and older; however, the version used in the primary study must be used for 1 year after the Baseline assessment of the primary study, as described in Section 10.8.7)
- Bayley-III scales (in subjects <18 months of age at study entry; the same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) assessment (version consistent with age at the visit; however, the version used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 10.8.8)
- PedsQL assessment (form consistent with age at the visit; however, the form used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 9.3)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made in approximately 4 weeks (end of Week 24, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 8 weeks.

### 8.1.6 Visit 6 (Week 28)

At Visit 6 (end of Week 28 ±7 days relative to Visit 1), subjects will return for a clinic visit and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Urine pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 4 weeks after Visit 6 (end of Week 32, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 8 weeks.

### 8.1.7 Visit 7 (Week 36) and Visit 8 (Week 44)

Subjects will return to the clinic at Visit 7 (end of Week 36 ±7 days relative to Visit 1) and Visit 8 (end of Week 44 ±7 days relative to Visit 1), and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment

- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- Urine pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 4 weeks after Visit 7 (end of Week 40) and approximately 4 weeks after Visit 8 (end of Week 48, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit approximately 8 weeks after Visit 8.

### 8.1.8 Visit 9 (Week 52)

At Visit 9 (end of Week 52 ±7 days relative to Visit 1), subjects will return for a clinic visit and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (complete)
- Tanner Stage (only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Head circumference
- Neurological examination (complete)

- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Clinical Global Impression of Change assessment
- Caregiver's Global Impression of Change assessment
- Achenbach CBCL (the CBCL/1½-5 for children from 1.5 to 5 years old and the CBCL/6-18 for children 6 years and older; however, the version used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 10.8.7)
- Bayley-III scales (in subjects <18 months of age at study entry; the same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) assessment (version consistent with age at the visit; however, the version used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 10.8.8)
- PedsQL assessment (form consistent with age at the visit; however, the form used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 9.3)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 4 weeks after Visit 9 (end of Week 56, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 8 weeks.

### 8.1.9 Visit 10 (Week 60)

At Visit 10 (end of Week 60 ±7 days relative to Visit 1), subjects will return for a clinic visit and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- Urine pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 6 weeks after Visit 10 (end of Week 66, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 12 weeks.

### 8.1.10 Visit 11 (Week 72)

At Visit 11 (end of Week 72 ±7 days relative to Visit 1), subjects will return for a clinic visit and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)

- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Head circumference
- Neurological examination (brief)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Clinical Global Impression of Change assessment
- Caregiver's Global Impression of Change assessment
- Achenbach CBCL (the CBCL/1½-5 for children from 1.5 to 5 years old and the CBCL/6-18 for children 6 years and older)
- Bayley-III scales (in subjects <18 months of age)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) assessment (version consistent with age at the visit)
- PedsQL assessment (form consistent with age at the visit)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

A telephone contact will be made approximately 6 weeks after Visit 11 (end of Week 78, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 12 weeks.

### 8.1.11 Visit 12 (Week 84)

At Visit 12 (end of Week 84 ±7 days relative to Visit 1), subjects will return for a clinic visit, and the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- Urine pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Contact IXRS
- Review LCM return and compliance
- Dispense LCM (the investigator may adjust the LCM dose according to Table 7-1)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting
- Health care resource use

Subjects will be scheduled to return to the clinic for the Termination Visit in approximately 12 weeks.

### 8.1.12 Visit 13/Termination Visit (Week 96)

Visit 13 (end of Week 96 ±7 days relative to Visit 1) will be the treatment Termination Visit for subjects who complete up to 2 years of treatment. Subjects who prematurely discontinue the study must return for an Early Termination Visit as soon as possible (Section 8.1.13).

At Visit 13/Termination Visit, the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment

- VNS assessment (if applicable)
- Physical examination (complete)
- Tanner Stage (only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Clinical Global Impression of Change assessment
- Caregiver's Global Impression of Change assessment
- Achenbach CBCL (the CBCL/1½-5 for children from 1.5 to 5 years old and the CBCL/6-18 for children 6 years and older)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) assessment (version consistent with age at the visit)
- PedsQL assessment (form consistent with age at the visit)
- Contact IXRS (only if LCM will be dispensed for taper, as described below)
- Review LCM return and compliance
- Dispense LCM (if applicable for taper, as described below)
- Reminder to complete subject diary on a daily basis
- Adverse event reporting
- Health care resource use

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 legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

Subjects who complete the study and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or legal representative) should enter the Taper Period after the Visit 13/Termination Visit and taper LCM gradually as described in Section 7.2.2. A Taper Visit will be performed at the end of the Taper Period, followed by the Safety Follow-Up Visit that occurs 2 weeks (±2 days) after the final dose of LCM, and then the Safety Follow-Up Telephone Contact that occurs 30 days (-1/+3 days) after the final dose of LCM.

Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets (Section 7.2.2). It is recommended that the dose be tapered gradually in weekly decrements. A slower taper is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

### 8.1.13 Early Termination Visit

Subjects who prematurely discontinue from the study must complete an Early Termination Visit as soon as possible.

The following will be performed at the Early Termination Visit:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (complete)
- Tanner Stage (only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Head circumference
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)

- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)
- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Clinical Global Impression of Change assessment
- Caregiver's Global Impression of Change assessment
- Achenbach CBCL (the CBCL/1½-5 for children from 1.5 to 5 years old and the CBCL/6-18 for children 6 years and older; however, the version used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 10.8.7)
- Bayley-III scales (in subjects <18 months of age at study entry; the same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period)
- BRIEF-P (≥2 years to <5 years of age)/BRIEF (≥5 years of age) assessment (version consistent with age at the visit; however, the version used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 10.8.8)
- PedsQL assessment (form consistent with age at the visit; however, the form used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 9.3)
- Contact IXRS (only if LCM will be dispensed for taper, as described below)
- Review LCM return and compliance
- Dispense LCM (if applicable for taper, as described below)
- Reminder to complete subject diary on a daily basis
- Adverse event reporting
- Health care resource use

At the time of withdrawal from 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 withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s). These subjects should complete the Early Termination Visit and then complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM, followed by the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Subjects who withdraw from the study prematurely and discontinue use of LCM (as determined by the investigator in consultation with the subject and/or legal representative) should taper LCM gradually as described in Section 7.2.2. These subjects should complete the Early Termination Visit and enter the Taper Period. A Taper Visit will be performed at the end of the Taper Period, followed by the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM, and then the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM.

Lacosamide for taper will be dispensed only for subjects who achieve a dose of LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets (Section 7.2.2). It is recommended that the dose be tapered gradually in weekly decrements. A slower taper is permitted, if medically necessary. In case of an emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

## 8.2 Taper Period

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from the study prematurely, if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects entering EP0151 or EP0152.

During the Taper Visit, the following will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (brief)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (brief)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)

- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Review LCM return and compliance
- Reminder to complete subject diary on a daily basis
- Adverse event reporting
- Health care resource use

Subjects will be scheduled to return to the clinic for the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM.

## 8.3 Safety Follow-Up Visit

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM (including that from LCM taper). The Safety Follow-Up Visit is not required for subjects who complete the study or withdraw prematurely from the study but do not undergo taper of LCM. The Safety Follow-Up Visit is not required for subjects who participate in EP0151 or EP0152.

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

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Physical examination (complete)
- Tanner Stage (only for subjects who are pubescent at Visit 1 or who enter puberty during the course of the study)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects
- Body weight and height assessments
- Neurological examination (complete)
- 12-lead ECG (2 interpretable recordings, approximately 20 to 30 minutes apart, to be performed prior to any blood draws and vital signs assessment and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording)
- Blood sample for clinical chemistry and hematology
- Blood sample for endocrinology
- Urine sample for urinalysis (for subjects aged ≥5 years) ( urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])
- Serum pregnancy test (for female subjects of childbearing potential)

- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Subject diary return (for subjects who enter the Safety Follow-Up Period, the subject diary will be returned at the Safety Follow-Up Visit, and subjects who do not enter the Safety Follow-Up Period will return the diary at Visit 13/Termination Visit)
- Adverse event reporting
- Health care resource use

## 8.4 Safety Follow-Up Telephone Contact

Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Telephone Contact is not required for subjects who participate in EP0151 or EP0152.

The following should be performed via telephone:

- Concomitant medications assessment
- Concomitant AEDs assessment
- Adverse event reporting (if an AE is reported at this telephone contact, the investigator will follow the AE 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 [Section 10.1.4]).

## 8.5 Unscheduled Visit

An Unscheduled Visit may be performed at the investigator's discretion.

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added, will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

If an Unscheduled Visit is needed, then the following assessments will be performed:

- Concomitant medications assessment
- Concomitant AEDs assessment
- VNS assessment (if applicable)
- Blood pressure and pulse rate, including orthostatic assessments in ambulatory subjects

- Body weight assessment
- C-SSRS (only if the Unscheduled Visit is due to safety or efficacy reasons; for subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)
- Reminder to complete subject diary on a daily basis
- Review withdrawal criteria
- Adverse event reporting

Additional assessments can be performed at the investigator's discretion.

## 8.6 Study conduct due to coronavirus disease 2019 pandemic

The protocol-mandated visit schedule should be followed to the extent possible, considering the individual benefit-risk assessment by the investigator. If necessary, remote visits may be conducted, and the subjects or caregivers will be contacted by telephone or videoconference. Remote follow up, at minimum with a telephone call after 3 months, must be done (preferably more frequently and as needed to follow up on subject safety assessments).

Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the coronavirus disease 2019 (COVID-19) pandemic (eg, any measures that may limit access to the site or may require additional actions by the subject prior to entry to the site).

If a subject needs to be discontinued and cannot come into the clinic, then appropriate tapering instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible.

In situations where a subject is unable to return to the study site, investigators will assess and document the subject's safety via telephone contact. Based on information gathered from the telephone contact, investigators will confirm whether the subject could continue the current study treatment based upon the outcome of the safety assessments. Subjects' agreement to implement this procedure should be obtained and documented prior to implementing any changes. Changes in the study treatment supply in this situation are described in Section 7.2.3.

If a subject visits another facility for a medical issue (or has to switch sites for a COVID-19-related reason), the investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the clinical study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

Deviations to data collection including inability to perform some assessments, such as ECG, blood collection for safety laboratory assessments and PK, or alternative methods of assessment, such as phone calls, should be recorded in the source documentation and notated as "not done" in the eCRF.

In cases where subjects cannot return to the clinic, and it will not be possible to dispense a new seizure diary, subjects will be instructed to continue recording of seizures in a manner that is

mutually agreed with the investigator (eg, hand-written notes, recording on a smart device). Any recording of seizures in a manner outside of the study seizure diary must be carefully documented in the source medical records (copies/print-screen printouts of these recordings will be brought to and retained at the site).

# 9 ASSESSMENT OF EFFICACY

## 9.1 Seizure frequency

Efficacy variables based on seizures will be measured using data obtained from subject diaries. If an electronic diary was used in the primary study, the subject will continue to use the same diary in EP0034; otherwise, a new diary will be dispensed at admission to EP0034. Subjects or their caregivers will keep a diary to record the daily seizure activity from the beginning of the Treatment Period (Visit 1) until the last study visit, recording both seizure type and seizure frequency. The seizure records will be checked by the investigator with regards to correct and thorough daily completion by the subject, and to determine if a dose adjustment is required. At each visit and telephone contact subject and/or legal representative should be reminded to complete subject diaries on a daily basis.

## 9.2 Global Impression of Change

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

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

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

## 9.3 PedsQL

The PedsQL is a validated instrument that consists of generic core scales suitable for use with pediatric populations, including those with acute or chronic health conditions (Varni et al, 2001). The PedsQL will be administered according to the tabular schedules of study procedures (Section 5.2). The PedsQL will only be administered in countries where a validated translated version is available.

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

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.

### 9.4 Health care resource use

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

## 10 ASSESSMENT OF SAFETY

### 10.1 Adverse events

#### 10.1.1 Definition of adverse event

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

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

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.

#### 10.1.2 Procedures for reporting and recording adverse events

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

"Did you notice anything unusual about your health (since your last visit)?"

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

#### 10.1.3 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words

on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

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

### 10.1.4 Follow up of adverse events

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

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

### 10.1.5 Rule for repetition of an adverse event

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

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

### 10.1.6 Pregnancy

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

- The subject should return for an Early Termination Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the Early Termination Visit.
- A Safety Follow-Up Visit should be scheduled 2 weeks (±2 days) after the subject has discontinued IMP.

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

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, UCB will ask the investigator or designee to contact the subject and his partner to request consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the subject's partner for completion.

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

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

A pregnancy becomes 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.

### 10.1.7 Overdose of IMP

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability or Study Drug Dosing module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events 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).

### 10.1.8 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Drug Safety representative.

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

### 10.1.9 Occurrence of COVID-19

Occurrence of COVID-19 in subjects should be reported as either “suspected COVID-19” or “confirmed COVID-19” along with all available relevant data including diagnostic and laboratory data. For subjects where COVID-19 is still suspected despite a negative viral test, please report as “suspected COVID-19” and provide relevant data to support the diagnosis as well as the test results.

## 10.2 Serious adverse events

### 10.2.1 Definition of serious adverse event

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

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity

- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include but are not limited to, potential Hy's Law [see Section 10.3], 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.)

### 10.2.2 Procedures for reporting serious adverse events

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

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

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

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a

translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

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

### 10.2.3 Follow up of serious adverse events

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

Information on SAEs obtained after clinical database lock will be captured through the Drug Safety database without limitation of time. 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 10.6.1.

## 10.3 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 (<45beats/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 ≥2×ULN
- AST ≥2×ULN

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

## 10.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 10.3)

## 10.5 Anticipated serious adverse events

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

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 10.2.2.

**Table 10–1: Anticipated SAEs for the pediatric epilepsy population**

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

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

## 10.6 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedules of study procedures (Section 5.2). Urine assessments will be performed for subjects aged ≥5 years. For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.7). The procedures for handling and shipping these specimens will be provided to the sites. In exceptional circumstances, local laboratory analysis may be performed. The medical monitor should be contacted beforehand to discuss these circumstances.

The following laboratory parameters will be measured:

**Table 10–2: Laboratory measurements**

| Hematology | Chemistry | Endocrinology | Urinalysis[a] |
|---|---|---|---|
| Hematocrit | Calcium | FSH | pH |
| Hemoglobin | Phosphorus | LH | Ketones |
| Platelet count | Serum electrolytes (sodium, potassium, chloride, bicarbonate) | Testosterone | Glucose |
| RBC count | Creatinine | TSH | Albumin |
| WBC count | BUN | $T_3$ (total and serum free) | Specific gravity |
| Differential count | AST | $T_4$ (total and serum free) | Microscopic exam for blood cells or casts/hpf |
| | ALT | | |
| | Total bilirubin | | |
| | Alkaline phosphatase | | |
| | GGT | | |
| | Glucose | | |
| | Albumin | | |
| | Total serum protein | | |
| | Uric acid | | |
| | Total cholesterol | | |
| | Triglycerides | | |

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; GGT=gamma-glutamyltransferase; hpf=high power field; LH=luteinizing hormone; RBC=red blood cells; $T_3$=triiodothyronine; $T_4$=thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cell
[a] Urinalysis will be performed for subjects ≥5 years of age only.

### 10.6.1 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 10.6.1.2, 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 10.3), and, if applicable, also reported as an SAE (see Section 10.2).

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 10.6.1.1). The local

hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.6.1.4).

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

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

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

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Table 10–3 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 10.6.1.3); recommended to occur at the site with HCP. | Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d] |
| ≥5xULN | NA | NA | | | | |
| ≥3xULN | NA | Yes | | Immediate, 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 10.6.1.2). | 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 10.6.1.3). | Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d] |

## Table 10–3: Required investigations and follow up for PDILI

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |

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

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

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

[c] Details provided in Section 10.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

#### 10.6.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 10.6.1.3) and SAE report (if applicable).

#### 10.6.1.2 Immediate action: determination of IMP discontinuation

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

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

#### 10.6.1.3 Testing: identification/exclusion of alternative etiology

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

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

The following measurements are to be assessed:

**Table 10–4: PDILI laboratory measurements**

| | |
|---|---|
| **Virology-related** | Hepatitis A IgM antibody |
| | HBsAg |
| | Hepatitis E IgM antibody |
| | HBcAb-IgM |
| | Hepatitis C RNA |
| | Cytomegalovirus IgM antibody |

**Table 10–4: PDILI laboratory measurements**

| | |
|---|---|
| | Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing) |
| **Immunology** | Anti-nuclear antibody (qualitative and quantitative) |
| | Anti-smooth muscle antibody (qualitative and quantitative) |
| | Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative) |
| **Hematology** | Hematocrit |
| | Hemoglobin |
| | Platelet count |
| | RBC count |
| | WBC count |
| | Differential count |
| **Urinalysis** | Toxicology screen |
| **Chemistry** | Amylase |
| | Bilirubin (If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin) |
| | Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation |
| | AST |
| | ALT |
| | ALP |
| | GGT |
| | Albumin |
| **Additional** | Prothrombin time/INR[a] |
| | Serum pregnancy test in women of childbearing potential |
| | PK sample |

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

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

The following additional information is to be collected:

**Table 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:<br>• History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease")<br>• Adverse reactions to drugs<br>• Allergies<br>• Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)<br>• Recent travel<br>• 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

#### 10.6.1.4 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.

## 10.7 Pregnancy testing

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

## 10.8 Other safety measurements

### 10.8.1 Physical examination

Physical examinations will be performed according to the tabular schedules of study procedures (Section 5.2) by a medically qualified clinician licensed to perform the examination. Clinically significant physical examination findings are to be reported as AEs.

#### 10.8.1.1 Complete physical examination

The complete physical examination will include cardiac and respiratory function via auscultation, temperature, and review of all body systems. Genitourinary and breast examinations will be performed for the assessment of Tanner Stage only.

#### 10.8.1.2 Brief physical examination

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

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

### 10.8.2 Neurological examination

Neurological examinations will be performed according to the tabular schedules of study procedures (Section 5.2) by a medically qualified clinician with documented training in the conduct of neurological examinations. If possible, the same clinician should conduct all neurological examinations for the same subject during the study. The investigator or subinvestigator is responsible for confirming the diagnosis of partial-onset seizures.

#### 10.8.2.1 Complete neurological examination

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

The head circumference will be measured according to the tabular schedules of study procedures (Section 5.2).

#### 10.8.2.2 Brief neurological examination

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

### 10.8.3 Tanner Stage

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

### 10.8.4 12-lead ECG

Standard 12-lead ECGs will be performed according to the tabular schedules of study assessments (Section 5.2). Two interpretable recordings should be made approximately 20 to 30 minutes apart. Care should be taken to ensure proper lead placement and quality ECG recordings. The ECGs will be performed prior to any blood draws and vital signs assessment.

Subjects should rest in a supine position approximately 5 minutes prior to each recording and during the recording.

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

#### 10.8.4.1 Overall ECG interpretation

Electrocardiograms will be reviewed locally by the investigator, subinvestigator, or qualified designated reader and at a central ECG laboratory. If the reading identifies second or third degree AV block or another abnormal ECG finding that is assessed by the investigator to be clinically significant, then the ECG should be repeated on the same day. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study (see Section 6.3). The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

### 10.8.5 Vital signs, body weight, and height

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

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

### 10.8.6 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 subject's eligibility for the study as well as to assess suicidal ideation and behavior that may occur during the study.

The C-SSRS will be completed according to the tabular schedules of study procedures (Section 5.2). This scale will be completed for subjects ≥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 at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits.

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

### 10.8.7 Achenbach CBCL

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

Depending on the subject's age, 2 versions of the Achenbach CBCL will be used. The CBCL/1½-5 checklist is intended for use in children 18 months to 5 years and 11 months of age (Achenbach and Rescorla, 2000). For subjects ≥6 years to <17 years of age, the CBCL/6-18 version will be used (Achenbach and Rescorla, 2001). 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.

The Achenbach CBCL will be completed according to the tabular schedules of study procedures (Section 5.2). The completion of the Achenbach CBCL will require approximately 45 minutes.

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

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

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

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

### 10.8.8 BRIEF-P and BRIEF

The BRIEF-P and the BRIEF are validated tools that will be used for the evaluation of subjects ≥2 years to <5 years of age and ≥5 years of age, respectively (Gioia et al, 2000). 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 only be administered in countries where a validated translated version is available.

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.

### 10.8.9 Bayley Scales of Infant and Toddler Development, Third Edition

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

This scale is validated as a tool for assessment of neurological development in young pediatric subjects and is therefore considered appropriate for EP0034.

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

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

The scale will be completed according to the tabular schedules of study procedures (Section 5.2). The same scale should be completed for 1 year after the Baseline assessment of the primary study, even if the subject turns >18 months of age during that period.

# 11 STUDY MANAGEMENT AND ADMINISTRATION

## 11.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the Clinical Project Manager of the sponsor within 24 hours and follow any local regulatory requirements.

## 11.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization (CRO) or a contract monitor.

The investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

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

### 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). Photocopies of CRFs are not considered acceptable source documents.

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

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated

by the investigator and become a permanent part of the subject's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

### 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 study will be performed using remote data capture (RDC). The investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic CRFs and in all required reports.

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

### 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 is performed using RDC; the data are entered into the electronic CRFs 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 Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

## 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 study drug 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 medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

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

## 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 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

Analysis sets will be defined as follows:

- The Safety Set (SS) will consist of all enrolled subjects who took at least 1 dose of LCM in this long-term study. All safety analyses will be performed on the SS.
- The Full Analysis Set will be used for the analysis of seizure data and will consist of all subjects in the SS, who have at least 1 completed post-Baseline seizure diary.

## 12.2 General statistical considerations

Descriptive statistics will be used to provide an overview of the safety and efficacy 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 n, mean, standard deviation (SD), median, minimum, and maximum. No statistical hypothesis testing will be performed. Baseline values for safety and efficacy variables will be determined from Baseline values of the primary study.

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

## 12.3 Planned safety analyses

The long-term safety of LCM at individualized doses will be evaluated by means of the safety analyses. Summary tables will be presented over the Treatment Period by 3-month periods and by categories of total duration of exposure. All safety variables will be analyzed by descriptive methods on the SS. Treatment-emergent AEs will be defined as those events which started on or after the date of first EP0034 dose of LCM, or whose severity worsened on or after the date of first EP0034 dose of LCM. Adverse events which occur within 30 days after last dose of LCM will be considered treatment emergent. Treatment-emergent AEs will be summarized by categories of total duration of exposure, 3-month period, Medical Dictionary for Regulatory Activities (MedDRA®) Primary System Organ Class and Preferred Term in incidence tables. Separate tables will be provided by categories of total duration of exposure for AEs leading to withdrawal from the study and SAEs.

The safety variables such as changes in ECG, vital signs, laboratory parameters, height, body weight measurements, and Tanner Stage scores will be analyzed descriptively. The results for occurrence of these variables during long-term treatment will be summarized overall, and by visit. Subjects will be grouped by dose for summary purposes. The procedure for grouping

subjects by dose will be defined in the SAP. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared to their Baseline status.

Changes from Baseline in laboratory, ECG, and vital sign values will be tabulated. In addition, physical and neurological examination abnormalities will be listed by visit. Markedly abnormal values will be summarized descriptively for laboratory, vital sign, body weight, and ECG parameters.

Achenbach CBCL scores, BRIEF/BRIEF-P scores, and Bayley-III scores and the respective change from primary LCM study Baseline scores will be analyzed in a descriptive manner.

## 12.4 Planned efficacy and other analyses

### 12.4.1 Efficacy analyses

Efficacy variables will be summarized descriptively. Efficacy evaluation for seizures will be based on subject diaries, which include type, date, and number of seizures.

Descriptive statistics will also be presented for the Clinical and Caregiver's Global Impression of Change, PedsQL scores, and the number of health care resources used (concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol).

## 12.5 Handling of protocol deviations

After all CRFs have been entered and queries addressed, and prior to locking the clinical database, a data evaluation meeting (DEM) will be held. The purpose of this DEM will be to assess the quality of the data for subsequent database lock, identify protocol deviations, and finalize analysis sets.

## 12.6 Handling of dropouts or missing data

No imputation of missing values for analysis parameters is planned unless otherwise noted. Imputations for missing or partial values for dates for AEs and concomitant medications will be applied to determine if an event is to be considered treatment emergent or concomitant. Across safety and efficacy analyses, only reported data will be used in each analysis time interval.

Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.

## 12.7 Planned interim analysis and data monitoring

No formal 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

Approximately 500 subjects from the SP0967 and the SP0969 study will be eligible to enroll in this open-label extension study. No formal hypothesis testing will be conducted in this study; therefore, no formal sample size calculations have been performed.

# 13 ETHICS AND REGULATORY REQUIREMENTS

## 13.1 Informed consent

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

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

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

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

All studies conducted at centers in the United States 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 ICF. 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 to participate in the study.

## 13.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency contact information. The investigator will instruct the subject to keep the card with him/her at all times.

## 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, ICF, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if

applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

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

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

## 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 at Screening.

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

## 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.

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# 16 APPENDICES

## 16.1 Protocol Amendment 1

### Rationale for the amendment

The primary purpose of this substantial amendment is to add further clarification regarding the addition of extra procedures (ECGs) in case of LCM dose increases to ≥8mg/kg/day and ≥400mg/day in accordance with the FDA request and based on program specific guidelines. Furthermore, at the request of the Spanish IEC, additional inclusion criteria (Inclusion Criterion #5 and #6) were added to clarify age and diagnosis requirements for enrollment.

Additional changes have been implemented for consistency with other protocols in the LCM pediatric program.

Furthermore, administrative changes including the update of the study team and minor corrections, and update of the Sponsor Declaration for electronic signature, have been made.

### Modifications and changes

### Global changes

The following changes were made throughout the protocol:

- Text has been added to clarify the extra ECG assessments related to LCM dose increases of ≥8mg/kg/day and ≥400mg/day, respectively.
- Inclusion Criterion #5 has been added to clarify the enrollment requirements for age of subjects (1 month to ≤17 years).
- Inclusion Criterion #6 has been added to clarify the enrollment requirements for diagnosis of subjects (epilepsy with partial-onset seizures).
- Text has been modified to clarify that the C-SSRS needs to be completed at an Unscheduled Visit if the visit is scheduled due to safety or efficacy reasons.
- Text has been added to clarify which C-SSRS versions to use if a subject becomes 6 years of age (at that specific visit and all subsequent visits).
- Text has been updated to clarify protocol adherence.
- Efficacy variables have been added.
- Text has been modified to clarify the handling of dropouts or missing data.
- Exclusion Criterion #2 has been amended and Exclusion Criterion #4 has been deleted to clarify that subjects are excluded if they meet the mandatory withdrawal criteria for SP0967 or SP0969.
- Text has been added to clarify that the subject's parent(s)/caregiver(s)/legal representative(s) are also given the opportunity to report AEs spontaneously.

- Text has been added to clarify that urine assessment will be performed on subjects aged ≥5 years and the assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container).
- Text has been added to clarify that implantation of and changes in vagal nerve stimulation settings are permitted.
- For subjects choosing to enroll in EP0034 from SP0969, the final Transition Visit, which will serve as Visit 1 of EP0034, has been corrected from Transition Visit 3 to Transition Visit 4.
- Text has been corrected to clarify that the LCM doses will be divided between the morning and the evening dose (but not equally divided).
- Text has been modified to correct the duration of the Taper Period from 6 weeks to 4 weeks.
- The Sponsor Study Physician, Clinical Project Manager, and Clinical Trial Biostatistician have changed and their contact details, as well as those of the Clinical Monitoring Research Organization, have been updated.
- The Sponsor Declaration has been updated for electronic signature.
- Other changes made in this amendment are to provide clarification, are administrative in nature, or are to correct errors.

## Specific changes

## Change #1

**SPONSOR DECLARATION**

**Clinical Project Manager**

[redacted]

_____

Date/Signature

**Clinical Trial Biostatistician**

[redacted]

_____

Date/Signature

**Study Physician**

[redacted]

_____

Date/Signature

**Clinical Program Director**

[redacted]

_____

Date/Signature

## Has been revised and moved to Section 18:

## 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.

## Change #2

**STUDY CONTACT INFORMATION**

### Sponsor Study Physician

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

### Clinical Project Manager

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

### Clinical Trial Biostatistician

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

## Clinical Monitoring Contract Research Organization

| | |
|---|---|
| Name: | Pharmaceutical Research Associates, Inc. |
| Address: | 4130 Park Lake Avenue, Suite 400<br>Raleigh, NC 27612<br>UNITED STATES |
| Phone: | +1 919 786 8200 |
| Fax: | +1 919 786 8201 |

## Has been changed to:

## Sponsor Study Physician

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

## Clinical Project Manager

| | |
|---|---|
| Name: | [redacted] |
| Address: | UCB BIOSCIENCES GmbH.<br>Alfred-Nobel-Str. 10<br>40789 Monheim<br>GERMANY |
| Phone: | [redacted] |
| Fax: | [redacted] |

## Clinical Trial Biostatistician

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

## Clinical Monitoring Contract Research Organization

| | |
|---|---|
| Name: | PRA Health Sciences |
| Address: | 4130 Park Lake Avenue, Suite 400<br>Raleigh, NC 27612<br>UNITED STATES |
| Phone: | +1 919 786 8200 |
| Fax: | +1 919 786 8201 |

## Change #3

**SERIOUS ADVERSE EVENT REPORTING**

| Serious adverse event reporting (24h) | |
|---|---|
| **Fax** | **Europe and Rest of the World (except Japan):** +32 2 386 24 21<br>**USA:** +1 800 880 6949<br>**Canada:** +1 877 582 8842<br>**Japan:** +81 3 6864 7400 |
| **Email** | **Global:** DS_ICT@ucb.com |

## Has been changed to:

| Serious adverse event reporting (24h) | |
|---|---|
| **Fax** | **Europe and Rest of the World:** +32 2 386 24 21<br>**USA:** +1 800 880 6949<br>**Canada:** +1 877 582 8842 |
| **Email** | **Global:** DS_ICT@ucb.com |

## Change #4

**LIST OF ABBREVIATIONS**

DRM data review meeting

## Has been changed to:

DEM data evaluation meeting

## Change #5

**Section 1 SUMMARY, paragraphs 3, 7, and 8**

The study medication is LCM in either the oral solution formulation or tablet formulation. Subjects may take either oral solution or tablets during the Treatment Period, based on clinical judgment, regardless of their weight. Lacosamide will be administered twice daily (bid) at approximately 12-hour intervals, once in the morning and once in the evening, in equally divided doses. The oral solution formulation will be measured and administered via a dosing syringe.

The efficacy variables will be based on seizure diary data and will include the percentage of seizure-free days during the study. The following other efficacy variables based on seizure diary data will be computed for subjects from SP0969: the percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline) and the percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline, and absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline (Baseline is defined as the period before receiving study medication in the previous pediatric study). The following other efficacy variables will be computed for all subjects in EP0034: achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized), Clinical Global Impression of Change, and Caregiver's Global Impression of Change.

Other evaluations will include behavioral and cognition assessments (Achenbach Child Behavior Checklist [CBCL], Behavior Rating Inventory of Executive Function [BRIEF®]/BRIEF Preschool Version [BRIEF® P], and Bayley Scales of Infant and Toddler Development, Third Edition [Bayley-III®] for subjects enrolled in English-speaking countries), quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]), plasma concentrations of LCM, and health care resource use (concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays).

## Has been changed to:

The study medication is LCM in either the oral solution formulation or tablet formulation. Subjects may take either oral solution or tablets during the Treatment Period, based on clinical judgment, regardless of their weight. Lacosamide will be administered twice daily (bid) at approximately 12 hour intervals, once in the morning and once in the evening, in divided doses. The oral solution formulation will be measured and administered via a dosing syringe.

The efficacy variables will be based on seizure diary data and will include the percentage of seizure-free days during the study. The following other efficacy variables based on seizure diary data will be computed for subjects from SP0969: the percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline) and the percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline, the percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline) and the percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline, absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline (Baseline is defined as the period before receiving study medication in the previous pediatric study), and partial-onset seizure frequency per 28 days. The following other efficacy variables will be computed for all subjects in EP0034: achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized), Clinical Global Impression of Change, and Caregiver's Global Impression of Change.

Other evaluations will include behavioral and cognition assessments (Achenbach Child Behavior Checklist [CBCL], Behavior Rating Inventory of Executive Function [BRIEF®]/BRIEF Preschool Version [BRIEF® P], and Bayley Scales of Infant and Toddler Development, Third Edition [Bayley-III®] for subjects enrolled in English-speaking countries), quality of life assessments (Pediatric Quality of Life Inventory [PedsQL™]), health care resource use (concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol).

## Change #6

**Section 4.4 Other efficacy variables**

The following other efficacy variables will be computed for subjects from SP0969 and include the following:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline

The following other efficacy variables will be computed for all subjects in EP0034 and include the following:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in PedsQL for subjects ≥2 years of age
- Health care resource use: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays

## Has been changed to:

The following other efficacy variables will be computed for subjects from SP0969 and include the following:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline

- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034 and include the following:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in PedsQL for subjects ≥2 years of age
- Health care resource use: concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol

## Change #7

**Section 5.1 Study description, Taper Period**

The Taper Period (up to 6 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period.

## Has been changed to:

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period.

## Change #8

**Section 5.2 Schedule of study assessments, Table 5-1 footnote i and Table 5-2 footnote h**

A 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) will be performed prior to any blood draws and vital signs and, if possible, after the subject has been in a

supine position for approximately 5 minutes preceding the ECG recording. All subjects will be required to have a 12 lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day or when a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state $C_{max}$).

## Has been changed to:

A 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) will be performed prior to any blood draws and vital signs and, if possible, after the subject has been in a supine position for approximately 5 minutes preceding the ECG recording. All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

## Change #9

**Section 5.2 Schedule of study assessments, Table 5-1 footnote j, Table 5-2 footnote i, and Table 5-3 footnote g**

## The following footnote has been added:

For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container).

## Change #10

**Section 5.2 Schedule of study assessments, Table 5-1 footnote k, Table 5-2 footnote j, and Table 5-3 footnote h**

For all subjects ≥6 years of age, the "Since Last Visit" version of the C-SSRS should be completed. If a subject turns 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.

## Has been changed to:

For all subjects ≥6 years of age, the "Since Last Visit" version of the C-SSRS should be completed. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits.

## Change #11

**Section 5.2 Schedule of study assessments, Table 5-1 footnote l and Table 5-2 footnote k**

The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

## Has been changed to:

The C-SSRS assessment should be completed if the Unscheduled Visit is due to a safety or efficacy reason.

## Change #12

**Section 5.2 Schedule of study assessments, Table 5-3 footnote a**

The Taper Period (up to 6 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets. The Taper Visit will be performed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

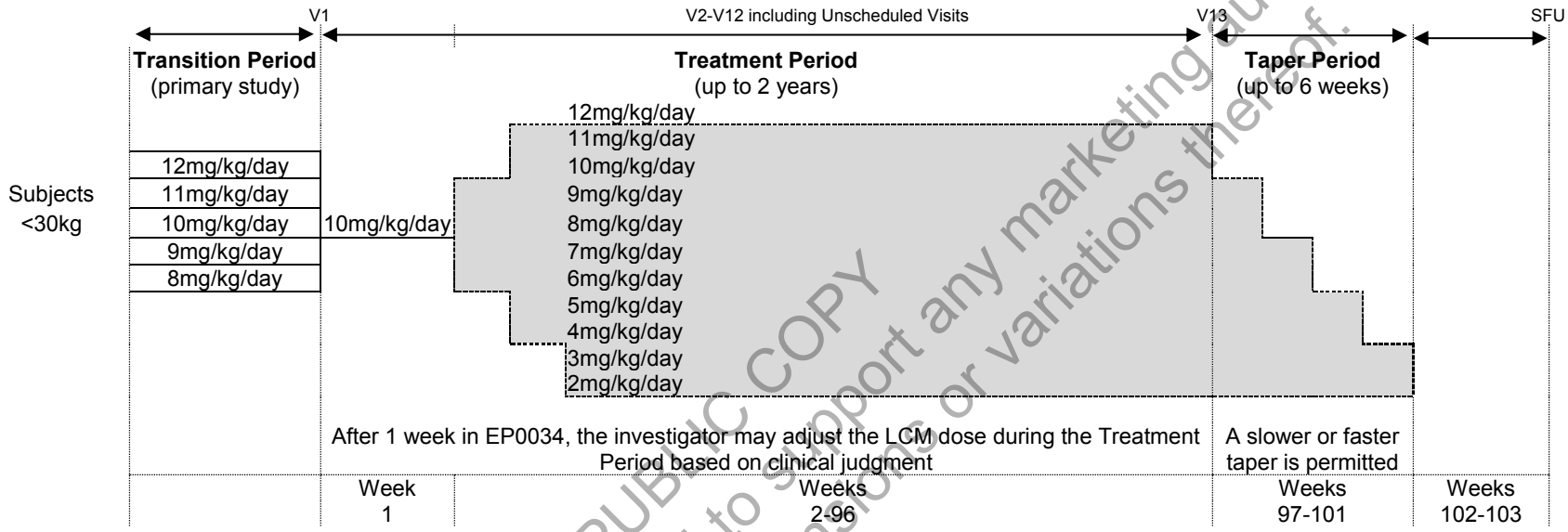
## Has been changed to:

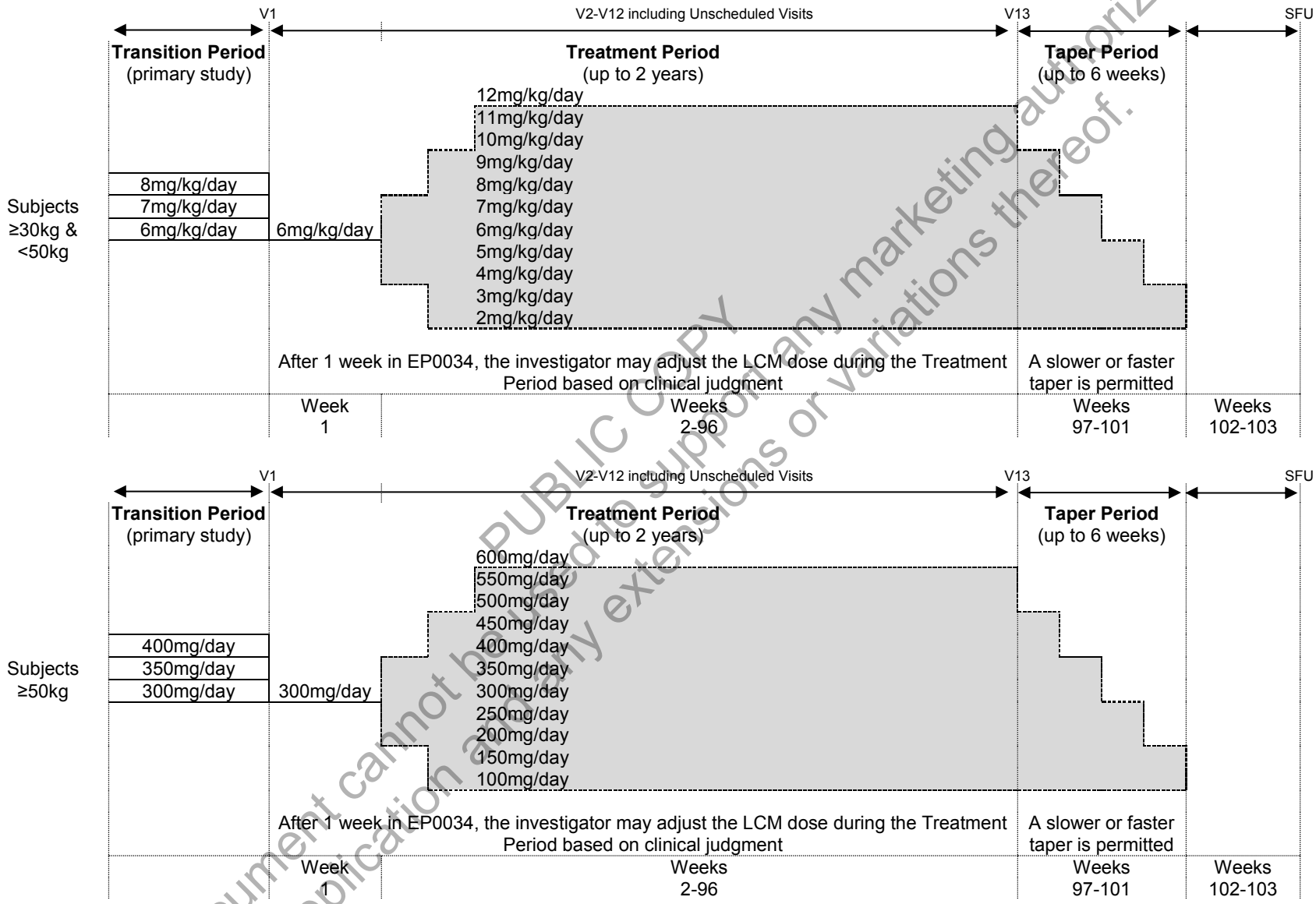
The Taper Period (up to 4 weeks, depending on dose level achieved, see Section 7.2.2 for details) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets. The Taper Visit will be performed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete

the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

## Change #13

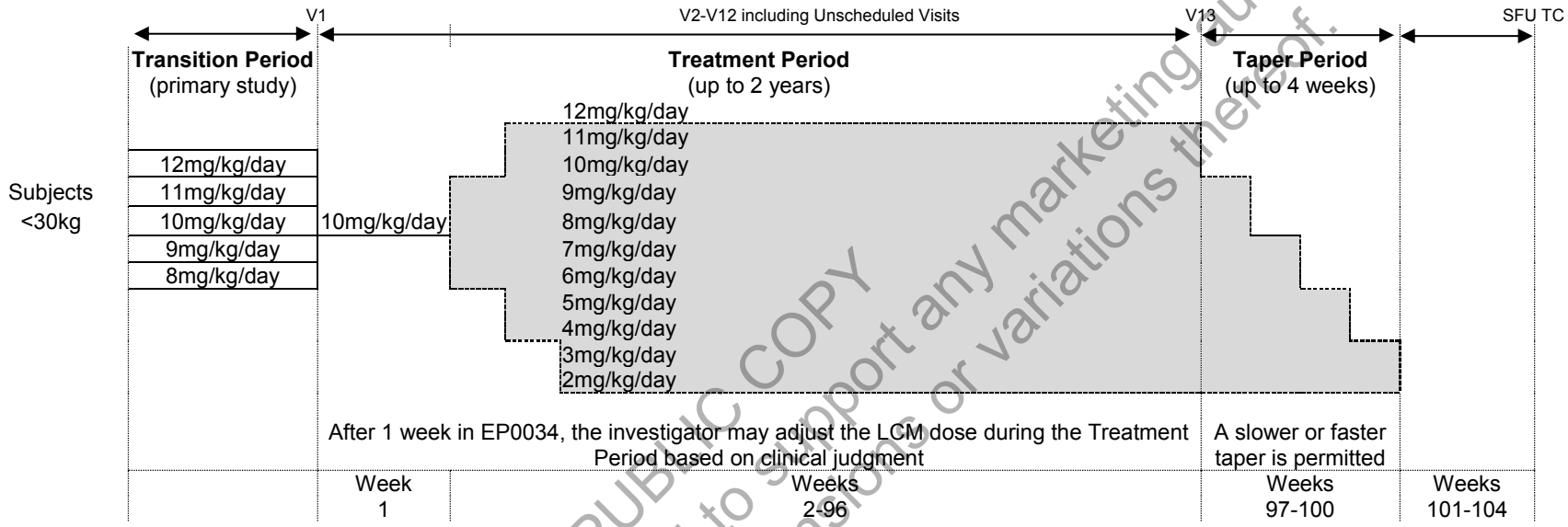
### Section 5.3 Schematic diagram, Figure 5-1

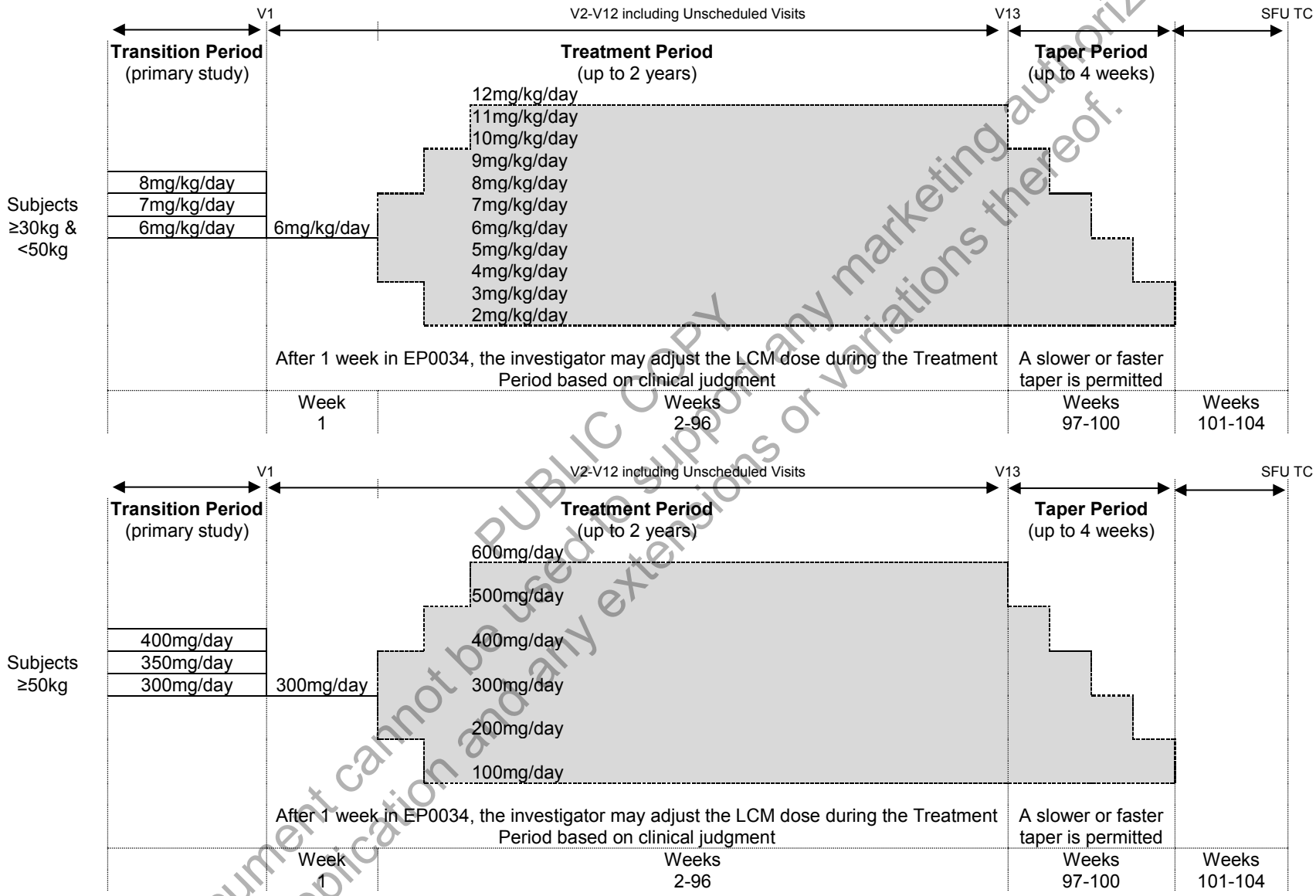





LCM=lacosamide; SFU=Safety Follow-Up; V=visit

## Has been changed to:






LCM=lacosamide; SFU=Safety Follow-Up; TC=telephone contact; V=visit

## Change #14

**Section 6.1 Inclusion criteria, Criterion #5 and #6**

## The following 2 criteria have been added:

4. Subject is male or female aged 1 month to ≤17 years.
5. Subject has a diagnosis of epilepsy with partial-onset seizures.

## Change #15

**Section 6.2 Exclusion criteria, Criterion #2**

2. Subject is experiencing an ongoing serious AE (SAE).

## Has been changed to:

2. Subject meets a mandatory withdrawal criterion (ie, MUST withdraw criterion) for SP0967 or SP0969, or is experiencing an ongoing serious AE (SAE).

## Change #16

**Section 6.2 Exclusion criteria, Criterion #4**

## The following criterion has been deleted:

4. Subjects with a major protocol deviation during the primary study (or a deviation related to enrollment criteria for primary study).

## Change #17

**Section 7.2 Treatment(s) to be administered, paragraph 1**

Lacosamide will be administered bid (at approximately 12-hour intervals, once in the morning and once in the evening) in equally divided doses. The oral solution formulation will be measured and administered via a dosing syringe.

## Has been changed to:

Lacosamide will be administered bid (at approximately 12-hour intervals, once in the morning and once in the evening) in divided doses. The oral solution formulation will be measured and administered via a dosing syringe.

## Change #18

**Section 7.2.2 Taper Period, Table 7-3**

**Table 7-3: Dose taper steps for subjects taking tablets**

| LCM dose achieved | LCM doses for the Taper Period | | | | |
|---|---|---|---|---|---|
| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 |
| >500 to 600mg/day | 500mg/day | 300mg/day | 200mg/day | 100mg/day | – |
| >400 to 500mg/day | 400mg/day | 300mg/day | 200mg/day | 100mg/day | – |
| >300 to 400mg/day | 300mg/day | 200mg/day | 100mg/day | 100mg/day | – |
| >200 to 300mg/day | 200mg/day | 100mg/day | 100mg/day | – | – |
| >150 to 200mg/day | 100mg/day | 100mg/day | – | – | – |

## Has been changed to:

**Table 7-3: Dose taper steps for subjects taking tablets**

| LCM dose achieved | LCM doses for the Taper Period | | | | |
|---|---|---|---|---|---|
| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 |
| >500 to 600mg/day | 500mg/day | 300mg/day | 200mg/day | 100mg/day | – |
| >400 to 500mg/day | 400mg/day | 300mg/day | 200mg/day | 100mg/day | – |
| >300 to 400mg/day | 300mg/day | 200mg/day | 100mg/day | 100mg/day | – |
| >200 to 300mg/day | 200mg/day | 100mg/day | 100mg/day | – | – |
| ≥150 to 200mg/day | 100mg/day | 100mg/day | – | – | – |

## Change #19

**Section 7.8.1 Permitted and prohibited concomitant treatments (medications and therapies), after paragraph 4**

## The following paragraph has been added:

Implantation of and changes in vagal nerve stimulation settings are permitted.

## Change #20

**Section 8 STUDY PROCEDURES BY VISIT, paragraph 4**

Subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM maximum plasma concentration ($C_{max}$) 1 week after a LCM dose increase to ≥8mg/kg/day or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit (Section 8.5), if necessary. Subjects having

a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state $C_{max}$).

## Has been changed to:

Subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM maximum plasma concentration ($C_{max}$) 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit (Section 8.5), if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

## Change #21

**Section 8.1.1 Visit 1 (Week 0), paragraph 1, sentence 1**

For subjects completing the Transition Period of the primary studies and choosing to enroll in EP0034, the final Transition Visit (Transition Visit 3 in SP0969 and Final Transition Visit in SP0967) will serve as Visit 1 of EP0034.

## Has been changed to:

For subjects completing the Transition Period of the primary studies and choosing to enroll in EP0034, the final Transition Visit (Transition Visit 4 in SP0969 and Final Transition Visit in SP0967) will serve as Visit 1 of EP0034.

## Change #22

**Section 8.1.1 Visit 1 (Week 0), Section 8.1.5 Visit 5 (Week 20), Section 8.1.8 Visit 9 (Week 52), Section 8.1.10 Visit 11 (Week 72), Section 8.1.12 Visit 13/Termination Visit (Week 96), Section 8.1.13 Early Termination Visit, Section 8.2 Taper Period, and Section 8.3 Safety Follow-Up Visit**

- Urine sample for urinalysis (for subjects aged ≥5 years)

## Has been changed to:

- Urine sample for urinalysis (for subjects aged ≥5 years) (urine assessments will be based on the subject's ability to void and staff's ability to collect urine [in an appropriate container])

## Change #23

**Section 8.1.1 Visit 1 (Week 0), Section 8.1.3 Visit 2 (Week 4), Section 8.1.4 Visit 3 (Week 8) and Visit 4 (Week 12), Section 8.1.5 Visit 5 (Week 20), Section 8.1.6 Visit 6 (Week 28), Section 8.1.7 Visit 7 (Week 36) and Visit 8 (Week 44), Section 8.1.8 Visit 9 (Week 52), Section 8.1.9 Visit 10 (Week 60), Section 8.1.10 Visit 11 (Week 72), Section 8.1.11 Visit 12 (Week 84), Section 8.1.12 Visit 13/Termination Visit (Week 96), Section 8.1.13 Early Termination Visit, Section 8.2 Taper Period, and Section 8.3 Safety Follow-Up Visit**

- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject turns 6 years of age during the study, the "Already Enrolled" version should be used once, followed by the "Since Last Visit" version at subsequent visits)

## Has been changed to:

- C-SSRS (for all subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)

## Change #24

**Section 8.1.1 Visit 1 (Week 0), last paragraph**

A telephone contact will be made approximately 2 weeks after Visit 1 (end of Week 2, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 4 weeks. If the investigator wants to adjust the LCM dosage after 1 week in EP0034, the subject should return to the clinic for an Unscheduled Visit, at the discretion of the investigator.

## Has been changed to:

A telephone contact will be made approximately 2 weeks after Visit 1 (end of Week 2, Section 8.1.2). Subjects will be scheduled to return to the clinic for the next visit in approximately 4 weeks after Visit 1. If the investigator wants to adjust the LCM dosage after 1 week in EP0034, the subject should return to the clinic for an Unscheduled Visit, at the discretion of the investigator.

## Change #25

**Section 8.2 Taper Period, paragraph 1**

The Taper Period (up to 6 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from the study prematurely, if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period.

## Has been changed to:

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from the study prematurely, if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period.

## Change #26

**Section 8.5 Unscheduled Visit, paragraph 2**

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state $C_{max}$).

## Has been changed to:

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject

reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

## Change #27

**Section 8.5 Unscheduled Visit**

- C-SSRS (only if the Unscheduled Visit is due to an AE; for subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject turns 6 years of age during the study, the "Already Enrolled" version should be used once, followed by the "Since Last Visit" version at subsequent visits)

## Has been changed to:

- C-SSRS (only if the Unscheduled Visit is due to safety or efficacy reasons; for subjects ≥6 years of age, the "Since Last Visit" version should be completed; if a subject becomes 6 years of age during the study, the "Already Enrolled" version should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits)

## Change #28

**Section 9.4 Health care resource use**

For health care resource use, the following will be evaluated: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays.

## Has been changed to:

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

## Change #29

**Section 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.

## Has been changed to:

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

## Change #30

**Section 10.6 Laboratory measurements, paragraph 1**

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedules of study procedures (Section 5.2). Urine assessments will be performed for subjects aged ≥5 years. A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.8). The procedures for handling and shipping these specimens will be provided to the sites.

## Has been changed to:

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedules of study procedures (Section 5.2). Urine assessments will be performed for subjects aged ≥5 years. For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.8). The procedures for handling and shipping these specimens will be provided to the sites.

## Change #31

**Section 10.6 Laboratory measurements, Table 10-2**

## The following footnote was added:

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

## Change #32

**Section 10.9.4 12-lead ECG, paragraph 2**

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day or when a new concomitant AED is introduced. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM (ie, at LCM steady state $C_{max}$).

## Has been changed to:

All subjects will be required to have a 12-lead ECG (2 interpretable recordings approximately 20 to 30 minutes apart) conducted at LCM $C_{max}$ 1 week after a LCM dose increase to ≥8mg/kg/day, after subsequent dose increases (ie, the first time a subject reaches a LCM dose of 8mg/kg/day, 9mg/kg/day, 10mg/kg/day, etc) or for LCM doses of ≥400mg/day (ie, the first time a subject reaches a LCM dose of 400mg/day, 500mg/day, etc), or when a new concomitant AED is introduced during the study. This ECG can be conducted at an Unscheduled Visit, if necessary. Subjects having a LCM dose increase to ≥8mg/kg/day or to ≥400mg/day, or when a new concomitant AED is added will be required to arrive at the clinic prior to taking their morning dose of LCM. Subjects will be administered their morning LCM dose by study personnel at the clinic so that an ECG (2 interpretable recordings approximately 20 to 30 minutes apart prior to any blood sample collection or vital signs assessment) can be performed 30 minutes to 1 hour after the administration of LCM.

## Change #33

**Section 10.9.6 Assessment of suicidality, paragraph 2**

The C-SSRS will be completed according to the tabular schedules of study procedures (Section 5.2). This scale will be completed for subjects ≥6 years of age. The "Since Last Visit" version of the C-SSRS should be used. If a subject turns 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.

## Has been changed to:

The C-SSRS will be completed according to the tabular schedules of study procedures (Section 5.2). This scale will be completed for subjects ≥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 at the first visit at which the subject is 6 years of age and the "Since Last Visit" version at subsequent visits.

## Change #34

**Section 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.

## Has been changed to:

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the Clinical Project Manager of the sponsor within 24 hours and follow any local regulatory requirements.

## Change #35

**Section 12.4.1 Efficacy analyses**

Efficacy variables will be summarized descriptively. Efficacy evaluation for seizures will be based on subject diaries, which include type, date, and number of seizures.

Descriptive statistics will also be presented for the Clinical and Caregiver's Global Impression of Change, PedsQL scores, and the number of health care resources used (concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays).

## Has been changed to:

Efficacy variables will be summarized descriptively. Efficacy evaluation for seizures will be based on subject diaries, which include type, date, and number of seizures.

Descriptive statistics will also be presented for the Clinical and Caregiver's Global Impression of Change, PedsQL scores, and the number of health care resources used (concomitant medications,

medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol).

## Change #36

**Section 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.

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

## Has been changed to:

No imputation of missing values for analysis parameters is planned unless otherwise noted. Imputations for missing or partial values for dates for AEs and concomitant medications will be applied to determine if an event is to be considered treatment emergent or concomitant. Across safety and efficacy analyses, only reported data will be used in each analysis time interval.

## 16.2 Protocol Amendment 2

The primary purposes of this substantial amendment are to allow administration of the Pediatric Quality of Life Inventory (PedsQL) to subjects under 2 years of age and to implement language regarding potential drug-induced liver injury (PDILI) events, based on new standard language which is being applied across all protocols at UCB. Addition of this language is to align with FDA guidance regarding monitoring of PDILI events and does not reflect a change in the liver safety signal for LCM.

### Modifications and changes

### Global changes

The following changes were made throughout the protocol:

- The PedsQL measurement model text was updated so it consists of developmentally appropriate forms for pediatric subjects ≥1 month to ≤12 months, ≥13 months to <24 months.
- To update the protocol information pertaining to PDILI monitoring in the exclusion criteria, withdrawal criteria, adverse events of special interest, and assessment of safety.
- Minor editorial changes have been made throughout the protocol.

### Specific changes

### Change #1

### SERIOUS ADVERSE EVENT REPORTING

| Serious adverse event reporting (24h) | |
|---|---|
| **Fax** | **Europe and Rest of the World:** +32 2 386 24 21<br>**USA:** +1 800 880 6949<br>Canada: +1 877 582 8842 |
| **Email** | **Global:** DS_ICT@ucb.com |

## Has been changed to:

## SERIOUS ADVERSE EVENT REPORTING

| Serious adverse event reporting (24h) | |
|---|---|
| **Fax** | **Europe and Rest of the World:** +32 2 386 24 21<br>**USA and Canada:** +1 800 880 6949 or +1 866 890 3175 |
| **Email** | **Global:** DS_ICT@ucb.com |

## Change #2

**Section 2 INTRODUCTION, paragraphs 1, 3 and 5**

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).

Among the newer AEDs, only 5 (gabapentin, lamotrigine, oxcarbazepine, topiramate, and levetiracetam) have successfully demonstrated efficacy as adjunctive therapy in children with difficult to treat partial-onset seizures (Glauser et al, 2006; Glauser et al, 2000; Appleton et al, 1999; Duchowny et al, 1999; Elterman et al, 1999). Despite the availability of new AEDs, more than 25% of pediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007).

Lacosamide has been approved as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the United States (tablets, oral solution, and solution for intravenous [iv] infusion) and as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (tablets, oral solution, and solution for iv infusion).

## Has been changed to:

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy worldwide (Ngugi et al, 2011).

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

Lacosamide has been approved as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older in the United States (tablets, oral solution, and solution for intravenous [iv] infusion) and as monotherapy or adjunctive therapy in the

treatment of partial onset seizures with or without secondary generalization in patients 16 years of age and older in the European Union (tablets, oral solution, and solution for iv infusion).

## Change #3

**Section 4.4 Other efficacy variables, 10th bullet**

The variable for PedsQL has been amended to include subjects ≤2 years of age.

- Change from Baseline in PedsQL for subjects ≥2 years of age

## Has been changed to:

- Change from Baseline in PedsQL

## Change #4

**Table 5.1**

**Superscript 'g' has been removed for the Achenbach CBCL and BRIEF/BRIEF-P scales**

## Table 5-1: Schedule of study assessments: Treatment Period up to Week 28

| Assessments | Treatment Period[a] | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | TC1 | V2 | TC2 | V3 | TC3 | V4 | TC4 | V5 | TC5 | V6 | | |
| | W0 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W28 | | |
| Achenbach CBCL[n] | X[g] | | | | | | | | X | | | X | |
| BRIEF/BRIEF-P[p] | X[g] | | | | | | | | X | | | X | |

AE=adverse event; AED=antiepileptic drug; Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition; BRIEF-P/BRIEF=Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; $C_{max}$=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; TC=telephone contact; Unsch=Unscheduled; V=Visit; VNS=vagus nerve stimulation; W=week

[g] Assessments may have already been completed during the final Maintenance Visit of the primary study (SP0969 or SP0967) and should not be repeated at Visit 1 of EP0034.

## Has been changed to

## Table 5-1: Schedule of study assessments: Treatment Period up to Week 28

| Assessments | Treatment Period[a] | | | | | | | | | | | ETV[b] | Unsch Visit[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | TC1 | V2 | TC2 | V3 | TC3 | V4 | TC4 | V5 | TC5 | V6 | | |
| | W0 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W28 | | |
| Achenbach CBCL[n] | X | | | | | | | | X | | | X | |
| BRIEF/BRIEF-P[p] | X | | | | | | | | X | | | X | |

AE=adverse event; AED=antiepileptic drug; Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition; BRIEF-P/BRIEF=Behavior Rating Inventory of Executive Function-Preschool Version/Behavior Rating Inventory of Executive Function; CBCL=Child Behavior Checklist; $C_{max}$=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ETV=Early Termination Visit; GIC=Global Impression of Change; IXRS=interactive voice/web response system; LCM=lacosamide; PedsQL=Pediatric Quality of Life Inventory; TC=telephone contact; Unsch=Unscheduled; V=Visit; VNS=vagus nerve stimulation; W=week

[g] Assessments may have already been completed during the final Maintenance Visit of the primary study (SP0969 or SP0967) and should not be repeated at Visit 1 of EP0034.

## Change #5

**Section 6.2 Exclusion criteria**

## The following new bullet has been added:

6. Subject has >2x the upper limit of normal (ULN) of any of the following: ALT, AST, 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 enrolled subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

## Change #6

**Section 6.3 Withdrawal criteria**

## The following "must" criterion has been removed:

6. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x the upper limit of normal (ULN) to <5x ULN and total bilirubin ≥2x ULN or transaminases (AST, ALT, or both) ≥5x ULN, the study medication must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

## And the following "may" criterion has been removed:

4. Transaminases (AST, ALT, or both) ≥3x ULN to <5x ULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3x ULN to <5x ULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3x ULN or stable condition). The investigator is to decide whether or not to stop the study medication.

## Change #7

## The following new section has been added:

**Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria**

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if 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:

- Subjects with either of the following:

- ALT or AST ≥5xULN
- ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

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

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

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

Evaluation of PDILI must be initiated as described in Section 10.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

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



## Change #8

**Section 7.8.1, Permitted and prohibited concomitant treatments (medications and therapies), paragraphs 1 to 3**

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

The use of neuroleptics, monoamine oxidase inhibitors, barbiturates (except for treatment of epilepsy), and long-term narcotic analgesics is prohibited throughout the study. The use of short term (2 to 3 weeks) narcotic analgesics may be allowed for management of acute pain (eg, fractures or during the perioperative period for subjects requiring surgery).

The use of amphetamines and sedative antihistamines is allowed during the study. Also, low doses of anxiolytics or hypnotics (eg, 5mg/day of diazepam) are allowed for nonepilepsy indications.

## Have been changed to:

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

The following concomitant medications are prohibited during the study:

- Clozapine
- Monoamine oxidase-A inhibitors
- Barbiturates (except as AEDs)
- Cannabidiols (not approved or indicated for epilepsy by local health authority)
  - Long-term use of narcotic analgesics (the use of short-term [2 to 3 weeks] narcotic analgesics may be allowed for management of acute pain (eg, fractures or during the perioperative period for subjects requiring surgery).

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

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

## Change #9

**Sections 8.1.1, 8.1.5, 8.1.8, 8.1.10, 8.1.12, and 8.1.13, Treatment Period Visits**

*The PedsQL bullet point has been amended to include patients ≤2years*

- PedsQL assessment ([M]) (for subjects ≥2 years of age; form consistent with age at the visit; however, the form used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 9.3)

## Has been changed to:

- PedsQL assessment ([M]) (form consistent with age at the visit; however, the form used in the primary study must be used for at least 1 year after the Baseline assessment of the primary study, as described in Section 9.3)

## Change #10

**Section 9.3 PedsQL, 2nd paragraph**

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

## Has been changed to:

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

## Change #11

**Section 10.2.1 Definition of serious adverse event, 5th bullet**

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

## Has been changed to:

- 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 10.3], 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.)

## Change #12

**Section 10.2.3 Follow up of serious adverse events, paragraph 2**

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

## Has been changed to:

Information on SAEs obtained after clinical database lock will be captured through the Drug Safety database without limitation of time. 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 10.6.1.

## Change #13

**Section 10.3 Adverse events of special interest**

## The following bullet 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 #14

**Section 10.6.1 Liver function tests**

10.6.1 Liver function tests

Refer to Section 6.3 for LFT withdrawal criteria.

Transaminases (AST, ALT, or both) ≥3×ULN but <5×ULN, in the presence of total bilirubin ≥2×ULN, or transaminases (AST, ALT, or both) ≥5×ULN will result in immediate discontinuation of study medication and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

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

Referral to a specialist (ie, hepatologist or gastroenterologist) is at the discretion of the investigator. This is recommended especially if the transaminase abnormalities >3xULN persist after discontinuation of the study medication.

## Has been changed to:

Section 10.6.1 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 10.6.1.2, 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 Section10.3), and, if applicable, also reported as an SAE (see Section 10.2).

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 10.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.6.1.4).

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

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

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

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Table 10–3 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 10.6.1.3); recommended to occur at the site with HCP. | Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d] |
| ≥5xULN | NA | NA | | | | |
| ≥3xULN | NA | Yes | | Immediate, 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 10.6.1.2). | Not required unless otherwise medically indicated (at discretion of investigator). | |

## 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** |
| ≥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 10.6.1.3). | Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.d |

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

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

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

[c] Details provided in Section 10.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

#### 10.6.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 10.6.1.3) and SAE report (if applicable).

#### 10.6.1.2 Immediate action: determination of IMP discontinuation

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

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

#### 10.6.1.3 Testing: identification/exclusion of alternative etiology

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

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

The following measurements are to be assessed:

**Table 10-4: PDILI laboratory measurements**

| | |
|---|---|
| **Virology-related** | Hepatitis A IgM antibody |
| | HBsAg |
| | Hepatitis E IgM antibody |
| | HBcAb-IgM |
| | Hepatitis C RNA |
| | Cytomegalovirus IgM antibody |
| | Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing) |
| **Immunology** | Anti-nuclear antibody (qualitative and quantitative) |

### Table 10-4: PDILI laboratory measurements

| | |
|---|---|
| | 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 in women of childbearing potential |
| | PK sample |

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:<br>• History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease")<br>• Adverse reactions to drugs<br>• Allergies<br>• Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)<br>• Recent travel<br>• 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 |

**Table 10-5: PDILI information to be collected**

| New or updated information |
|---|
| 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

#### 10.6.1.4 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 #15

**Section 15 REFERENCES**

### The following reference has been removed:

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

### And the following references have been added:

Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence ofepilepsy: A systematic review and meta-analysis. Neurology. 2011; 77(10): 1005–12.

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

## 16.3 Protocol Amendment 3

### Rationale for the amendment

The primary purpose of this nonsubstantial amendment is to clarify when both the Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required. In addition, language specifying the use of local laboratories in exceptional circumstances and applicable study conduct modifications due to the COVID-19 pandemic have been added.

Furthermore, minor administrative changes have been made, including the update of the study team.

### Modifications and changes

### Global changes

- The name and contact information for the Sponsor Study Physician, Clinical Project Manager, and Clinical Trial Biostatistician were updated.
- Text updated to clarify the Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact.
- Text added to clarify study conduct due the COVID-19 pandemic.
- Study variables were reorganized to clarify categorization of primary, secondary, and other.
- Text added to clarify the use of local laboratories in exceptional circumstances.
- Assessments added for PDILI laboratory measurements.
- Minor editorial changes have been made throughout the protocol.

### Specific changes

### Change #1

**STUDY CONTACT INFORMATION**

### Sponsor Study Physician

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

## Clinical Project Manager

| | |
|---|---|
| Name: | [redacted] |
| Address: | UCB BIOSCIENCES GmbH<br>Alfred-Nobel-Str. 10<br>40789 Monheim<br>GERMANY |
| Phone: | [redacted] |
| Fax: | [redacted] |

## Clinical Trial Biostatistician

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

## Has been changed to:

## Sponsor Study Physician

| | |
|---|---|
| Name: | [redacted] |
| Address: | UCB BIOSCIENCES GmbH<br>Alfred-Nobel-Str. 10<br>40789 Monheim<br>GERMANY |
| Phone: | [redacted] |
| Email: | [redacted] |

## Clinical Project Manager

| | |
|---|---|
| Name: | [redacted] |
| Address: | UCB Biopharma SRL<br>208 Bath Road<br>Slough, Berkshire, SL1 3WE<br>UNITED KINGDOM |
| Phone: | [redacted] |

| | |
|---|---|
| Email: | [redacted] |

## Clinical Trial Biostatistician

| | |
|---|---|
| Name: | [redacted] |
| Address: | UCB BIOSCIENCES, Inc.<br>8010 Arco Corporate Drive<br>Raleigh, NC 27617<br>UNITED STATES |
| Phone: | [redacted] |
| Email: | [redacted] |

## Change #2

**Section 1 SUMMARY, paragraph 5:**

During the Treatment Period, study visits are scheduled at Weeks 0, 4, 8, 12, 20, 28, 36, 44, 52, 60, 72, 84, and 96. Telephone contacts are scheduled at Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56, 66, and 78. Subjects who withdraw from treatment during the study should taper off LCM if the following doses are achieved: LCM ≥3mg/kg/day (oral solution) for subjects receiving LCM oral solution, or LCM ≥150mg/day (tablet) for subjects taking tablets; lower doses will not require a taper. An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study. Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM. A Safety Follow-Up Telephone Contact will be made 30 days (-1/+3 days) after the final dose of LCM. 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 or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

## Has been changed to:

During the Treatment Period, study visits are scheduled at Weeks 0, 4, 8, 12, 20, 28, 36, 44, 52, 60, 72, 84, and 96. Telephone contacts are scheduled at Weeks 2, 6, 10, 16, 24, 32, 40, 48, 56, 66, and 78. Subjects who withdraw from treatment during the study should taper off LCM if the following doses are achieved: LCM ≥3mg/kg/day (oral solution) for subjects receiving LCM oral solution, or LCM ≥150mg/day (tablet) for subjects taking tablets; lower doses will not require a taper. An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study. Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM. A Safety Follow-Up Telephone Contact will be made 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152. 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 or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

## Change #3

**Section 4, STUDY VARIABLES, all subsections (4.1, 4.2, 4.3, and 4.4):**

**4.1 Safety variables**

The safety variables include the following:

- Adverse event reporting
- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyltransferase [GGT]; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms
- Physical (Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations
- Vital signs (blood pressure and pulse rate)
- Body weight and height

**4.2 Other safety variables**

The other safety variables include the following:

- Change from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1.5 to 5 years of age and the Achenbach CBCL/6-18 for children ≥6 years of age
- Change from Baseline in the BRIEF-P score for subjects ≥2 and <5 years of age
- Change from Baseline in the BRIEF score for subjects ≥5 years of age
- Change from Baseline in the Bayley-III scales in subjects <18 months of age at study entry (applicable only to subjects enrolled in English-speaking countries)

**4.3 Efficacy variables**

The efficacy variables planned for analysis will be based on seizure diary data from EP0034 and will include the following for all subjects:

- Percentage of seizure-free days during the study

**4.4 Other efficacy variables**

The following other efficacy variables will be computed for subjects from SP0969 and include the following:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034 and include the following:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in PedsQL
- Health care resource use: concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol

## Have been changed to:

**4.1 Safety variables**

**4.1.1 Primary safety variables**

The primary safety variables include the following:

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs leading to study discontinuation

**4.1.2 Other safety variables**

The other safety variables include the following:

- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyltransferase [GGT]; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms

- Physical (Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations
- Vital signs (blood pressure and pulse rate)
- Body weight and height
- Change from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1.5 to 5 years of age and the Achenbach CBCL/6-18 for children ≥6 years of age
- Change from Baseline in the BRIEF-P score for subjects ≥2 and <5 years of age
- Change from Baseline in the BRIEF score for subjects ≥5 years of age
- Change from Baseline in the Bayley-III scales in subjects <18 months of age at study entry (applicable only to subjects enrolled in English-speaking countries)

### 4.2 Efficacy variables

#### 4.2.1 Primary efficacy variables

No primary efficacy variables are defined for this study.

#### 4.2.2 Secondary efficacy variables

The efficacy variables planned for analysis will be based on seizure diary data from EP0034 and will include the following for all subjects:

- Percentage of seizure-free days during the study (presented for the overall Treatment Period only)

#### 4.2.3 Other efficacy variables

The following other efficacy variables will be computed for subjects from SP0969 and include the following:

- Percentage of 50% responders (subjects with at least a 50% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 50% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Percentage of 75% responders (subjects with at least a 75% reduction in total partial-onset seizure frequency per 28 days compared to Baseline), with Baseline defined as the period before receiving study medication in the previous pediatric study
- Percentage of 75% responders per seizure type (simple partial, complex partial, or secondarily generalized) compared with Baseline
- Absolute and percent reduction in total partial-onset seizures and per partial-onset seizure type (simple partial, complex partial, or secondarily generalized) compared to Baseline
- Partial-onset seizure frequency per 28 days

The following other efficacy variables will be computed for all subjects in EP0034 and include the following:

- Achievement of seizure-free status (no seizure) during the study for total partial-onset seizure and per seizure type (simple partial, complex partial, or secondarily generalized)
- Clinical Global Impression of Change
- Caregiver's Global Impression of Change
- Change from Baseline in PedsQL
- Health care resource use: concomitant medications, medical procedures, and health care provider consultations including hospitalizations not foreseen by the protocol

## Change #4

**Section 5.1, Study description, paragraphs 6, 10, and 11:**

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 legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit is not required for subjects who complete the study and who do not undergo taper of LCM.

…

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period.

…

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM. A Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM.

## Have been changed to:

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 legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The

Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

…

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

…

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM. A Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

## Change #5

**Section 5.2, Schedule of study assessments, Table 5-2, footnote s:**

[s] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis.

## Has been changed to:

[s] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis. For subjects who enter the Safety Follow-Up Period, the subject diary will be returned at the Safety Follow-Up Visit. Subjects who do not enter the Safety Follow-Up Period will return the diary at V13/TermV.

## Change #6

**Section 5.2, Schedule of study assessments, Table 5-3, footnotes b, c, and j:**

[b] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM (including that from LCM taper). The Safety Follow-Up Visit is not required for subjects who complete the study and do not undergo taper of LCM.
[c] The Safety Follow-Up Telephone Call occurs 30 days (-1/+3 days) after the final dose of LCM.
[j] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis. The subject diary will be returned at the Safety Follow-Up Visit.

## Have been changed to:

[b] Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM (including that from LCM taper). The Safety Follow-Up Visit is not required for subjects who complete the study and do not undergo taper of LCM. The Safety Follow-Up Visit is not required for subjects who participate in EP0151 or EP0152.

[c] The Safety Follow-Up Telephone Call occurs 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Telephone Call is not required for subjects who participate in EP0151 or EP0152.

[j] Subjects and/or legal representative(s) will be reminded to complete the diary on a daily basis. For subjects who enter the Safety Follow-Up Period, the subject diary will be returned at the Safety Follow-Up Visit. Subjects who do not enter the Safety Follow-Up Period will return the diary at V13/TermV.

## Change #7

**Section 5.3, Schematic diagram, Figure 5-1, a footnote was added:**

Note: Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

## Change #8

**Section 7.2.2, Taper Period, paragraph 2:**

Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

## Has been changed to:

Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects who participate in EP0151 or EP0152.

## Change #9

**Section 7.2.3, Alternative study treatment supply due to coronavirus disease 2019 pandemic, was added:**

When a subject can no longer return to the study site due to general circumstances but will continue in the study, the following methods may be used to provide study treatment:

- Site to subject: In instances where site staff can ship study treatment dispensed from the site pharmacy supply directly to the subject.
- Depot to subject: In instances where it is not possible for the site staff to access study treatment in the site pharmacy and/or ship study treatment dispensed from the site pharmacy supply directly to the subject.

## Change #10

**Section 8.1.12, Visit 13/Termination Visit (Week 96), paragraph 3:**

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 legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit is not required for subjects who complete the study and who do not undergo taper of LCM.

## Has been changed to:

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 legal representative(s). These subjects should complete Visit 13/Termination Visit and then complete the Safety Follow-Up Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Visit is not required for subjects who complete the study and who do not undergo taper of LCM. The Safety Follow-Up Visit and the Safety Follow-Up Telephone Contact are not required for subjects who participate in EP0151 or EP0152.

## Change #11

**Section 8.2, Taper Period, paragraph 1:**

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from the study prematurely, if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period.

## Has been changed to:

The Taper Period (up to 4 weeks, depending on dose level achieved) will be required for subjects who complete the study or withdraw from the study prematurely, if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution, or LCM ≥150mg/day for subjects taking tablets; lower doses will not require a taper (refer to Section 7.2.2). A Taper Visit must be completed at the end of the Taper Period. Taper of LCM may not be required for some subjects who complete the study or withdraw from the study prematurely, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s) or for subjects entering EP0151 or EP0152.

## Change #12

**Section 8.3, Safety Follow-Up Visit, paragraph 1 and bullet 15:**

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM (including that from LCM taper). The Safety Follow-Up Visit is not required for subjects who complete the study or withdraw prematurely from the study but do not undergo taper of LCM.

…

- Subject diary return

## Has been changed to:

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete the Safety Follow-Up Visit 2 weeks (±2 days) after the final dose of LCM (including that from LCM taper). The Safety Follow-Up Visit is not required for subjects who complete the study or withdraw prematurely from the study but do not undergo taper of LCM. The Safety Follow-Up Visit is not required for subjects who participate in EP0151 or EP0152.

…

- Subject diary return (for subjects who enter the Safety Follow-Up Period, the subject diary will be returned at the Safety Follow-Up Visit and subjects who do not enter the Safety Follow-Up Period will return the diary at Visit 13/Termination Visit)

## Change #13

**Section 8.4, Safety Follow-Up Telephone Contact, paragraph 1:**

Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM.

## Has been changed to:

Safety Follow-Up Telephone Contact is required for all subjects (those who complete the study as planned or have withdrawn prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM. The Safety Follow-Up Telephone Contact is not required for subjects who participate in EP0151 or EP0152.

## Change #14

**Section 8.6, Study conduct due to coronavirus disease 2019 pandemic, was added:**

The protocol-mandated visit schedule should be followed to the extent possible, considering the individual benefit-risk assessment by the investigator. If necessary, remote visits may be conducted, and the subjects or caregivers will be contacted by telephone or videoconference. Remote follow up, at minimum with a telephone call after 3 months, must be done (preferably more frequently and as needed to follow up on subject safety assessments).

Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the coronavirus disease 2019 (COVID-19) pandemic (eg, any measures that may limit access to the site or may require additional actions by the subject prior to entry to the site).

If a subject needs to be discontinued and cannot come into the clinic, then appropriate tapering instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible.

In situations where a subject is unable to return to the study site, investigators will assess and document the subject's safety via telephone contact. Based on information gathered from the telephone contact, investigators will confirm whether the subject could continue the current study treatment based upon the outcome of the safety assessments. Subjects' agreement to implement this procedure should be obtained and documented prior to implementing any changes. Changes in the study treatment supply in this situation are described in Section 7.2.3.

If a subject visits another facility for a medical issue (or has to switch sites for a COVID-19-related reason), the investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the clinical study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

Deviations to data collection including inability to perform some assessments, such as ECG, blood collection for safety laboratory assessments and PK, or alternative methods of assessment, such as phone calls, should be recorded in the source documentation and notated as "not done" in the eCRF.

In cases where subjects cannot return to the clinic, and it will not be possible to dispense a new seizure diary, subjects will be instructed to continue recording of seizures in a manner that is mutually agreed with the investigator (eg, hand-written notes, recording on a smart device). Any recording of seizures in a manner outside of the study seizure diary must be carefully documented in the source medical records (copies/print-screen printouts of these recordings will be brought to and retained at the site).

## Change #15

**Section 10.1.1, Definition of adverse event, paragraph 2:**

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

## Has been changed to:

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

all AEs that recurred or worsened after the initial visit. For results disclosure, only TEAEs are applicable.

## Change #16

**Section 10.1.9, Occurrence of COVID-19, was added:**

Occurrence of COVID-19 in subjects should be reported as either "suspected COVID-19" or "confirmed COVID-19" along with all available relevant data including diagnostic and laboratory data. For subjects where COVID-19 is still suspected despite a negative viral test, please report as "suspected COVID-19" and provide relevant data to support the diagnosis as well as the test results.

## Change #17

**Section 10.6, Laboratory measurements, paragraph 1:**

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedules of study procedures (Section 5.2). Urine assessments will be performed for subjects aged ≥5 years. For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.7). The procedures for handling and shipping these specimens will be provided to the sites.

## Has been changed to:

Blood and urine specimens for routine assay of hematology, clinical chemistry, endocrinology, and urinalysis testing will be collected according to the tabular schedules of study procedures (Section 5.2). Urine assessments will be performed for subjects aged ≥5 years. For subjects aged ≥5 years, urine assessments will be based on the subject's ability to void and staff's ability to collect urine (in an appropriate container). A central laboratory will perform the routine analysis of blood and urine specimens. Pregnancy testing will also be performed (see Section 10.7). The procedures for handling and shipping these specimens will be provided to the sites. In exceptional circumstances, local laboratory analysis may be performed. The medical monitor should be contacted beforehand to discuss these circumstances.

## Change #18

**Section 10.6.1.3, Testing: identification/exclusion of alternative etiology, Table 10-4:**

### Table 10-4 PDILI laboratory measurements

| | |
|---|---|
| **Virology-related** | Hepatitis A IgM antibody |
| | HBsAg |
| | Hepatitis E IgM antibody |

### Table 10-4 PDILI laboratory measurements

| | |
|---|---|
| | 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 in women of childbearing potential |
| | PK sample |

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) |

**Table 10-4: PDILI laboratory measurements**

| | |
|---|---|
| | Anti-smooth muscle antibody (qualitative and quantitative) |
| | Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative) |
| **Hematology** | Hematocrit |
| | Hemoglobin |
| | Platelet count |
| | RBC count |
| | WBC count |
| | Differential count |
| **Urinalysis** | Toxicology screen |
| **Chemistry** | Amylase |
| | Bilirubin (If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin) |
| | Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation |
| | AST |
| | ALT |
| | ALP |
| | GGT |
| | Albumin |
| **Additional** | Prothrombin time/INR[a] |
| | Serum pregnancy test in women of childbearing potential |
| | PK sample |

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

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



## Change #19

**Section 12.6, Handling of dropouts or missing data, paragraph 2 was added:**

Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.

# 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:** ep0034-protocol-amend-3

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**Title:** EP0034 Protocol Amendment 3 Multicentre, Open-label, Long-term Extension Study, Safety and Efficacy of LCM Adjunctive Therapy in Pediatrics with POS

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| Document Approvals | |
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