PROTOCOL EP0060 AMENDMENT 3

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN (≥1 MONTH TO <17 YEARS OF AGE) WITH EPILEPSY

PHASE 2/3

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Confidential Material

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Serious adverse event reporting (24h)	
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AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
bid	twice daily
BP	blood pressure
CDMS	clinical data management system
CHMP	Committee for Medicinal Products for Human Use
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
EMA/EMEA	European Medicines Agency
EMU	epilepsy monitoring unit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IIL	initiating intravenous lacosamide
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
iv	intravenous
LCM	lacosamide

LFT	liver function test
MAOI	monoamine oxidase inhibitor
OLL	open-label lacosamide
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic-Per Protocol Set
PS	Patient Safety
QTc	corrected QT interval
RxL	prescribed lacosamide (eg, VIMPAT)
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedure
SS	Safety Set
ULN	upper limit of normal
VNS	vagus nerve stimulation

1 SUMMARY

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous (iv) lacosamide (LCM; VIMPAT®) infusions in pediatric subjects ≥1 month to <17 years of age with epilepsy.

EP0060 will include approximately 100 subjects. The following subjects will be eligible for enrollment in EP0060:

- Open-label LCM (OLL) subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- Prescribed-LCM (RxL) subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- Initiating iv LCM (IIL) subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: Subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an epilepsy monitoring unit (EMU) or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: Subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: Subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: Subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation. Subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the

option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America, Europe, and Asia. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥1 month to <17 years with epilepsy. EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including approximately 44 subjects who are ≥1 month to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. Within Cohort 2, every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.

A Data Monitoring Committee (DMC) will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2).

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration: up to 10 doses or up to 5 days
    (2) Elective administration: up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, 12-lead electrocardiogram [ECG], laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral

LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days for clinical need administration or up to 2 consecutive doses [over approximately 24 hours]) for elective administration. For OLL and RxL subjects, the daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg bid (subjects weighing <50kg) or 50mg bid (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg) or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and detailed safety assessments will be performed.

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose of iv LCM if time permits to complete all assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue antiepileptic drug (AED) treatment at the discretion of the treating physician. For RxL subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and taper at the discretion of the treating physician.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, approximately 44 subjects ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
- OR Cohort 2 should be stopped.

This design will result in a total exposure of approximately 100 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. It is estimated that almost 70 million people suffer from epilepsy (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, classification systems for seizure types and syndromes, gaps in information about epilepsy, and general recommendations (Institute of Medicine, 2012). In the past 2 decades, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

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

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

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; 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). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Shorvon, 2009).

Intravenous formulations are particularly helpful as short-term replacement of oral formulations for patients unable to take oral products (eg, preoperative and postoperative patients, patients with acute gastrointestinal disorders). Such formulations allow patients to be maintained on the same AED on their stable dose when they are unable to take the drug orally. Intravenous formulations may also be helpful in the initiation of treatment in certain situations when the patient is unable to take oral medications.

In the US, oral tablets and oral solution (syrup) of LCM are indicated for the treatment of partial-onset seizures in patients 4 years of age and older. As the safety of LCM injection for iv use has not been established in pediatric patients, LCM injection for iv use at infusion durations of 15 to 60 minutes is indicated for the treatment of partial-onset seizures only in patients 17 years of age and older as an alternative when oral administration is temporarily not feasible.

Additionally, LCM has been approved in the EU (oral tablets, oral solution [syrup], and solution for iv infusion), as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 4 years of age and older. The iv formulation

at infusion durations of 15 to 60 minutes is approved as an alternative for patients when oral administration is temporarily not feasible.

Recently, a retrospective evaluation was conducted to examine the use of iv LCM in 47 infants and children from 4 months to <12 years of age (Arkilo et al, 2016). The median age across the 47 children was 6.5 years, and 18 children were <3 years of age. Intravenous LCM was administered as adjunctive treatment along with ≥2 other AED. Lacosamide dose levels ranged from 1 to 11mg/kg, and the infusion was given over 30 minutes. Fifteen of the children were administered iv LCM either as replacement treatment for oral maintenance dose (n=10) or to initiate maintenance dose (n=5). For the remaining children, iv LCM was used to treat acute exacerbation of seizure frequency (n=18), status epilepticus (n=11) or epilepsia partialis continua (n=3). Children were observed for at least 48 hours after infusion. The 11 children with status epilepticus were not able to respond to inquiries about adverse effects. Of the remaining 36 subjects, 5 experienced adverse effect of sedation which resolved in all 5 within 24 hours. No other observable adverse effects were noted. No cardiac events were noted during the infusions for the 80% of children who had ECG evaluation during the infusion. This study shows an initial positive benefit-risk profile for the use of iv LCM in infants and children from 4 months to <12 years of age.

The results of EP0060 will provide safety, tolerability, and PK data regarding the use of the iv LCM formulation either as replacement for oral LCM or for adjunctive LCM treatment initiation in pediatric subjects ≥1 month to <17 years with epilepsy.

3 STUDY OBJECTIVE(S)

The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥1 month to <17 years with epilepsy. An additional objective is to evaluate the PK of iv LCM in pediatric subjects with epilepsy.

4 STUDY VARIABLES

4.1 Primary safety variables

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

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

4.2 Other safety variables

Other safety variables include the following:

- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (blood pressure [BP] and pulse rate)
- Changes in physical examinations
- Changes in neurological examinations

4.3 Other pharmacokinetic variables

Other PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

5 STUDY DESIGN

5.1 Study description

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric subjects ≥1 month to <17 years of age with epilepsy. EP0060 will include approximately 100 subjects. The following subjects will be eligible for enrollment in EP0060:

- OLL subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- RxL subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- IIL subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation while subjects in the IIL group will initiate adjunctive treatment with iv

LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America, Europe, and Asia. Additional sites or regions may be added if deemed necessary.

EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including approximately 44 subjects who are ≥1 month to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. Within Cohort 2, every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.

A DMC will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2). Details regarding the DMC are provided in Section 12.7.2.

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration (see above in this Section): up to 10 doses or up to 5 days
    (2) Elective administration (see above in this Section): up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time

from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration. For OLL and RxL subjects, the daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg bid (subjects weighing <50kg) or 50mg bid (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg) or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for PK analysis, and safety assessments will be performed (AEs, physical and neurological exams, pulse rate, BP, 12-lead ECG, clinical hematology and chemistry, and Columbia-Suicide Severity Rating Scale [C-SSRS] when applicable).

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose of iv LCM if time permits to complete all assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:

– Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue AED treatment at the discretion of the treating physician. For RxL subjects who directly enrolled and will discontinue use of LCM, the subject should complete the EP0060 Final Visit and taper at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes,
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, approximately 44 subjects ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped.

This design will result in a total exposure of approximately 100 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

5.1.1 Study duration per subject

For clinical need administration, the planned maximum iv LCM exposure will be up to 10 doses (or up to 5 days). For elective administration, the planned maximum iv LCM exposure will be up to 2 consecutive doses (over approximately 24 hours).

For OLL subjects, the planned maximum total study duration assuming clinical need administration will be approximately 16 days (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, and a safety follow-up Telephone Contact 1 at 1 to 3 days after the Final Visit).

For RxL and IIL subjects who will continue LCM treatment in SP848, the planned maximum total study duration assuming clinical need administration will be approximately 23 days to allow arrangement for assessments to transition to SP848 (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, safety follow-up Telephone Contact 1 at 1 to 3 days after the Final Visit, and the Transition Visit at 1 to 7 days after the last dose). The Final Visit and the Transition Visit may occur on the same day or separate days, depending on availability and scheduling.

For RxL and IIL subjects who will not continue LCM treatment in SP848, the planned maximum total study duration (assumes clinical need administration) will be approximately 45 days to allow for further safety follow-up (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, safety follow-up Telephone Contact 1 at 1 to 2 days after the Final Visit, and safety follow-up Telephone Contact 2 at 30 days [±2 days] after the last dose).

For those subjects electively receiving iv LCM, the above maximum total study durations are reduced by 4 days.

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

5.1.2 Planned number of subjects and site(s)

Approximately 100 subjects will be enrolled at approximately 40 sites.

The following cohorts are planned:

- Cohort 1: at least 40 subjects from ≥8 to <17 years of age, with at least 20 subjects from ≥12 to <17 years of age and at least 20 subjects from ≥8 to <12 years of age
- Cohort 2: every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.

The remaining subjects may be enrolled in either of the 2 cohorts.

5.1.3 Anticipated regions and countries

The study will be conducted at selected sites from North America, Europe, and Asia. Additional sites or regions may be added as deemed necessary.

5.2 Schedule of study assessments

The schedule of study assessments is provided in Table 5–1, and timing of infusion, blood sampling, and measurement of vital signs and ECG on treatment days is provided in Table 5–2.

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**
Written informed consent	X								
Inclusion/exclusion criteria	X	X[i]							
Demographics	X								
Medical procedures	X	X	X	X	X	X	X		X
Procedure history[j]	X								
Medical history/update[j]	X	X							
Diagnosis of epilepsy[j]	X								
Seizure history[k]	X								
Childbearing potential[j]	X								
LCM dosing history[l]	X	X							
LCM dosing information since Treatment Period							X	X	X
Prior and concomitant medications[m]	X	X	X	X	X	X	X	X	X
Concomitant AEDs/VNS settings/ ketogenic diet	X	X	X	X	X	X	X[n]		X[n]
Urine pregnancy testing (as applicable)	X	X				X			
Withdrawal criteria	X	X	X	X	X	X			
AE reporting	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**
Physical examination (complete)	X					X			
Physical examination (brief)		X	X[o]	X[o]	X				
Neurological examination (complete)	X					X			
Neurological examination (brief)		X	X[o]	X[o]	X				
Clinical chemistry and hematology[p,q]	X	X[r]				X			
12-lead ECG	X	X	X[s]	X[s]		X			
Vital signs	X	X	X[t]	X[t]	X	X			
Body weight and height	X								
PK blood sampling			X[u]	X[v]					
Intravenous LCM infusion[w]			X	X					
C-SSRS[x]	X	X[y]	X[o]	X[o]	X[d]	X			
Additional items for RxL and IIL subjects continuing into SP848									
Dispense transitional supply of oral LCM solution[g]			X[z]						
Collect transitional supply of oral LCM solution								X	
Visit 1 SP848 assessments (documented in SP848)								X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IIL=initiating iv

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	V1a[a]	V1b[b]	V2	V3[c]		Final Visit[e]	TC1[f]	Transition Visit[g]	TC2[h]
Study Day	-7 to 1	-1 to 1	1	2 to 5		1 to 6	2 to 9	1 to 13	29 to 37

LCM; iv=intravenous; LCM=lacosamide; OLL=open-label LCM; PK=pharmacokinetics; RxL=prescribed commercial LCM; TC=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

[a] The Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion, if necessary. In this case, it is required that all Screening procedures are performed and the results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility.

[b] Visit 1b only applies when Screening and Baseline occur on separate days.

[c] If iv LCM treatment is continued after Day 1, assessments for Visit 3 (excluding PK blood sampling [see footnote v]) must be completed for each infusion of iv LCM treatment in EP0060, unless otherwise noted (see footnote o).

[d] If an Unscheduled Visit is needed, the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the Unscheduled Visit is due to an AE, the C-SSRS assessment should be completed and collection of a blood sample for LCM PK analysis is at the discretion of the investigator.

[e] A Final Visit must be completed for all subjects who complete or withdraw prematurely from EP0060. The Final Visit may occur on the same day as the last dose of iv LCM, time permitting. Otherwise, the Final Visit should occur on the following day. For subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen for OLL subjects or taper at the discretion of the treating physician for RxL subjects.

[f] The Telephone Contact 1 Visit assessment should be performed 1 to 3 days after the Final Visit. During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

[g] The Transition Visit will only be conducted for RxL and IIL subjects who will continue LCM treatment in SP848. This visit can occur at the same time as the Final Visit or on another day up to and including 7 days after the Final Visit and should occur at the same time as Visit 1 for SP848.

[h] The Telephone Contact 2 Visit will only be conducted for RxL and IIL subjects who will not continue LCM treatment in SP848.

[i] Verification that the subject continues to meet inclusion/exclusion criteria if Screening and Baseline occur on separate days.

[j] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for RxL and IIL subjects at Screening. For OLL subjects, a medical history update will be captured in the previous long-term open-label study and not in EP0060.

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

[l] For OLL and RxL subjects, LCM dosing history will include date, time, and dosage information during the last 3 days.

[m] Prior medications will only be collected for direct-enroll subjects.

[n] At Telephone Contact follow-up calls, only concomitant AED and ketogenic diet information will be gathered (ie, settings for VNS will not be gathered).

[o] During the Treatment Period, brief physical examination, brief neurological examination, and C-SSRS should be performed once per day and after an infusion.

[p] Screening laboratory assessments may be conducted up to and including the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion. For all subjects, local laboratory results obtained for routine diagnostic and medical care can be used whenever possible if

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**

collected no more than 24 hours prior to Screening/Baseline Visit in order to minimize blood loss associated with the study. Use of the central or local laboratory is at the discretion of the investigator for all visits except the Final Visit. The central laboratory must be used for laboratory samples collected at the Final Visit.

[q] Bicarbonate testing is optional for subjects weighing less than 8kg. Consider testing for bicarbonate in subjects weighing less than 8kg in cases of suspected metabolic disturbances such as metabolic acidosis.

[r] If Screening and Baseline Visits are not performed on the same day, repetition of laboratory assessments at Baseline is at the discretion of the investigator.

[s] A 12-lead ECG will be performed approximately 20 minutes prior to each infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of each iv administration. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest (sitting or supine) at least 3 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[t] Vital signs will be performed approximately 10 minutes prior to each infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of each iv administration. Noninvasive BP (systolic and diastolic) and pulse rate will be measured at study visits after at least 3 minutes at rest, when feasible.

[u] Plasma samples will be obtained from a different region of the body from the region in which the solution for infusion was administered for the first iv LCM infusion (Day 1): predose for OLL and RxL subjects (within 1 hour prior to iv LCM infusion) and postdose for all subjects (within 1 to 4 hours after end of iv LCM infusion). If the postdose PK sample is taken at a similar time for ECG and vital signs (ie, the 2 hour time point), the PK sample will be drawn after ECG and vital signs have been taken. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

[v] If the subject has more than 1 iv LCM infusion, it is optional to also collect plasma samples for the final iv LCM infusion (Day 2 to 5/Early Termination): predose for all subjects (within 1 hour prior to iv LCM infusion) and postdose for all subjects (within 1 to 4 hours after end of iv LCM infusion). If the postdose PK sample is taken at a similar time for ECG and vital signs (ie, the 2 hour time point), the PK sample will be drawn after ECG and vital signs have been taken. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

[w] During the Treatment Period subjects will receive at least 1 dose of iv LCM. If more than 1 infusion is needed, infusions will occur bid at approximately 12-hour intervals up to either 2 doses (elective administration) or 10 doses (clinical need administration).

[x] All subjects ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version used at subsequent visits. If the subject is <6 years of age, assessment for signs of depression will be conducted as described in Section 10.7.5 of the protocol.

[y] The C-SSRS assessment does not need to be completed twice if Screening/Baseline assessments are done on the same day. If Screening/Baseline and Visit 2 occur on the same day, 2 assessments should be completed with 1 predose and 1 after infusion.

[z] For RxL and IIL subjects who are eligible and wish to enroll in SP848, a short-term oral LCM solution will be dispensed to allow continuity of LCM treatment while visits and assessments are scheduled for starting SP848. Subjects (or their caregivers) will administer the oral LCM solution twice a day,

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**

starting approximately 12 hours after the final iv LCM infusion, according to the investigator's instructions until the subject returns for the Transition Visit.

Table 5–2: Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Approximate time points in relation to iv LCM infusion	Vital signs[a]	12-lead ECG[b]	PK blood sampling[c]
-59min to -3min			X[d]
-20min (±10 min)		X	
-10min (±5 min)	X		
T0 (start of infusion)			
+5min (±2 min)	X		
+10min (±2 min)	X		
+15min (±5 min)		X	
+20min (±5 min)	X		
+30min (±5 min)		X	
+45min (±5 min)	X		
+60min (±10 min)	X	X	
+1h to +4h[e]			X
+2h (±15 min)	X	X	

AE=adverse event; BP=blood pressure; ECG=electrocardiogram; h=hours; iv=intravenous; LCM=lacosamide; min=minutes; PK=pharmacokinetics; T=time

[a] Noninvasive BP (systolic and diastolic) and pulse rate will be measured after at least 3 minutes at rest, when feasible, at the indicated approximate time points before and after the start of each iv LCM infusion.

[b] A 12-lead ECG will be performed at the indicated approximate time points before and after the start of each iv LCM infusion. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest (sitting or supine) at least 3 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[c] If the postdose PK sample is taken at a similar time for ECG and vital signs (ie, the 2 hour time point), the PK sample will be drawn after ECG and vital signs have been taken. Plasma samples will be obtained a different region of the body from the region in which the solution for infusion was administered for the first iv LCM infusion (Day 1). If the subject has more than 1 iv LCM infusion, it is optional to also collect plasma samples for the final iv LCM infusion (Day 2 to 5/Early Termination), predose and postdose, at the time points indicated in the table. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE. Depending on the target duration defined for the cohort and subject tolerability, end of infusion can be at 15, 30, or 60 minutes, or whenever the infusion is stopped (if prematurely terminated).

[d] For the first LCM infusion, the predose PK sample is required for OLL and RxL subjects and not required for IIL subjects. For optional PK sample collection of a subsequent LCM infusion, the predose sample should be collected from all subjects.

[e] Time points are in reference to T0 (start of infusion) except the postdose PK sample, which should be obtained within 1 to 4 hours after the end of the iv LCM infusion.

5.3 Rationale for study design and selection of dose

EP0060 is an open-label, multicenter study to investigate the safety and tolerability of iv LCM in pediatric subjects with epilepsy aged ≥1 month to <17 years. The results of EP0060 will provide

safety and PK data regarding the use of the iv LCM formulation in pediatric subjects (≥1 month to <17 years of age). The EP0060 design is based on components of the study design for SP757, which evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies. In an effort to maximize the patient pool used in the evaluation of the safety of iv LCM in pediatric subjects, EP0060 has opened enrollment to include OLL and RxL subjects who are on a stable dose of oral LCM and elect to receive iv LCM as well as IIL subjects who are not currently taking LCM and initiate adjunctive LCM treatment using iv LCM. The expansion of the subject population occurred prior to the start of study enrollment. EP0060 also includes the option for RxL and IIL subjects to continue oral LCM treatment after completion of iv LCM, if determined clinically appropriate, in SP848. If required, a short-term supply of oral LCM solution will be provided for RxL and IIL subjects transitioning to start SP848 to ensure continuity of LCM treatment while allowing flexibility to schedule a clinical visit to initiate SP848. For RxL and IIL subjects who do not continue into SP848 (either by choice or not clinically appropriate), an additional telephone contact approximately 30 days after last dose of iv LCM IMP is added in order to collect final safety data.

The iv LCM formulation at infusion durations of 15 to 60 minutes is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥17 years of age with epilepsy when oral administration is temporarily not feasible, which can also include initiation of LCM treatment. Additionally in the EU, the iv formulation at infusion durations of 15 to 60 minutes is also approved in pediatric subjects down to 4 years of age at maximum weight-based doses depending on weight band and whether LCM is administered as monotherapy or adjunctive therapy. An infusion duration of at least 30 minutes for administration >200mg per infusion (ie, >400mg/day) is preferred.

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for OLL and RxL subjects, with a maximum dose of 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, this range of doses above also includes the pediatric starting dose of 2mg/kg/day (subjects <50kg) or 100mg/day (subjects ≥50kg), which is the same as those used in the Phase 3 pediatric LCM studies. The LCM dose at initiation of treatment should remain constant for at least 7 days prior to a LCM dose increase.

EP0060 will initially enroll at least 40 older pediatric subjects (Cohort 1) and will include at least 20 subjects ≥12 to <17 years of age and at least 20 subjects ≥8 to <12 years of age. Cohort 2 will enroll approximately 44 subjects (with every attempt to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age) and will follow sequentially based on DMC recommendation. After completion of the first 20 subjects (Cohort 1) and after completion of 20 subjects (Cohort 2) have received iv LCM over infusion durations of 30 to 60 minutes, the DMC will review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort (ie, 30 to 60 minutes for all remaining subjects or 15 to 30 minutes [only for subjects

who would directly benefit from an increased infusion rate, in the opinion of the investigator; otherwise 30 to 60 minutes]), if the study/cohort should be stopped, and if the next cohort can be initiated (Section 12.7.2).

This design will result in a total exposure of approximately 100 pediatric subjects to assess the safety and tolerability of iv LCM in subjects ≥1 month to <17 years of age over a range of infusion durations.

Taken together, the iv LCM dosing scheme and planned target infusion durations being evaluated in EP0060 (2 to 12mg/kg/day or 100 to 600mg/day; 15 to 60 minutes) allow for administration of a range of pediatric doses, and include infusion durations that are the same as those approved for adults and adolescents.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in EP0060, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject is male or female from ≥1 month to <17 years of age.
3. Subject has a diagnosis of epilepsy with partial-onset seizures or primary generalized tonic-clonic seizures.
4. Subject meets 1 of the following criteria:
   - OLL subject: Subject is currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study); OR,
   - RxL subject: Subject is currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy; OR,
   - IIL subject: Subject is not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.
5. Subject is an OLL or RxL subject and meets both of the following criteria:
   - Subject has been administered LCM for the treatment of epilepsy for at least 2 weeks prior to Screening; AND,
   - Subject has been administered (OLL) or prescribed (RxL) oral LCM at a dose of 2mg/kg/day to 12mg/kg/day (for subjects <50kg) or 100mg/day to 600mg/day (for subjects ≥50kg). Open-label study drug LCM (OLL) or prescribed oral LCM dose (RxL) must be stable for at least 3 days prior to first LCM infusion.

-OR-

Subject is an ILL subject and is on a stable dosage regimen of at least 1 AED. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of at least 2 weeks prior to Screening.

6. Subject is an acceptable candidate for venipuncture and iv infusion.
7. Subject is, in the opinion of the investigator, able to comply with all study requirements. Subject (or parent[s] or legal representative) is willing to comply with all study requirements.
8. Subject weighs ≥4kg.

6.2 Exclusion criteria

Subjects are not permitted to enroll in EP0060 if any of the following criteria are met:

1. Subject has previously received iv LCM in this study.
2. Subject has any medical, neurological, or psychiatric condition that, in the opinion of the investigator, could jeopardize the subject's health or compromise the subject's ability to participate in EP0060.
3. Subject has clinically significant hypotension or bradycardia in the opinion of the investigator.
4. Subject ≥6 years of age has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by positive responses ("Yes") to either Question 4 or Question 5 of the C-SSRS at Screening.
5. Subject is taking monoamine oxidase A inhibitors (MAOI-A).

For OLL subjects, enrollment in EP0060 is not permitted if any of the following additional criteria are met:

6. Subject has any ongoing AE in their long-term, open-label study that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate EP0060 or the subject meets any of the criteria for required withdrawal from the long-term open-label study.

For RxL and IIL subjects, enrollment in EP0060 is not permitted if any of the following additional criteria are met:

7. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
8. Subject has a known hypersensitivity to any component of the investigational medicinal product (IMP).
9. Subject is a female of childbearing potential and does not practice an acceptable method of contraception for the duration of participation in EP0060.
    a) Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone,

oxcarbazepine]) which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.

b) The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit.

10. Subject has creatinine clearance less than 30mL/min.
11. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a QT prolongation greater than 450ms).
12. Subject has hemodynamically significant heart disease (eg, heart failure).
13. Subject has an arrhythmic heart condition requiring medical therapy.
14. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
15. Subject has an acute or subacutely progressive central nervous system disease. Subject has epilepsy secondary to a progressing cerebral disease or any other progressive or neurodegenerative disease (malignant brain tumor or Rasmussen syndrome).
16. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.
17. Lacosamide is intended for treatment of generalized convulsive status epilepticus.
18. Subject has exclusively typical absence (Type IIA1) or atypical absence (Type IIA2) seizures (no other generalized seizure types are reported).
19. Subject has diagnosis of Dravet's syndrome.
20. Subject has >2 upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For 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 Case Report form (CRF).

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

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

20a. Subject is currently participating in another study of an IMP.

For IIL subjects, enrollment in EP0060 is not permitted if the following additional criterion is met:

21. Subject has been treated with LCM within the last 3 months prior to Screening.

6.3 Withdrawal criteria

Subjects are free to withdraw from EP0060 at any time, without prejudice to their continued care. The following criteria for subject withdrawal from EP0060 are outlined below. Additional discontinuation criteria for potential drug-induced liver injury are presented in Section 6.3.1.

Subjects **must** be withdrawn from EP0060 if any of the following events occur:

1. Subject experiences intolerable AEs and AEs associated with iv administration that, in the opinion of the investigator, preclude further participation in EP0060.
2. The subject requires more than 10 iv LCM doses.
3. The sponsor or a regulatory agency requests withdrawal of the subject.
4. Subject has corrected QT interval (QTc) ≥500ms that is confirmed by a cardiologist over read on any ECG.
5. Subject becomes pregnant during the study, as evidenced by a positive urine pregnancy test.
6. Subject develops a second- or third-degree atrioventricular (AV) block or another clinically relevant change in medical condition (or ECG) as determined by the investigator, or if the investigator feels it is in the interest of the subject to withdraw.
7. 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 "Children's Since Last Visit" version of C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from EP0060.
8. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in EP0060.
9. Investigator decides that withdrawal from further participation would be in the subject's best interest.

Participation in EP0060 **may** be withdrawn for any of the following reasons:

10. Subject experiences generalized convulsive status epilepticus.
11. Subject has any clinically relevant change in medical or psychiatric condition (if, in the opinion of the investigator, the change in condition warrants discontinuation from EP0060).
12. Subject requires a medication that is not permitted by the protocol (see Section 7.8.1).
13. Subject and/or delegated caregiver is noncompliant with EP0060 procedures or medication, in the opinion of the investigator.
14. Subject who initiated adjunctive LCM treatment in EP0060 and requires a change in LCM dose during the Treatment Period.
15. Subject electively administering LCM requires more than 2 iv doses. If, in the opinion of the investigator, there is a clinical need to administer more than 2 iv doses, the subject may remain in the study. The investigator should document the clinical need in the medical record/source documents.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance. Investigators should also attempt to obtain information on subjects in the case of withdrawal. Withdrawal assessments, which are the same as those for Final Visit, will be recorded in EP0060. For subjects considered as lost to follow up, the investigator should make efforts (at least 1 phone call and 1 written message to the subject/subject's parent or legal guardian), and document his/her efforts (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The Case Report form (CRF) must document the primary reason for withdrawal.

For subjects returning to a long-term, open-label study, withdrawal assessments from the long-term open-label study should be evaluated separately from the EP0060 withdrawal assessments. The Medical Monitor may provide guidance on whether the subject should return to continued treatment within the long-term open-label study (OLL subject), be allowed to enroll in SP848 (RxL and IIL subjects), or withdraw completely. For the particular withdrawal criterion of requiring more than 10 iv doses or if the route of LCM administration (iv) is the sole reason for withdrawal of consent, subjects may be allowed to return to their long-term open-label study (OLL subjects) or enroll in SP848 (RxL and IIL subjects) after discussion with and agreement from the Medical Monitor. If an OLL subject is advised to withdraw from the long-term open-label study (EP0034 or SP848), the subject will be required to return to the long-term open-label study to complete the required withdrawal and safety follow-up assessments.

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

The PDILI criterion below requires discussion with Medical Monitor to decide whether subject is allowed to continue on IMP.

- 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 10.6.2. 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 CRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

7.1.1 Lacosamide solution for infusion

Investigational medicinal product for infusion will be provided as LCM solution for infusion in glass iv vials (10mg/mL in a 20mL vial; each vial contains LCM 200mg). Both the iv vials and the carton containing the vials will be labeled for the study.

Further details regarding dilution and storage of LCM solution for infusion are provided in the IMP Handling Manual.

7.1.2 Lacosamide oral solution for RxL and IIL subjects transitioning to SP848

Lacosamide syrup/oral solution will be provided in a polyethylene terephthalate bottle (10mg/mL in 200mL bottle). The bottle will be labeled for the study. Study medication will be measured and administered via a dosing syringe.

Lacosamide oral solution will only be distributed to those RxL and IIL subjects who are eligible and choose to participate in SP848. This supply, if required, will be dispensed at Visit 2 in the event that additional time is needed to coordinate scheduling of Visit 1 of SP848, and any remaining oral LCM solution will be returned to the site at the Transition Visit.

7.2 Treatment(s) to be administered

7.2.1 Treatment Period

During the Treatment Period, subjects will receive at least 1 dose of iv LCM at the dose levels noted below. The first iv LCM dose will be given on Day 1. If more than 1 infusion is given, iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration.

Specific dosing regimens for subjects who will receive iv LCM replacement therapy for oral treatment (OLL and RxL subjects) or for subjects who will initiate adjunctive LCM treatment (IIL subjects) are as follows:

- **Replacement for oral treatment:** For OLL and RxL subjects, the iv LCM daily dose will be equivalent (mg-for-mg) to the subject's current oral LCM dose or prescribed oral LCM (ie, VIMPAT) dose (always in bid regimen) of 2 to 12mg/kg/day or 100 to 600mg/day. The first infusion must be equivalent to the subject's stable oral LCM dose.
- **Adjunctive LCM treatment initiation:** For IIL subjects, the iv LCM daily dose will be 2mg/kg/day for subjects <50kg or 100mg/day for subjects ≥50kg. As LCM is given bid,

the actual dose for the first infusion will be LCM 1mg/kg (subjects weighing <50kg) or 50mg (subjects weighing ≥50kg). For these subjects, the LCM dose should remain unchanged for the duration of the iv Treatment Period (see Section 6.3).

A calibrated infusion pump should be used for delivering the iv LCM dose at a constant rate over the target duration defined for the cohort. A previously unused vial must be administered for each dose. Dilution is not required prior to administration of iv LCM. If needed to obtain a total volume compatible with the specified infusion duration, the iv LCM solution can be diluted; iv LCM is compatible with the following diluents: dextrose 5%, lactated ringers, and normal saline (NaCl 0.9%). The total volume of diluent should be calculated not to exceed a total volume of fluid intake/day based on the Holliday-Segar equation as follows:

- For children weighing ≤10kg: 100mL/kg body weight
- For children weighing >10 to ≤20kg: 1000mL + 50mL/kg for each kg body weight ≥10kg
- For children weighing ≥20kg: 1500mL + 20mL/kg for each kg body weight ≥20kg

Intravenous LCM administration should be completed within 4 hours after dilution.

For the first 20 subjects ≥8 to <17 years of age enrolled into Cohort 1 and the first 20 subjects ≥1 month to <8 years in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

The duration of infusion for the remaining subjects in each cohort will be based on DMC recommendation:

- EITHER target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR all remaining subjects will have a target infusion duration of 30 minutes but no longer than 60 minutes

Further details on the timing of DMC recommendations regarding infusion duration are provided in Section 12.7.2.

For OLL and RxL subjects, the iv LCM dose can be modified after the first infusion when necessary for the safety of the subject or when the investigator deems it appropriate; however, modification should not occur until after the Day 1 PK samples have been taken. Modification of iv LCM dose is not permitted for IIL subjects.

A subject cannot receive iv LCM for more than 10 doses (up to 5 days) within the Treatment Period of EP0060 (or more than 2 consecutive doses [over approximately 24 hours] for elective administration. If a subject requires iv LCM treatment for more than 5 days, the subject may continue on iv VIMPAT, but he/she will need to discontinue EP0060. Upon completion/discontinuation of EP0060, OLL subjects are eligible to resume participation in their respective open-label study, according to the protocol requirements. If a subject is withdrawn from EP0060 due to requirement of more than 10 iv LCM doses, the subject may be allowed to return to their long term open-label study (OLL subjects) or enroll in SP848 (RxL and IIL

subjects) after discussion with and agreement from the Medical Monitor. If an OLL subject meets any other "must withdrawal" criteria for the respective open-label study, the subject will return to the open-label study to complete the appropriate withdrawal assessments and safety follow-up.

For RxL and IIL subjects, AED treatment will continue at the discretion of the treating physician, upon completion/discontinuation of EP0060. If determined clinically appropriate, these subjects will be given the option to continue oral LCM treatment for up to 2 years in SP848. If LCM treatment is not continued in SP848 (either by choice or not clinically appropriate), RxL and IIL subjects will be followed for approximately 30 days after the Final Visit in order to collect safety data. All concomitant medications taken during this 30-day period, including prescribed AEDs, will be collected at TC2.

If subjects need to discontinue LCM, OLL subjects should be tapered off LCM as specified in their long-term, open-label study or at the discretion of the treating physician for RxL subjects. For OLL subjects, this taper should occur as a part of the long-term, open-label study and not as a part of EP0060.

7.2.2 Transition oral lacosamide

Oral LCM solution will only be distributed to those RxL and IIL subjects who are eligible and choose to participate in SP848.

For OLL and RxL subjects, the oral LCM daily dose will be equivalent (mg-for-mg) to the subject's current oral LCM dose or prescribed oral LCM (ie, VIMPAT) dose (always in bid regimen) of 2 to 12mg/kg/day.

For IIL subjects, the oral LCM solution daily dose (always in bid) will be 2mg/kg/day for subjects <50kg or 100mg/day for subjects ≥50kg if the subject has been taking LCM for less than 7 days. If the subject has reached 7 days of LCM exposure, an increase in dose titration can be initiated.

7.3 Packaging

Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. Lacosamide will be suitably packaged in such a way as to protect LCM from deterioration during transport and storage.

7.4 Labeling

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

7.5 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of LCM at the site. Lacosamide stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured by controlling the temperature and 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 reported as per instructions contained in the IMP Handling Manual.

In the case of dispensing oral LCM solution, the investigator (or designee) will instruct the subject's parent or guardian to store the IMP following the instructions on the label.

7.6 Drug accountability

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

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 LCM is used only in accordance with the protocol.

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

7.7 Procedures for monitoring drug accountability

Drug accountability must be recorded on the Drug Accountability form by site staff and reviewed by the UCB representative during periodic monitoring visits.

7.8 Concomitant medication(s)/treatment(s)

7.8.1 Permitted and prohibited concomitant treatments (medications and therapies)

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

Use of the following concomitant treatments (medications and therapies) is prohibited during EP0060:

- MAOI-A inhibitors
- Cannabidiols not approved or indicated for epilepsy by local health authority

Therapy which 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 therapy that is expressly not permitted. In such cases, the subject's participation in EP0060 may be discontinued.

7.9 Blinding

This is an open-label study.

7.10 Randomization and numbering of subjects

Subjects will not be randomized in EP0060. For an OLL subject, the unique identification number assigned to them in that study will be used to identify them and maintain subject confidentiality throughout EP0060. A unique identification number in EP0060 will be assigned for RxL and IIL subjects.

8 STUDY PROCEDURES BY VISIT

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

8.1 Screening/Baseline Period

8.1.1 Visit 1a and Visit 1b (Day -7 to Day 1) Screening and/or Baseline

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent form. When possible, or as required by the local IRB/IEC, an IRB/IEC-approved written Assent form will also be properly executed and documented. During the Screening Period, subjects will be evaluated for their suitability for enrollment. The Screening Period assessments may be conducted on more than 1 day and begin up to 7 days prior to Day 1 (Visit 2).

The Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion (Day 1), if necessary, provided all test results (ie, 12-lead ECG and laboratory results) are available and reviewed to assess inclusion and exclusion criteria prior to enrollment/treatment in the study. For all subjects, laboratory results obtained for routine diagnostic and medical care can be used whenever possible if collected no more than 24 hours prior to Screening/Baseline Visit in order to minimize blood loss associated with the study. At the Screening/Baseline Visit, the use of a central or local laboratory is at the discretion of the investigator.

If Screening/Baseline do not occur on the same day as the first infusion, oral LCM will be administered for OLL and RxL subjects during the Screening/Baseline Period from their open-label study or prescribed LCM supply in accordance with each subject's current stable LCM dosage regimen of 2 to 12mg/kg/day or 100 to 600mg/day. For IIL subjects, no LCM will be administered during the Screening Period.

Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria at Visit 1a and/or Visit 1b. Demographic data will be collected at Visit 1a. The following pretreatment assessments will be carried out at Visit 1a:

- Height and weight
- Medical procedures
- Procedure history
- Diagnosis of epilepsy

- Childbearing potential
- Complete medical history for RxL and IIL subjects (a medical history update will be captured in the previous long-term open-label study for OLL subjects)
- For OLL and RxL subjects, LCM dosing history (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Prior and concomitant medication(s) assessment (prior medications will only be collected for direct-enroll subjects)
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or use of ketogenic diet
- Urine pregnancy testing for subjects of childbearing potential
- Withdrawal criteria
- Complete neurological examination
- Complete physical examination
- Blood sample for clinical chemistry and hematology
- Vital signs (BP and pulse rate) assessment (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- 12-lead ECG (conducted on subjects who have rested [sitting or supine] at least 3 minutes prior to each ECG recording, when feasible)
- AE reporting (AEs occurring since signature of Informed Consent form). Ongoing AEs from the long-term open-label studies will be followed, as well as recording of new AEs during EP0060.
- C-SSRS (for subjects ≥6 years of age). For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.
- Seizure history for RxL and IIL subjects

If Screening/Baseline and the first infusion do not occur on the same day, oral LCM administration for OLL and RxL subjects will continue in accordance with each subject's LCM dosage regimen and using the subject's open-label study or prescribed oral LCM supply, respectively.

The following assessments will be carried out at Visit 1b if Screening and Baseline occur on separate days:

- Verification that the subject continues to meet the inclusion criteria
- For OLL and RxL subjects, the LCM dosing history will be collected (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Prior and concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or ketogenic diet

- AE reporting (AEs occurring since signature of Informed Consent form)
- Blood sample for clinical chemistry and hematology (Repetition of laboratory assessments is at the discretion of the investigator if Visit 1b is on a separate day from Visit 1a.)
- Withdrawal criteria
- Vital signs (BP and pulse rate) assessment (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- 12-lead ECG (conducted on subjects who have rested [sitting or supine] at least 3 minutes prior to each ECG recording, when feasible)
- C-SSRS (for subjects ≥6 years of age). For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.
- Medical procedures
- Medical history update for OLL subjects, or complete medical history for RxL and IIL subjects
- Urine pregnancy testing for subjects of childbearing potential
- Brief physical examination
- Brief neurological examination

If Screening/Baseline and the first infusion do not occur on the same day, oral LCM administration for OLL and RxL subjects will continue in accordance with each subject's LCM dosage regimen and using the subject's open-label study or prescribed oral LCM supply, respectively.

8.2 Treatment Period

8.2.1 Visit 2 (Day 1)

Intravenous LCM infusion treatment will begin at this visit. Subjects will receive at least 1 dose of iv LCM. If more than 1 infusion is given, iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration.

Screening laboratory assessments may be conducted up to and including the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion. Section 8.1.1 details under what conditions laboratory results within 24 hours of signing the Informed Consent form can be used.

The following assessments will be carried out:

- Intravenous LCM infusion
- Medical procedures
- Prior and concomitant medication(s) assessment

- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or use of ketogenic diet
- Withdrawal criteria
- AE reporting
- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion) (conducted on subjects who have rested [sitting or supine] for at least 3 minutes prior to each ECG recording, when feasible)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion) (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- Blood sample for LCM PK (Blood draws will be performed from a region of the body that is different from the region where the iv LCM infusion will be administered at the time points described in Section 9. An indwelling peripheral cannula used for the iv LCM infusion may not be used for PK blood sampling.)
- C-SSRS (for subjects ≥6 years of age) after infusion. For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.
- Brief physical examination
- Brief neurological examination
- For RxL and IIL subjects who are eligible and choose to participate in the long-term open-label oral LCM study SP848 after completion of EP0060, a short-term oral LCM solution will be dispensed at Visit 2. This supply is to allow continuity of LCM treatment after the last iv LCM infusion and the scheduled Transition Visit. Oral LCM solution administration should begin approximately 12 hours after the final iv LCM infusion.

If a second iv LCM infusion is given, it will be administered at approximately 12 hours after the start of the first infusion, and the following assessments will be carried out:

- Intravenous LCM infusion
- AE reporting
- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion) (conducted on subjects who have rested [sitting or supine] for at least 3 minutes prior to each ECG recording, when feasible)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion) (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- Withdrawal criteria

- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or use of ketogenic diet

If the subject has more than 1 iv LCM infusion, it is optional to also collect blood samples for LCM PK before and after the final iv LCM infusion at the time points described in Section 9. In addition, during the course of the study, additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

8.2.2 Visit 3 (Day 2 to Day 5)

If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed each day of iv LCM treatment in EP0060. Assessments for Visit 3 (Day 2 to 5) are the same as those described for Visit 2 (Day 1) in Section 8.2. If the subject has more than 1 iv LCM infusion, it is optional to also collect blood samples for LCM PK before and after the final iv LCM infusion at the time points described in Section 9. In addition, during the course of the study, additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

8.3 Unscheduled Visit

The following assessments will be carried out during the Unscheduled Visit:

- Medical procedures
- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose), VNS settings, and/or use of ketogenic diet
- AE reporting
- BP and pulse rate (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- Withdrawal criteria
- C-SSRS (for subjects ≥6 years of age). The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE. For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.
- Brief physical examination
- Brief neurological examination

Additional assessments can be performed at the investigator's discretion, including collection of a blood sample for LCM PK if the reason for the Unscheduled Visit is an AE.

8.4 End-of-Study Period

8.4.1 Final Visit (Day 1 to 6)/Termination Visit

The Final Visit may occur on the same day as the last infusion, time permitting. Otherwise, the Final Visit should occur on the following day.

The following assessments will be carried out after the last dose of iv LCM for subjects who complete the study, discontinue the study, or withdraw from the study prematurely:

- Medical procedures
- Concomitant medication(s) assessment
- Urine pregnancy testing for subjects of childbearing potential
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose), VNS settings, and/or use of ketogenic diet
- AE reporting
- Complete physical examination
- Complete neurological examination
- Blood sample for clinical chemistry and hematology which must be analyzed at the central laboratory
- 12-lead ECG (conducted on subjects who have rested [sitting or supine] for at least 3 minutes prior to each ECG recording, when feasible)
- BP and pulse rate (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- Withdrawal criteria
- Oral LCM administration, if applicable:
  - For OLL subjects, oral LCM administration will continue in accordance with each subject's LCM dosage regimen using the subject's open-label study LCM supply
  - For RxL subjects who are not eligible or do not wish to continue LCM treatment in SP848, oral LCM administration may continue from the subject's prescribed LCM supply at the physician's recommended dosage regimen.
  - For RxL and III subjects who are eligible and wish to enroll in SP848, oral LCM administration, from the short-term oral LCM solution that was dispensed at Visit 2, should begin approximately 12 hours after the final iv LCM infusion regardless of when the Final Visit occurs. Additional assessments will be conducted at the Transition Visit, as outlined in Section 8.4.3.
- C-SSRS (for subjects ≥6 years of age) For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.

8.4.2 Telephone Contact 1 (Day 2 to Day 9)

One to 3 days after the Final Visit, a safety follow-up/telephone assessment will be conducted during the End-of-Study Period. The following assessments will be collected:

- Medical procedures
- Concomitant medication(s) assessment
- AE reporting

- Information regarding LCM dosing since Final Visit
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose)

During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

8.4.3 Transition Visit (Day 1 to Day 13)

For RxL and IIL subjects who are eligible and wish to enroll in SP848, the Final Visit and Transition Visit may occur on the same day or may occur up to 7 days after the Final Visit. The Transition Visit for EP0060 should occur on the same day as Visit 1 in SP848.

The following assessments will be conducted at the Transition Visit if the visit is not conducted on the same day as the Final Visit:

- Collection of the short-term oral LCM solution, if dispensed at Visit 2
- Information regarding LCM dosing since Final Visit
- Concomitant medication(s) assessment
- AE reporting

Additional assessments for enrollment in SP848 (Visit 1) are detailed within the SP848 protocol.

8.4.4 Telephone Contact 2 (Day 29 to Day 37)

Thirty days (±2 days) after the Final Visit, a safety follow-up/telephone assessment will be conducted during the End-of-Study Period (29 to 37 days after Visit 2/Day 1). This assessment will only occur for those subjects who directly enrolled in EP0060 and will not be continuing LCM therapy in SP848.

The following assessments will be collected:

- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or use of ketogenic diet
- AE reporting
- Information regarding LCM dosing since Telephone Contact 1
- Medical procedures

During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

9 ASSESSMENT OF PHARMACOKINETICS

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). In each case, the time the subject received the most recent dose of IMP and the time of blood sampling must be recorded.

During the Treatment Period, plasma samples will be taken for LCM and SPM 12809 determination after ECG and vital signs have been taken. Plasma samples will be obtained from

a different region of the body from the region in which the solution for infusion was administered, at the following time points:

First iv LCM infusion (Day 1) – required samples:

- Predose (within 1 hour prior to iv LCM dose) for OLL and RxL subjects
- Postdose (within 1 to 4 hours after end of iv LCM infusion)

Final iv LCM infusion (Day 2 to 5/Early Termination) – optional samples:

- Predose (within 1 hour prior to iv LCM dose)
- Postdose (within 1 to 4 hours after end of iv LCM infusion)

Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

The study-related blood loss (including any losses in the maneuver), per study subject, will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90mL/kg body weight; 3% is 2.4mL of blood per kg of body weight. With today's microanalytical techniques, plasma samples for drug level determinations can be small, with less than 1mL needed.

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

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definition of adverse event

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

In order to ensure complete safety data collection, all AEs occurring during EP0060 (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol (excluding hospitalization procedures for other conditions other than those related to epilepsy), must be reported in the CRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

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

10.1.2 Procedures for reporting and recording adverse events

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

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

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

Details for completion of the Adverse Event CRF (including judgment of relationship to IMP) are described in the CRF 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 EP0060 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 IMP. Any ongoing AEs at the end of EP0060 for the subjects enrolled in the open-label studies will not need to be re-recorded in the long-term, open-label study.

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

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

- The subject may need to discontinue iv LCM. The decision to stop the intake of iv LCM will be at the discretion of the investigator.

- A Safety Follow-Up Visit should be scheduled 1 to 3 days after the subject has discontinued her iv LCM infusion.

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

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

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

10.1.7 Suspected transmission of an infectious agent via a medicinal product

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

10.1.8 Overdose of investigational medicinal product

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

10.1.9 Safety signal detection

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

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

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital

signs, laboratory, or ECG results) for which data will be periodically reviewed during the course of the study.

10.2 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 at least 1 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 or 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 that the investigator, when completing the SAE report form, includes 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. 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 10.6.2.

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

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 by the investigator to UCB:

- 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 is anticipated to occur in the epilepsy population at some frequency that is independent of drug exposure.

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

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

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity

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

MedDRA SOC	MedDRA PT
General disorders and administrative site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion[a]
	Incontinence
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder
Reproductive system and breast disorders	Menstrual disorder

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

[a] Convulsion if consistent with the seizure type known for the subject.

10.6 Laboratory measurements

Blood specimens for routine assay of hematology and clinical chemistry testing will be collected according to the tabular schedule of study assessments (Section 5.2). To minimize risk from blood loss associated with this study, local laboratory results obtained for routine diagnostic and medical care can be used whenever possible if collected no more than 24 hours prior to Screening/Baseline Visit. Use of the central or local laboratory is at the discretion of the investigator for all visits except the Final Visit. The central laboratory must be used for laboratory samples collected at the Final Visit. Samples will be prepared and evaluated by a central laboratory as described in the laboratory manual.

All laboratory values that are outside the normal reference range must be assessed by the investigator for clinical relevance. The following parameters will be measured:

Table 10–2: Laboratory tests

Hematology	Clinical chemistry
Hematocrit	Calcium
Hemoglobin	Phosphorus
Platelet count	Serum electrolytes (sodium, potassium, chloride, bicarbonate[a])
Red blood cell count	Creatinine
White blood cell (WBC) count	Blood urea nitrogen
WBC differential count	AST
	ALT
	Total bilirubin
	Alkaline phosphatase
	Gamma-glutamyltransferase
	Glucose
	Albumin
	Total protein
	Cholesterol
	Triglycerides
	Uric acid

ALT=alanine aminotransferase; AST=aspartate aminotransferase; WBC=white blood cell
[a] Bicarbonate testing is optional for subjects weighing less than 8kg. Consider testing for bicarbonate in subjects weighing less than 8kg in cases of suspected metabolic disturbances such as metabolic acidosis.

10.6.1 Pregnancy testing

Females of childbearing potential will have pregnancy testing performed according to the tabular schedule of study procedures (Section 5.2).

10.6.2 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 10.6.2.2 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 10.2.1).

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 10.6.2.1). 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 10.6.2.4).

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

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

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

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued.

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

The table below summarizes the approach to investigate PDILI.

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.6.2.3); 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				
≥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 10.6.2.2).	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 10.6.2.3).	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 10.6.2.1. 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.

10.6.2.1 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 10.6.2.3) and SAE report (if applicable).

10.6.2.2 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.

10.6.2.3 Testing: identification/exclusion of alternative etiology

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

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

The following measurements are to be assessed:

Table 10–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Hematocrit
	Hemoglobin
	Platelet count
	RBC count
	WBC count
	WBC differential 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
	ALT
	AST
	ALP
	GGT
	Albumin
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

Table 10–4: PDILI laboratory measurements

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

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

10.6.2.4 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 Other safety measurements

10.7.1 Vital signs, body weight, and height

Noninvasive measurements of BP (systolic and diastolic) and pulse rate will be performed after at least 3 minutes at rest, when feasible, according to the tabular schedule of study assessments (Section 5.2). Body weight will be determined without shoes and wearing light clothing, and height will be measured without shoes; body weight and height will be assessed according to the tabular schedule of study procedures (Section 5.2).

10.7.2 12-lead ECG

Standard 12-lead ECGs will be performed according to the tabular schedule of study procedures (Section 5.2).

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest at least 3 minutes prior to each recording and should be motionless during the recording, when feasible.

10.7.3 Overall ECG interpretation

An immediate initial review of the ECGs will be conducted locally by the investigator, subinvestigator, or qualified designated reader. If this reading identifies abnormal ECG findings that are assessed by the investigator or subinvestigator to be clinically significant, then the ECG should be repeated in 1 hour, unless circumstances require a more rapid assessment. If the clinically significant abnormality is confirmed by the repeat ECG or if the investigator feels it is medically necessary, the subject must be withdrawn from EP0060 (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 EP0060. Additionally, the ECGs will be sent to a central reader for review.

10.7.4 Physical examination

10.7.4.1 Complete physical examination

The complete physical examination will include cardiac and respiratory function via auscultation, and review of all body systems. Clinically significant physical examination findings are to be reported as AEs.

10.7.4.2 Brief physical examination

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

10.7.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Table 5–1). If the Screening and Baseline visit is on the same day, the C-SSRS does not need to be completed twice. The C-SSRS should be performed once per day during the Treatment Period. If Screening/Baseline

and Visit 2 occur on the same day, 2 assessments should be completed with 1 predose and 1 after infusion.

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

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

10.7.6 Neurological examination

10.7.6.1 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. Clinically significant neurological examination findings are to be reported as AEs.

10.7.6.2 Brief neurological examination

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

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 IEC/IRB or sponsor.

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

11.2 Monitoring

UCB (or designee) will monitor the study according to UCB (or designee) approved Standard Operating Procedures (SOPs), ICH-GCP guidelines, and applicable regulatory requirements, to ensure that study initiation, conduct, and closure are adequate.

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

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

11.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Printouts of electronic CRF screens are not considered acceptable source documents.

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

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the subject's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the CRF 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 is performed using electronic data capture (EDC); 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 CRF 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 need to be reapproved by the investigator.

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

Detailed instructions will be provided in the CRF 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. As the study is performed using EDC, 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 IMP and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The investigator will maintain adequate records for the study, including CRFs, 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 IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she

relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

11.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, 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

Selected disposition, exposure, demographic, and Baseline summaries will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Within cohort and infusion duration, presentation will include the IIL subject group and the OLL and RxL subject group.

Descriptive statistics will be displayed to provide an overview of the Baseline characteristics, PK, and safety results.

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

12.1 Definition of analysis sets

The Safety Set (SS) will include subjects who received at least 1 dose of EP0060 study drug LCM (oral and/or iv). Selected safety summaries will be presented for the SS.

The Safety Set iv (SS-iv) will include subjects in the SS who received at least 1 dose of EP0060 study drug iv LCM. The SS-iv will be the primary analysis set for the analysis of safety data.

The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all subjects in the SS-iv having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 study day with documented iv LCM intake times and without important protocol deviations impacting the interpretability of the PK analysis.

12.2 General statistical considerations

All computations for the non-PK analyses will be performed using SAS® version 9.1 or later (SAS Institute, NC, USA).

Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation [SD], minimum, and maximum) will be tabulated. For PK parameters, the coefficient of variation (CV) and geometric mean may also be presented.

12.3 Planned pharmacokinetic analyses

Descriptive statistics for LCM and SPM 12809 plasma concentrations, including but not limited to geometric mean and CV, will be computed for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected.

12.4 Planned safety analyses

Safety analyses will be presented by age cohort.

Inferential statistical tests are not planned for the safety variables. In general, for continuous safety variables (eg, ECG measurements including QTc, and vital signs measurements), the descriptive analyses (n, mean, SD, median, minimum, maximum) for the actual measurement and its change from Baseline (defined as pre-iv LCM measurement) will be presented by day/time of collection for each infusion day. When analyzing categorical data, the number and percentage of subjects in each category will be presented. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-iv LCM status when compared with their pre-iv LCM status.

12.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

12.6 Handling of dropouts or missing data

There will be no special procedures for handling withdrawals and missing data.

12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 subjects in Cohort 1 and after completion of the first 20 subjects in Cohort 2.

12.7.1 Definition of stopping rules

No formal stopping rule will be applied. The DMC may give a recommendation to stop the study after reviewing the safety data as described in Section 12.7.2. A recommendation for stopping should be based on the collective experience of the DMC members. After meeting to review data from each cohort, the DMC will provide a recommendation in writing regarding whether to continue or to stop the study. UCB will consider this recommendation and ensure the study investigators are informed of the sponsor's decision on how to continue as described below.

12.7.2 Data Monitoring Committee

The DMC members will be defined in the DMC charter.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion durations as follows:
  - 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator; OR,
  - 30 minutes but no longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the investigator
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, approximately 44 subjects ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion durations as follows:
  - 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator; OR,
  - 30 minutes but no longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the investigator
- OR approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped.

12.8 Determination of sample size

Approximately 100 subjects will be enrolled, which includes up to 2 cohorts of at least 40 subjects for Cohort 1 and approximately 44 subjects for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

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.

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

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

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

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

The subject's legal representative(s) may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when his/her legal representative(s) has signed the Informed Consent form. A CRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained written consent from his/her legal representative(s) in order 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, Informed Consent form, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

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

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 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 contract research organization 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 design of the study, the definition of the clinical situation in which a subject will qualify for enrollment in this study, and to provide further clarification regarding the PK assessments in accordance with the US Food and Drug Administration (FDA) request. It is clarified that this study will enroll approximately 75 subjects ≥4 to <17 years of age and that another Phase 2/3 study is planned to investigate the use of iv LCM in subjects with epilepsy ≥1 month to <4 years of age. EP0060 will initially enroll older pediatric subjects (Cohort 1), which will include at least 20 subjects ≥12 to <17 years of age. After the first 10 subjects in each cohort have completed their iv LCM treatment over infusion durations of 30 to 60 minutes, the enrollment will be temporarily put on hold for the DMC to review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration to be used (30 minutes to 60 minutes or 15 to 30 minutes) for the remaining subjects in the cohort, whether the study/cohort should be stopped, and whether the next cohort can be initiated.

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 update of the Sponsor Declaration have been made.

At the time of approval of this amendment, no subjects were enrolled in EP0060.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Text has been modified to clarify that approximately 75 subjects ≥4 to <17 years of age with epilepsy will be included in EP0060 and that another study is planned to investigate the use of iv LCM in subjects with epilepsy ≥1 month to <4 years of age.
- Text has been modified to allow an age staggered approach to enrollment. The enrollment will begin with the older pediatric subjects (Cohort 1: at least 20 subjects ≥12 to <17 years of age) followed sequentially by younger pediatric subjects (Cohort 2: at least 20 subjects ≥8 to <12 years of age, and Cohort 3: at least 20 subjects ≥4 to <8 years of age).
- Text has been modified to clarify that after completion of the first 10 subjects in each cohort, the enrollment will be temporarily put on hold for the DMC to review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort, whether the study/cohort should be stopped, and whether the next cohort can be initiated.
- Inclusion Criterion #2 has been amended as diaries are not used in this study.
- Inclusion Criterion #3 has been amended to clarify that subjects from ≥4 to <17 years of age can be enrolled in the study.

- Inclusion Criterion #4 has been deleted as it is no longer applicable based on the amended age of the subjects in the study.
- Inclusion Criterion #5 (new numbering) has been added to clarify the clinical situation in which a subject will qualify for enrollment in this study.
- Inclusion Criterion #10 has been reworded to clarify the allowed use of prescribed oral VIMPAT depending on subject's weight.
- Inclusion Criterion #11 has been reworded to clarify that intake of the prescribed total daily dose of prescribed oral VIMPAT must be confirmed for at least 3 days prior to first infusion.
- Inclusion Criterion #12 has been reworded to clarify requirements in case of concomitant AEDs.
- Exclusion Criterion #2 has been deleted as any subject expected to be hospitalized longer than 5 days may enter the study, but may not receive iv LCM in EP0060 longer than 5 days.
- Exclusion Criterion #8 (new numbering) has been revised to clarify that subjects who have a medical condition that could reasonably be expected to interfere with oral LCM absorption are not excluded from the study.
- Exclusion Criterion #11 (new numbering) has been amended to clarify that subjects are excluded from the study with creatinine clearance of less than 30mL/min.
- Exclusion Criterion #18 has been deleted as vigabatrin is permitted during the study.
- Exclusion Criterion #19 (new numbering) has been amended to specify that subjects with known cardiac sodium channelopathy are excluded from the study.
- Text has been modified to clarify the equation to be used to calculate the total volume of fluid according to the subject's weight.
- Text has been modified regarding concomitant treatments so that subjects who have been treated with ethosuximide are not excluded from the study, treatment with vigabatrin or ethosuximide and with neuroleptics is allowed during the course of the study, any doses of anxiolytics or hypnotics are allowed for nonepilepsy indications, and use of benzodiazepines is not restricted.
- Text has been revised to clarify the procedures by visit; details of prior and concomitant medications recording; timing of the Telephone Contact assessments; morning or evening timing of some procedures during the study visits; and timing of infusion, blood sampling, vital signs, and ECG measurements; and to clarify the required subject positions during vital signs and ECG measurements.
- Text has been modified to indicate that the LCM metabolite SPM 12809 will also be analyzed. Furthermore, additional PK assessments may be obtained at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.
- Text has been revised to clarify actions in case of pregnancy.
- Text has been revised to clarify the version of the C-SSRS that needs to be completed by subjects who are ≥6 years of age.

- The use of some terms has been revised: the terms "inpatient" and "BMI" have been deleted, and the terms "hospital" and "hospitalization" have been replaced with "health care facility" and "admission to the health care facility," respectively, where appropriate.
- The Clinical Project Manager has been changed and contact details have been updated.
- The Sponsor Declaration has been updated as the protocol will be signed electronically.
- Other changes made in this amendment are to provide clarification, are administrative in nature, or are to correct errors.

Specific changes

Change #1

Title page

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE AS REPLACEMENT FOR ORAL LACOSAMIDE IN CHILDREN (≥1 MONTH TO <17 YEARS OF AGE) WITH EPILEPSY

Has been changed to:

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE AS REPLACEMENT FOR ORAL LACOSAMIDE IN CHILDREN (≥4 TO <17 YEARS OF AGE) WITH EPILEPSY

Change #2

STUDY CONTACT INFORMATION

Clinical Project Manager

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Project Manager

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc.

	8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
Fax:	[redacted]

Change #3

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	Europe and Rest of the World: +32 2 386 24 21 USA: +1 800 880 6949 Canada: +1 877 582 8842 Japan: +81 3 6864 7400
Email	Global: DS_ICT@ucb.com (for interventional clinical studies) Japan: JDSO@ucb.com

Has been changed to:

Serious adverse event reporting (24h)	
Fax	Europe and Rest of the World: +32 2 386 24 21 USA: +1 800 880 6949 Canada: +1 877 582 8842
Email	Global: DS_ICT@ucb.com (for interventional clinical studies)

Change #4

LIST OF ABBREVIATIONS

BMI and CRO have been deleted and FDA has been added.

Change #5

Section 1 SUMMARY

EP0060 is a Phase 2/3, multicenter, open-label, inpatient study to evaluate the safety and tolerability of adjunctive intravenous (iv) lacosamide (LCM) infusions as replacement for oral LCM in pediatric subjects with epilepsy where the subject is currently taking oral LCM and needs to undergo a procedure, be admitted to an epilepsy monitoring unit (EMU) or hospital, or other situations where iv administration is clinically appropriate. Up to 75 subjects, who are participating in a long-term, open-label study with LCM (SP848, EP0034, EP0012, or other

future study) or who are currently prescribed VIMPAT® (LCM) will be enrolled. Pediatric subjects entering into EP0060 from a long-term, open-label study will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll directly into EP0060 will temporarily switch from their prescribed VIMPAT oral treatment to the iv LCM formulation. Subjects will be enrolled from approximately 40 sites in North America, Europe, Asia Pacific, and Latin America. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) administered over target durations of 30 minutes or 15 minutes in pediatric subjects ≥1 month to <17 years with epilepsy.

EP0060 will be comprised of up to 3 cohorts.

- Approximately 25 subjects will be enrolled into Cohort 1 in order to receive iv LCM, which should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of Cohort 1, enrollment into EP0060 will be temporarily put on hold to allow for a Data Monitoring Committee (DMC) review of the safety and tolerability data from Cohort 1. Based on the review of the Cohort 1 data, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 2.

- EITHER approximately 25 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 25 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible.

The DMC will reconvene after the completion of Cohort 2. If the Cohort 2 target infusion duration was 30 minutes but no longer than 60 minutes, enrollment into the study will be stopped once Cohort 2 has completed. If the Cohort 2 target infusion duration was 15 but no longer than 30 minutes, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 3.

- EITHER approximately 25 additional subjects will be enrolled into Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 25 additional subjects will be enrolled into Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of Cohort 3, the DMC will reconvene to review the final data to provide their overall impression.

This design will result in a total exposure of at least approximately 50 pediatric subjects (up to 75 pediatric subjects) to assess the safety of iv LCM administered over a range of infusion durations.

EP0060 is comprised of the following: Screening and/or Baseline Period (up to 7 days); Treatment Period (up to 5 days); an End-of-Study/Final Visit (1 day); and a Follow-Up Period/Telephone Contact (up to 2 days). During the Screening Period (Day -1), oral LCM tablets will be administered in accordance with each subject's oral LCM dosage regimen. During

the Treatment Period, subjects will receive iv LCM infusion twice daily (bid) at approximately 12-hour intervals. The daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and safety assessments will be collected (physical and neurological exams, pulse rate, blood pressure, and 12-lead electrocardiogram [ECG]). An End-of-Study/Final Visit will be conducted the day after the last dose of iv LCM after completion of or withdrawal from the Treatment Period. A safety follow-up assessment will be collected during the Follow-Up Period by phone or in person, 1 to 2 days after the last dose of iv LCM in the Treatment Period.

The maximum study duration for an individual subject will be approximately 15 days. After completion of or discontinuation from EP0060, only subjects who enrolled into EP0060 from a long-term, open-label study will resume their participation in that study and resume oral LCM treatment accordingly. Subjects who were prescribed VIMPAT should continue antiepileptic drug (AED) treatment at the discretion of the treating physician.

Has been changed to:

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous (iv) lacosamide (LCM) infusions as replacement for oral LCM in pediatric subjects ≥4 to <17 years of age with epilepsy. A separate Phase 2/3 study investigating the use of iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned. EP0060 will include subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure, be admitted to an epilepsy monitoring unit (EMU) or health care facility, or other situations where iv administration is clinically appropriate. Approximately 75 subjects, who are participating in a long-term, open-label study with LCM (SP848, EP0034, EP0012, or other future study) or who are currently prescribed VIMPAT® (LCM) will be enrolled. Pediatric subjects entering into EP0060 from a long-term, open-label study will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll directly into EP0060 will temporarily switch from their prescribed VIMPAT oral treatment to the iv LCM formulation. Subjects will be enrolled from approximately 40 sites in North America, Europe, Asia Pacific, and Latin America. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy, after temporarily switching from the equivalent stable oral LCM dose. EP0060 is planned to include up to 3 age-based cohorts of at least 20 subjects per cohort: ≥12 to <17 years (Cohort 1), ≥8 to <12 years (Cohort 2), and ≥4 to <8 years (Cohort 3). A Data Monitoring Committee (DMC) will review the safety and tolerability data for each cohort to make recommendations for the progression of subsequent cohort enrollment and iv infusion durations to be evaluated.

EP0060 is comprised of the following study periods:

- Screening and/or Baseline Period (up to 7 days),
- Treatment Period (up to 5 days),
- End-of-Study/Final Visit (1 day),
- End-of-Study/Telephone Contact (1 to 2 days).

During the Screening Period (Day -7 to Day -1), oral LCM will be administered in accordance with each subject's oral LCM dosage regimen. During the Treatment Period, subjects will receive iv LCM infusions twice daily (bid) at approximately 12-hour intervals for up to 5 days. The daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and detailed safety assessments will be performed. An End-of-Study/Final Visit will be conducted the day after the last dose of iv LCM after completion of or withdrawal from the Treatment Period. A safety follow-up Telephone Contact should occur 1 to 2 days after the End-of-Study/Final Visit.

The maximum study duration for an individual subject will be approximately 15 days. After completion of or discontinuation from EP0060, only subjects who enrolled into EP0060 from a long-term, open-label study will resume their participation in that study and resume oral LCM treatment accordingly. Subjects who were prescribed VIMPAT should continue antiepileptic drug (AED) treatment at the discretion of the treating physician.

EP0060 will begin with Cohort 1, where at least 20 subjects ≥12 to <17 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 1, enrollment into Cohort 1 will be temporarily put on hold to allow for the DMC review of the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥8 to <12 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, enrollment into Cohort 2 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 2 should be stopped,
- AND whether Cohort 3 can be initiated.

For Cohort 3, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 3, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 3, enrollment into Cohort 3 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1, Cohort 2, and Cohort 3. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 3 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations.

Change #6

Section 2 INTRODUCTION, last paragraph

The results of EP0060 will provide safety and PK data regarding the use of the iv LCM formulation in pediatric subjects ≥1 month to <17 years with epilepsy.

Has been changed to:

The results of EP0060 will provide safety, tolerability, and PK data regarding the use of the iv LCM formulation as replacement for oral LCM in pediatric subjects ≥4 to <17 years with epilepsy.

Change #7

Section 3 STUDY OBJECTIVE(S)

The primary objective of this study is to evaluate the safety and tolerability of adjunctive iv LCM infusion(s) in pediatric subjects ≥1 month to <17 years with epilepsy, after temporarily switching from the equivalent stable oral LCM dose. An additional objective is to evaluate the PK of iv LCM in pediatric subjects with epilepsy.

Has been changed to:

The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy, after temporarily switching from the equivalent stable oral LCM dose. An additional objective is to evaluate the PK of iv LCM replacement in pediatric subjects with epilepsy.

Change #8

Section 4.2 Pharmacokinetic variable(s)

The PK variables will include plasma concentration of LCM and its metabolite, SPM12809.

Has been changed to:

The PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

Change #9

Section 5.1 Study description

EP0060 is a Phase 2/3, multicenter, open-label, inpatient study to evaluate the safety and tolerability of adjunctive iv LCM infusions as replacement for oral LCM in pediatric subjects with epilepsy where the subject is currently taking oral LCM and needs to undergo a procedure, be admitted to an EMU or hospital, or other situations where iv administration is clinically appropriate. Up to approximately 75 subjects, who are participating in long-term, open-label studies with LCM or who are currently prescribed VIMPAT, will be enrolled. Pediatric subjects entering into EP0060 from a long-term, open-label study will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll directly into EP0060 will temporarily switch from their prescribed oral VIMPAT treatment to the iv LCM formulation. Subjects will not be prescribed or maintained on VIMPAT for the purposes of participating in EP0060. Subjects will be enrolled from approximately 40 sites in North America, Europe, Asia Pacific, and Latin America. Additional sites or regions may be added if deemed necessary.

EP0060 will be comprised of up to 3 cohorts.

- Approximately 25 subjects will be enrolled into Cohort 1 in order to receive iv LCM, which should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of Cohort 1, enrollment into EP0060 will be temporarily put on hold to allow for a Data Monitoring Committee (DMC) review of the safety and tolerability data from Cohort 1. Based on the review of the Cohort 1 data, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 2.

- EITHER approximately 25 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 25 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible.

The DMC will reconvene after the completion of Cohort 2. If the Cohort 2 target infusion duration was 30 minutes but no longer than 60 minutes, enrollment into the study will be stopped once Cohort 2 has completed. If the Cohort 2 target infusion duration was 15 but no longer than 30 minutes, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 3.

- EITHER approximately 25 additional subjects will be enrolled into Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 25 additional subjects will be enrolled into Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of Cohort 3, the DMC will reconvene to review the final data to provide their overall impression.

This design will result in a total exposure of approximately 50 pediatric subjects (up to approximately 75 pediatric subjects) to assess the safety of iv LCM administered over a range of infusion durations.

EP0060 is comprised of the following: Screening and/or Baseline Period (up to 7 days); Treatment Period (up to 5 days); an End of Study/Final Visit (1 day); and a Follow-Up Period/Telephone Contact (up to 2 days). During the Screening Period (Day -1), oral LCM tablets will be administered in accordance with each subject's LCM dosage regimen. For subjects enrolled in a long-term, open-label study, the oral LCM will be administered from the long-term, open-label study supply. For subjects prescribed VIMPAT and enrolling directly into EP0060, oral LCM will be administered from the subject's prescribed VIMPAT supply.

Subjects will be under medical care at a healthcare facility for the duration of the iv LCM infusion treatment in EP0060. If necessary, the Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion. In both cases, it is required that all screening procedures are performed and the results of examinations (ie, ECG) are available to allow verification of subject eligibility. During the Treatment Period, subjects will receive iv LCM infusion twice daily (bid) at 12-hour intervals. The daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and safety assessments will be collected (physical and neurological exams, pulse rate, blood pressure, and 12-lead ECG). An End-of-Study/Final Visit will be conducted the day after the last dose of iv LCM after completion of or withdrawal from the Treatment Period. A safety follow-up assessment will be collected during the Follow-Up Period by telephone or in person 1 to 2 days after the last dose of iv LCM in the Treatment Period.

The maximum study duration for an individual subject will be approximately 15 days. After completion of or discontinuation from EP0060, subjects who enrolled into EP0060 from a long-term, open-label study will resume their participation in that study and resume oral LCM treatment accordingly. Subjects who were prescribed VIMPAT should continue AED treatment at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

Has been changed to:

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions as replacement for oral LCM in pediatric subjects ≥4 to <17 years of age with epilepsy. EP0060 will include subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure, be admitted to an EMU or health care facility, or other situations where iv administration is clinically appropriate. Approximately 75 subjects, who are participating in long-term, open-label

studies with LCM or who are currently prescribed VIMPAT, will be enrolled. Pediatric subjects entering into EP0060 from a long-term, open-label study will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll directly into EP0060 will temporarily switch from their prescribed oral VIMPAT treatment to the iv LCM formulation. Subjects will not be prescribed or maintained on VIMPAT for the purposes of participating in EP0060. Subjects will be enrolled from approximately 40 sites in North America, Europe, Asia Pacific, and Latin America. Additional sites or regions may be added if deemed necessary.

EP0060 is planned to include up to 3 age-based cohorts of at least 20 subjects per cohort: ≥12 to <17 years (Cohort 1), ≥8 to <12 years (Cohort 2), and ≥4 to <8 years (Cohort 3). A DMC will review the safety and tolerability data for each cohort to make recommendations for the progression of subsequent cohort enrollment and iv infusion durations to be evaluated. Details regarding the DMC are provided in Section 12.7.2.

EP0060 is comprised of the following study periods:

- Screening and/or Baseline Period (up to 7 days),
- Treatment Period (up to 5 days),
- End-of-Study/Final Visit (1 day),
- End-of-Study/Telephone Contact (1 to 2 days).

During the Screening Period (Day -7 to Day -1), oral LCM will be administered in accordance with each subject's oral LCM dosage regimen. For subjects enrolled in a long-term, open-label study, the oral LCM will be administered from the long-term, open-label study supply. For subjects prescribed VIMPAT and enrolling directly into EP0060, oral LCM will be administered from the subject's prescribed VIMPAT supply.

Subjects will be under medical care at a healthcare facility for the duration of the iv LCM infusion treatment in EP0060. If necessary, the Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion. In this case, it is required that all screening procedures are performed and the results of examinations (ie, ECG) are available to allow verification of subject eligibility. During the Treatment Period, subjects will receive iv LCM infusion bid at approximately 12-hour intervals for up to 5 days. The daily dose of iv LCM will be the same as the subject's current stable bid dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). During the Treatment Period, blood samples will be obtained for PK analysis, and safety assessments will be performed (physical and neurological exams, pulse rate, BP, 12-lead ECG, clinical hematology and chemistry, and Columbia-Suicide Severity Rating Scale [C-SSRS] when applicable). An End-of-Study/Final Visit will be conducted the day after the last dose of iv LCM after completion of or withdrawal from the Treatment Period. A safety follow-up Telephone Contact should occur 1 to 2 days after the End-of-Study/Final Visit.

The maximum study duration for an individual subject will be approximately 15 days. After completion of or discontinuation from EP0060, subjects who enrolled into EP0060 from a long-term, open-label study will resume their participation in that study and resume oral LCM treatment accordingly. Subjects who were prescribed VIMPAT should continue AED treatment at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

EP0060 will begin with Cohort 1, where at least 20 subjects ≥12 to <17 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 1, enrollment into Cohort 1 will be temporarily put on hold to allow for the DMC review of the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥8 to <12 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, enrollment into Cohort 2 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 2 should be stopped,
- AND whether Cohort 3 can be initiated.

For Cohort 3, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 3, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 3, enrollment into Cohort 3 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1, Cohort 2, and Cohort 3. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 3 should be stopped,

- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations.

Change #10

Section 5.1.1 Study duration per subject

The maximum iv LCM exposure per subject will be up to 5 days with a total study duration of up to 15 days (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, and Telephone Contact/Follow-Up up to 2 days after last dose of iv LCM.

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

Has been changed to:

The maximum iv LCM exposure per subject will be up to 5 days with a total study duration of up to 15 days (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, and a safety follow-up Telephone Contact 1 to 2 days after the Final Visit).

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

Change #11

Section 5.1.2 Planned number of subjects and site(s)

Up to 75 subjects currently participating in long-term, open-label studies with LCM or who are currently prescribed VIMPAT will be enrolled at approximately 40 sites.

In each cohort, the following target number of subjects will be enrolled in each age group:

- At least 4 subjects ≥1 month to <4 years of age
- At least 4 subjects ≥4 to <8 years of age
- At least 4 subjects ≥8 to <12 years of age
- At least 4 subjects ≥12 to ≤16 years of age

In total, across all cohorts, at least 8 subjects (for a 2-cohort study) or 12 subjects (for a 3-cohort study) will be enrolled in each age group.

Has been changed to:

Approximately 75 subjects currently participating in long-term, open-label studies with LCM or who are currently prescribed VIMPAT will be enrolled at approximately 40 sites.

The following cohorts are planned:

- Cohort 1: at least 20 subjects from ≥12 to <17 years of age
- Cohort 2: at least 20 subjects from ≥8 to <12 years of age

- Cohort 3: at least 20 subjects from ≥4 to <8 years of age

The remaining subjects may be enrolled in any of the 3 cohorts.

Change #12

Section 5.2 Table 5-1: Schedule of study assessments

Table 5-1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period				Unscheduled Visit[b]	End-of-Study Period	
Visit	V1a	V1b[a]	V2		V3			Final Visit[c]	TC[d]
Study Day	-7 to -1	-1	1		2 - 5			2 - 6	2 - 9
			AM	PM	AM	PM			
Written informed consent	X								
Inclusion/exclusion criteria	X	X[e]	X		X				
Demographics	X								
Medical procedures	X								
Procedure history[f]	X								
Medical history/update[f]	X								
Diagnosis of epilepsy[f]	X								
Childbearing potential[f]	X								
LCM dosing history[g]	X								
Prior and concomitant medications[h]	X	X	X	X	X	X	X	X	X
Concomitant AEDs/VNS settings	X	X	X	X	X	X	X	X	
Pregnancy testing[i]	X							X	
Withdrawal criteria	X	X		X		X	X	X	
AE reporting[j]	X	X	X	X	X	X	X	X	X
ILAE seizure classification	X								

Physical examination (complete)	X							X	

Table 5-1: Schedule of study assessments (continued)

Assessments	**Screening/ Baseline**		**Treatment Period**				**Unscheduled Visit[b]**	**End of Study Period**	
Visit	**V1a**	**V1b[a]**	**V2**		**V3**			**Final Visit[c]**	**TC[d]**
Days in study	**-7 to -1**	**-1**	**1**		**2 - 5**			**2 - 6**	**2 - 7**
			AM	**PM**	**AM**	**PM**			
Neurological examination (complete)	X							X	
Clinical chemistry and hematology[k]	X	X	X					X	
12-lead ECG	X	X[l]	X[l]	X[l]	X[l]	X[l]	X	X	
Vital signs	X	X[l]	X[l]	X[l]	X[l]	X[l]	X	X	
Body weight, height, and BMI	X								
Blood sample for LCM PK[m]			X	X	X	X	X		
Admission to the unit[n]	X	X							
Oral LCM administration[o]	X	X						X	X
Intravenous LCM infusion			X	X	X	X	X		
C-SSRS[p]	X	X[q]	X		X		X[b]	X	
Signs and symptoms of depression	X	X	X	X	X	X	X	X	
Discharge from the unit								X	

AE=adverse event; AED=antiepileptic drug; BMI=body mass index; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ILAE=International League against Epilepsy; iv=intravenous; LCM=lacosamide; PK=pharmacokinetics; TC=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

[a] Visit 1b only applies when Screening and Baseline occur on separate days.

[b] If an Unscheduled Visit is needed, the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[c] A Final Visit must be completed the day after the last dose of iv LCM for all subjects who complete or withdraw prematurely from EP0060. For subjects

who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and refer to the long-term, open-label studies taper regimen.

[d] The Telephone Contact assessment should be performed 1 to 2 days after the last dose of iv LCM in the Treatment Period during the Follow-Up Period (2 to 7 days after Visit 2/Day 1). During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

[e] Verification that the subject continues to meet inclusion/exclusion criteria if Screening and Baseline occur on separate days.

[f] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for direct-enroll subjects who were prescribed VIMPAT prior to entering the study. Medical history update will be collected for subjects from the long-term open-label studies.

[g] Lacosamide dosing history will include date, time, and quantity during the last 3 days.

[h] Prior medications will only be collected for direct-enroll subjects. Concomitant medications from the long-term open-label studies will be followed, as well as the recording of new concomitant medications during EP0060.

[i] Pregnancy testing for subjects of childbearing potential will be serum testing at the Screening Visit for direct-enroll subjects who are prescribed VIMPAT and urine testing for subjects enrolled in long-term, open-label studies. Urine pregnancy testing (or serum pregnancy test if no urine sample can be obtained) will be conducted on all subjects of childbearing potential at the Final Visit.

[j] Ongoing AEs from the long-term open-label studies will be followed, as well as recording of new AEs during EP0060.

[k] Laboratory assessments will be performed for subjects who are directly enrolled into EP0060. Screening laboratory assessments may be conducted up to the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion.

[l] Vital Signs will be performed 5 minutes prior to infusion and at 5, 10, 20, 45, 60 minutes, and 2 hours from the start of each iv administration. Noninvasive BP (systolic and diastolic) and pulse rate will be measured at study visits in a sitting position after at least 3 minutes at rest, when feasible. 12-lead ECG will be performed 5 minutes prior to infusion and at 15, 30, 60 minutes, and 2 hours from the start of each iv administration. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position at least 5 minutes prior to each ECG recording and should be motionless during the recording.

[m] Samples for PK will be drawn after ECG and vital signs have been taken on Day 1 (within 1 hour prior to the first iv LCM dose and 1 to 4 hours after the second iv LCM dose) and on the Final Treatment Visit (within 1 hour prior to the first iv LCM dose and 1 to 4 hours after the second iv LCM dose) from the opposite arm in which the solution for infusion was administered.

[n] Admission to the hospital to participate in the study should take place at least the day prior to the start of the first iv LCM infusion. However, when necessary for the wellbeing of the subject or when the investigator deems it appropriate, the hospitalization and the first iv LCM infusion can start on the same day.

[o] On Day -1, oral LCM will be administered in accordance with each subject's LCM dosage regimen.

[p] For all subjects ≥6 years of age, the "since last visit" version of the C-SSRS assessment should be completed for all visits after the initial (Screening/Baseline) assessment. Signs and symptoms of depression for patients <6 years of age will also be assessed whenever a C-SSRS assessment is performed.

[q] The C-SSRS assessment (see Section 10.1.1.1) does not need to be completed twice if Screening/Baseline assessments are done on the same day.

Has been changed to:

Table 5-1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visitc	End-of-Study Period	
Visit	**V1a**	**V1ba**	**V2**	**V3b**		**Final Visitd**	**TCe**
Study Day	**-7 to -1**	**-1**	**1**	**2 to 5**		**2 to 6**	**2 to 9**
Written informed consent	X						
Inclusion/exclusion criteria	X	X[f]					
Demographics	X						
Medical procedures	X	X	X	X	X	X	X
Procedure history[g]	X						
Medical history/update[g]	X	X	X	X	X	X	X
Diagnosis of epilepsy[g]	X						
Childbearing potential[g]	X						
LCM dosing history[h]	X						
Prior and concomitant medications[i]	X	X	X	X	X	X	X
Concomitant AEDs/VNS settings	X	X	X	X	X	X	
Pregnancy testing[j]	X					X	
Withdrawal criteria	X	X	X	X	X	X	
AE reporting[k]	X	X	X	X	X	X	X
ILAE seizure classification	X						
Physical examination (complete)	X					X	
Neurological examination (complete)	X					X	
Clinical chemistry and hematology[l]	X	X	X			X	

Table 5-1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visitc	End-of-Study Period	
Visit	**V1a**	**V1ba**	**V2**	**V3b**		**Final Visitd**	**TCe**
Study Day	**-7 to -1**	**-1**	**1**	**2 to 5**		**2 to 6**	**2 to 9**
12-lead ECG	X	X[m]	X[m]	X[m]	X	X	
Vital signs	X	X[n]	X[n]	X[n]	X	X	
Body weight and height	X						
PK blood sampling[o]			X	X	X		
Admission to the unit[p]	X	X					
Oral LCM administration[q]	X	X				X	X
Intravenous LCM infusion[r]			X	X	X		
C-SSRS[s]	X	X[t]	X	X	X[c]	X	
Discharge from the unit						X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ILAE=International League against Epilepsy; iv=intravenous; LCM=lacosamide; PK=pharmacokinetics; TC=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

[a] Visit 1b only applies when Screening and Baseline occur on separate days.

[b] If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed each day of iv LCM treatment in EP0060.

[c] If an Unscheduled Visit is needed, the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[d] A Final Visit must be completed the day after the last dose of iv LCM for all subjects who complete or withdraw prematurely from EP0060. For subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and refer to the long-term, open-label studies taper regimen.

[e] The Telephone Contact assessment should be performed 1 to 2 days after the Final Visit (2 to 7 days after Visit 2/Day 1). During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

[f] Verification that the subject continues to meet inclusion/exclusion criteria if Screening and Baseline occur on separate days.

[g] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for direct-enroll subjects who were prescribed VIMPAT prior to entering the study. Medical history update will be collected for subjects from the long-term open-label studies.

[h] Lacosamide dosing history will include date, time, and dosage information during the last 3 days.

Table 5-1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visitc	End-of-Study Period	
Visit	V1a	V1ba	V2	V3b		Final Visitd	TCe
Study Day	-7 to -1	-1	1	2 to 5		2 to 6	2 to 9

[i] Prior medications will only be collected for direct-enroll subjects. Concomitant medications from the long-term open-label studies will be followed, as well as the recording of new concomitant medications during EP0060 for all enrolled subjects.

[j] Pregnancy testing for subjects of childbearing potential will be serum testing at the Screening Visit for direct-enroll subjects who are prescribed VIMPAT and urine testing for subjects enrolled in long-term, open-label studies. Urine pregnancy testing (or serum pregnancy test if no urine sample can be obtained) will be conducted on all subjects of childbearing potential at the Final Visit.

[k] Ongoing AEs from the long-term open-label studies will be followed, as well as recording of new AEs during EP0060.

[l] Laboratory assessments will be performed for subjects who are directly enrolled into EP0060. Screening laboratory assessments may be conducted up to the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion.

[m] 12-lead ECG will be performed approximately 20 minutes prior to each infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of each iv administration. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest at least 5 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[n] Vital signs will be performed approximately 10 minutes prior to each infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of each iv administration. Noninvasive BP (systolic and diastolic) and pulse rate will be measured at study visits after at least 3 minutes at rest, when feasible.

[o] Samples for PK will be drawn after ECG and vital signs have been taken. Plasma samples will be obtained from the opposite arm in which the solution for infusion was administered for the first iv LCM infusion (Day 1): predose (within 1 hour prior to iv LCM infusion) and postdose (within 1 to 4 hours after end of iv LCM infusion), and for the final iv LCM infusion (Day 2 to 5/Early Termination): predose (within 1 hour prior to iv LCM infusion) and postdose (within 1 to 4 hours after end of iv LCM infusion). Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

[p] Admission to the health care facility to participate in the study should take place at least the day prior to the start of the first iv LCM infusion. However, when necessary for the wellbeing of the subject or when the investigator deems it appropriate, the admission to the health care facility and the first iv LCM infusion can start on the same day.

[q] On Day -1, oral LCM will be administered in accordance with each subject's LCM dosage regimen.

[r] LCM will be administered twice daily at approximately 12-hour intervals, once in the morning and once in the evening, for up to 5 days.

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

[t] The C-SSRS assessment (see Section 10.7.5) does not need to be completed twice if Screening/Baseline assessments are done on the same day.

Change #13

Section 5.2 Table 5-2: Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Table 5-2: Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Approximate time (min/hrs)	T0									T12h[b]						
	-3min to -59min	-5min	T0 (Start of infusion)	+5min	+15min	+30min (End of infusion)[a]	+60min	+1h to +4h	+2h	-5min	T12h	+5min	+15min	+30min	+60min	+2h
Pulse rate[c]		X		X	X	X	X		X	X		X	X	X	X	X
Blood pressure[c]		X		X	X	X	X		X	X		X	X	X	X	X
12-lead ECG		X			X	X	X		X	X			X	X	X	X
Blood sampling LCM PK	X[d]							X[d]								

ECG=electrocardiogram; iv=intravenous; LCM=lacosamide; PK=pharmacokinetics; T=time

a Depending on the target duration defined for the cohort and patient tolerability, end of infusion can be at 15, 30, or 60 minutes or whenever the infusion is stopped (if prematurely terminated).

b T12 will be approximately 12 hours after T0.

c Pulse rate and blood pressure will be taken predose and post dose at least once daily, where clinically appropriate.

d Samples for PK will be drawn after ECG and vital signs have been taken on Day 1 (within 1 hour prior to the first iv LCM dose and 1 to 4 hours after the second iv LCM dose) and on the Final Treatment Visit (within 1 hour prior to the first iv LCM dose and 1 to 4 hours after the second iv LCM dose) from the opposite arm in which the solution for infusion was administered.

Has been changed to:

Table 5-2: Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Approximate time points referred to iv infusion	Vital signsa	12-lead ECGb	PK blood samplingc
-59min to -3min			X
-20min		X	
-10min	X		
T0 (start of infusion)			
+5min	X		
+10min	X		
+15min		X	
+20min	X		
+30min		X	
+45min	X		
+60min	X	X	
+1h to +4h[d]			X
+2h	X	X	

AE=adverse event; BP=blood pressure; ECG=electrocardiogram; h=hours; iv=intravenous; LCM=lacosamide; min=minutes; PK=pharmacokinetics; T=time

a Noninvasive BP (systolic and diastolic) and pulse rate will be measured after at least 3 minutes at rest, when feasible, at the indicated approximate time points before and after the start of each iv LCM infusion.

b A 12-lead ECG will be performed at the indicated approximate time points before and after the start of each iv LCM infusion. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest at least 5 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

c Samples for PK will be drawn after ECG and vital signs have been taken. Plasma samples will be obtained from the opposite arm in which the solution for infusion was administered for the first iv LCM infusion (Day 1) and the final iv LCM infusion (Day 2 to 5/Early Termination), predose and postdose, at the time points indicated in the table. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE. Depending on the target duration defined for the cohort and subject tolerability, end of infusion can be at 15, 30, or 60 minutes, or whenever the infusion is stopped (if prematurely terminated).

d Time points are in reference to T0 (start of infusion) except the postdose PK sample, which should be obtained within 1 to 4 hours after the end of the iv LCM infusion.

Change #14

Section 5.3 Rationale for study design and selection of dose

EP0060 is an open-label, multicenter, inpatient study to investigate the safety and tolerability of adjunctive iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy aged

≥1 month to <17 years. The results of EP0060 will provide safety and PK data regarding the use of the iv LCM formulation in pediatric subjects. The EP0060 design is based on the study design for SP757, which evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies.

The iv LCM formulation is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥16 years of age (depending on country-specific labeling) with epilepsy when oral administration is temporarily not feasible.

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for subjects enrolling from the long-term open-label studies and for subjects currently prescribed VIMPAT and enrolling directly into EP0060.

The planned pediatric iv LCM labeling will be consistent with the approved adult iv LCM labeling and will also include infusion durations of 15 to 60 minutes depending on the evaluation of iv LCM PK, safety, and tolerability in pediatric subjects enrolled into EP0060. EP0060 will be comprised of up to 3 cohorts, and will first evaluate a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible (Cohort 1). After a DMC review of the safety and tolerability data from subjects in Cohort 1, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 2: EITHER 15 minutes but no longer than 30 minutes whenever possible, OR 30 minutes but no longer than 60 minutes whenever possible. If the 30 to 60 minutes infusion duration is repeated, enrollment into the study will be stopped once Cohort 2 has completed. If the Cohort 2 infusion is initiated at 15 to 30 minutes duration, the DMC will either recommend further evaluation at the 15 to 30 minutes infusion duration in Cohort 3, or to repeat evaluation of the 30 to 60 minutes infusion duration in Cohort 3. After completion of the enrollment of approximately 25 subjects in Cohort 3, the DMC will reconvene to review the final data to provide their overall impression.

This design will result in a total exposure of at least 50 pediatric subjects (up to 75 pediatric subjects) to assess the safety of iv LCM administered over a range of infusion durations. Taken together, the iv LCM dosing scheme and planned target infusion durations being evaluated in EP0060 (2 to 12mg/kg/day or 100 to 600mg/day; 15 to 60 minutes) allow for administration of a range of pediatric doses at infusion durations that are the same as those approved for adults and adolescents.

Has been changed to:

EP0060 is an open-label, multicenter study to investigate the safety and tolerability of iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy aged ≥4 to <17 years. A separate Phase 2/3 study investigating the use of iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned. The results of EP0060 will provide safety and PK data regarding the use of the iv LCM formulation in pediatric subjects (≥4 to <17 years of age). The EP0060 design is based on the study design for SP757, which

evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies.

The iv LCM formulation is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥16 years of age (depending on country-specific labeling) with epilepsy when oral administration is temporarily not feasible.

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for subjects enrolling from the long-term open-label studies and for subjects currently prescribed VIMPAT and enrolling directly into EP0060.

EP0060 will initially enroll older pediatric subjects (Cohort 1), which will include at least 20 subjects ≥12 to <17 years of age. Cohort 2 (at least 20 subjects ≥8 to <12 years of age) and Cohort 3 (at least 20 subjects ≥4 to <8 years of age) will follow sequentially based on DMC recommendation. After the first 10 subjects in each cohort have received iv LCM over infusion durations of 30 to 60 minutes, the enrollment will be temporarily put on hold for the DMC to review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort (ie, 30 to 60 minutes or 15 to 30 minutes), if the study/cohort should be stopped, and if the next cohort can be initiated, and if a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age) can be initiated.

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM in subjects ≥4 to <17 years of age over a range of infusion durations. Taken together, the iv LCM dosing scheme and planned target infusion durations being evaluated in EP0060 (2 to 12mg/kg/day or 100 to 600mg/day; 15 to 60 minutes) allow for administration of a range of pediatric doses, and include infusion durations that are the same as those approved for adults and adolescents.

Change #15

Section 6.1 Inclusion criteria

2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female from ≥1 month to <17 years of age. Note: For preterm infants <1 year old, the corrected gestational age should be used (calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age).
5. Subject has, in the opinion of the investigator, adequate seizure control for participation in EP0060, and is able to comply with all study requirements including hospitalization, multiple

blood draws, and iv infusions. Subject (or parent[s] or legal representative) is willing to comply with all study requirements.

10. Subject has been prescribed oral VIMPAT at a dose of 2mg to 12mg/kg/day or 100mg to 600mg/day.
11. Subject has been prescribed oral VIMPAT for the treatment of epilepsy for at least 1 month prior to Screening and has not been prescribed or maintained on VIMPAT for the purposes of participating in EP0060. Prescribed oral VIMPAT dose must be stable for at least 7 days, and intake of the prescribed total daily dose confirmed for at least 3 days prior to participation.
12. Subject is on a stable dosage regimen of at least 1 AED. The daily dosage regimen of AED therapy must be kept constant for a period of at least 1 week prior to Screening. VNS is allowed, but settings must be kept constant for a period of at least 1 week prior to Screening.

Have been changed to:

2. Subject/legal representative is considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female from ≥4 to <17 years of age.
4. Subject has, in the opinion of the investigator, adequate seizure control for participation in EP0060, and is able to comply with all study requirements including admission to the health care facility, multiple blood draws, and iv infusions. Subject (or parent[s] or legal representative) is willing to comply with all study requirements.
10. Subject has been prescribed oral VIMPAT at a dose of 2mg/kg/day to 12mg/kg/day (for subjects <50kg) or 100mg/day to 600mg/day (for subjects ≥50kg).
11. Subject has been prescribed oral VIMPAT for the treatment of epilepsy for at least 1 month prior to Screening and has not been prescribed or maintained on VIMPAT for the purposes of participating in EP0060. Prescribed oral VIMPAT dose must be stable for at least 7 days, and intake of the prescribed total daily dose confirmed for at least 3 days prior to first infusion.
12. If the subject is on a concomitant AED, the daily dosage regimen of AED therapy must be kept constant for a period of at least 1 week prior to Screening. VNS is allowed, but settings must be kept constant for a period of at least 1 week prior to Screening.

The following inclusion criterion has been deleted:

4. Subject must be a minimum of 4kg in body weight.

And the following inclusion criterion has been added:

5. Subject is participating in a long-term, open-label study with LCM or is currently prescribed oral VIMPAT and needs to undergo a procedure, is admitted to an EMU or health care facility, or other situations where iv administration of LCM is clinically appropriate.

Change #16

Section 6.2 Exclusion criteria

6. Subject who do not have a diagnosis of epilepsy.

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

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

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

Have been changed to:

5. Subject does not have a diagnosis of epilepsy.

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

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

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

And the following exclusion criteria have been deleted:

2. Subject, in the investigator's opinion, would be expected to stay in the hospital or on iv LCM longer than 5 days.

18. Subject has been treated with vigabatrin for at least 12 months prior to entering EP0060 and has experienced any toxicity issues with this treatment. Note: Any subject who is currently treated with vigabatrin, and has received vigabatrin for a period of less than 12 months, is excluded from EP0060. Subjects who have received vigabatrin in the past must have documentation of an assessment for visual field defects after completion of vigabatrin therapy.

Change #17

Section 7.2 Treatment(s) to be administered

Treatment Period (up to 5 days)

During the Treatment Period, iv LCM will be administered twice daily at 12-hour intervals, once in the morning and once in the evening. The iv LCM dose will be equivalent (mg-for-mg) to the subject's current stable oral LCM dose or prescribed oral VIMPAT dose (always in bid regimen) of 2 to 12mg/kg/day or 100 to 600mg/day. The first iv LCM dose will be given on Day 1.

A calibrated infusion pump should be used for delivering the iv LCM dose at a constant rate over the target duration defined for the cohort. A previously unused vial must be administered for each dose. Dilution is not required prior to administration of iv LCM. If needed to obtain a total volume compatible with the specified infusion duration, the iv LCM solution can be diluted; iv LCM is compatible with the following diluents: dextrose 5%, lactated ringers, and normal saline (NaCl 0.9%). The total volume of diluent should be calculated not to exceed a total volume of fluid intake/day of 100mL/kg body weight. Intravenous LCM administration should be completed within 4 hours after dilution.

For subjects enrolled into Cohort 1, iv LCM should be infused as follows:

- Over a target duration of 30 minutes but no longer than 60 minutes whenever possible.

After review of the Cohort 1 data, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 2:

- EITHER 15 minutes but no longer than 30 minutes whenever possible,
- OR 30 minutes but no longer than 60 minutes whenever possible.

If the 30 minutes but no longer than 60 minutes infusion duration is repeated, enrollment into the study will be stopped once Cohort 2 has completed. If the Cohort 2 infusion is initiated at 15 minutes but no longer than 30 minutes duration, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 3:

- EITHER 15 minutes but no longer than 30 minutes whenever possible,
- OR 30 minutes but no longer than 60 minutes whenever possible.

When necessary for the safety of the subject or when the investigator deems it appropriate, the iv LCM dose can be modified after 1 day, once the Day 1 PK samples are taken.

A subject cannot receive iv LCM for more than 5 days in EP0060. Once the subject has completed the Treatment Period (up to 10 infusions from Day 1 to Day 5 of iv LCM), the subject will need to discontinue EP0060. If a subject requires iv LCM treatment for more than 5 days, the subject will need to discontinue EP0060. Subjects who were enrolled in a long-term, open-label study may be eligible to resume participation in that study, according to the protocol requirements. If subjects need to discontinue LCM, the subjects should be tapered off LCM gradually as specified in their long-term, open-label study. This taper should occur as a part of the long-term, open-label study.

Subjects who were prescribed oral VIMPAT should continue AED treatment at the discretion of the treating physician.

Has been changed to:

Treatment Period (up to 5 days)

During the Treatment Period, iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 5 days. The iv LCM dose will be equivalent (mg-for-mg) to the subject's current stable oral LCM dose or prescribed oral VIMPAT dose (always in bid regimen) of 2 to 12mg/kg/day or 100 to 600mg/day. The first iv LCM dose will be given on Day 1.

A calibrated infusion pump should be used for delivering the iv LCM dose at a constant rate over the target duration defined for the cohort. A previously unused vial must be administered for each dose. Dilution is not required prior to administration of iv LCM. If needed to obtain a total volume compatible with the specified infusion duration, the iv LCM solution can be diluted; iv LCM is compatible with the following diluents: dextrose 5%, lactated ringers, and normal saline (NaCl 0.9%). The total volume of diluent should be calculated not to exceed a total volume of fluid intake/day based on the Holliday-Segar equation as follows:

- For children weighing ≤10kg: 100mL/kg body weight
- For children weighing >10 to ≤20kg: 1000mL + 50mL/kg for each kg body weight ≥10kg

- For children weighing ≥20kg: 1500mL + 20mL/kg for each kg body weight ≥20kg

Intravenous LCM administration should be completed within 4 hours after dilution.

For the first 10 subjects ≥12 to <17 years of age enrolled into Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

The duration of infusion for the remaining subjects in Cohort 1 and subsequent cohort(s) will be based on DMC recommendation:

- 30 minutes but no longer than 60 minutes whenever possible,
- OR 15 minutes but no longer than 30 minutes whenever possible.

Further details on the timing on DMC recommendations regarding infusion duration are provided in Section 12.7.2.

When necessary for the safety of the subject or when the investigator deems it appropriate, the iv LCM dose can be modified after the first infusion, once the Day 1 PK samples have been taken.

A subject cannot receive iv LCM for more than 5 days in EP0060. If a subject requires iv LCM treatment for more than 5 days, the subject may continue on iv VIMPAT, but he/she will need to discontinue EP0060. Subjects who were enrolled in a long-term, open-label study may be eligible to resume participation in that study, according to the protocol requirements. If subjects need to discontinue LCM, the subjects should be tapered off LCM gradually as specified in their long-term, open-label study. This taper should occur as a part of the long-term, open-label study.

Subjects who were prescribed oral VIMPAT should continue AED treatment at the discretion of the treating physician.

Change #18

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

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

The following concomitant medications that influence the central nervous system are prohibited during EP0060:

- Neuroleptics
- MAOIs

Subjects who have been treated with ethosuximide are excluded from the study. Concomitant use of either vigabatrin or ethosuximide during the course of the study is prohibited.

Therapy which 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 therapy that is expressly not permitted. In such cases, the subject's participation in EP0060 will be discontinued.

Has been changed to:

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

Use of MAOIs is prohibited during EP0060.

Therapy which 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 therapy that is expressly not permitted. In such cases, the subject's participation in EP0060 may be discontinued.

Change #19

Section 7.8.2 Rescue medication

The use of oral or rectal benzodiazepines is restricted to intermittent use as rescue medication.

Has been deleted

Change #20

Section 8 STUDY PROCEDURES BY VISIT

The following subheadings have been added:

8.1 Screening/Baseline Period

8.2 Treatment Period

8.4 End-of-Study Period

Change #21

Section 8.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline

Prior to the conduct of any study related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent form. When possible, or as required by the local IRB/IEC, an IRB/IEC-approved written Assent form will also be properly executed and documented. During the Screening Period, subjects will be evaluated for their suitability for enrollment. The Screening Period assessments may be conducted on more than 1 day and begin up to 7 days prior to Day 1 (Visit 1a). Screening may also occur 1 day prior to Day 1 (Visit 1b) provided all test results are available and reviewed to assess inclusion and exclusion criteria prior to enrollment/treatment in the study. Oral LCM will be administered in accordance with each subject's current stable LCM dosage regimen of 2 to 12mg/kg/day or 100 to 600mg/day. For subjects enrolled in a long-term open-label study, the oral LCM will be taken from the long-term open-label study supply. For subjects who have been prescribed VIMPAT, oral LCM will be taken from the subject's prescribed VIMPAT supply.

When necessary for the well-being of the subject or when the investigator deems it appropriate, the hospitalization, screening laboratories, and the first iv LCM infusion can start on the same day provided all results are available and reviewed for inclusion/exclusion criteria prior to the start of infusion/treatment.

Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria and the results of the following pretreatment assessments at Visit 1a:

- Height, weight, and body mass index (BMI)
- Medical procedures
- Procedure history
- Diagnosis of epilepsy
- Childbearing potential
- Medical history update for subjects from long-term open-label studies, or complete medical history for subjects receiving prescribed VIMPAT
- Lacosamide dosing history (including time and quantity during the last 3 days)
- Prior and concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- Pregnancy testing for subjects of childbearing potential will be serum testing at the Screening Visit for subjects who are prescribed VIMPAT and urine testing for subjects enrolled in long-term, open-label studies
- Withdrawal criteria
- Complete neurological examination
- Complete physical examination
- Blood sample for clinical chemistry and hematology
- Vital signs (BP and pulse) assessment
- 12-lead ECG
- AE reporting (AEs occurring since signature of Informed Consent form). Ongoing AEs from the long-term open-label studies will be followed, as well as recording of new AEs during EP0060.
- ILAE (International League against Epilepsy) seizure classification
- Admission to the unit
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)
- Signs and symptoms of depression for subjects <6 years of age
- The following assessments will be carried out at Visit 1b if Screening and Baseline occur on separate days:
- Verification that the subject continues to meet the inclusion criteria
- Lacosamide dosing history (including time and quantity during the last 3 days)

- Prior and concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- AE reporting (AEs occurring since signature of Informed Consent form)
- Blood sample for clinical chemistry and hematology
- Withdrawal criteria
- Vital signs (BP and pulse) assessment
- 12-lead ECG
- Admission to the unit
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)
- Signs and symptoms of depression for subjects <6 years of age

Has been changed to:

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent form. When possible, or as required by the local IRB/IEC, an IRB/IEC-approved written Assent form will also be properly executed and documented. During the Screening Period, subjects will be evaluated for their suitability for enrollment. The Screening Period assessments may be conducted on more than 1 day and begin up to 7 days prior to Day 1 (Visit 1a). When necessary for the well-being of the subject or when the investigator deems it appropriate, the Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion (Day 1) provided all test results are available and reviewed to assess inclusion and exclusion criteria prior to enrollment/treatment in the study. Oral LCM will be administered in accordance with each subject's current stable LCM dosage regimen of 2 to 12mg/kg/day or 100 to 600mg/day. For subjects enrolled in a long-term open-label study, the oral LCM will be taken from the long-term open-label study supply. For subjects who have been prescribed VIMPAT, oral LCM will be taken from the subject's prescribed VIMPAT supply.

Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria at Visit 1a and/or Visit 1b. The following pretreatment assessments will be carried out at Visit 1a:

- Height and weight
- Medical procedures
- Procedure history
- Diagnosis of epilepsy

- Childbearing potential
- Medical history update for subjects from long-term open-label studies, or complete medical history for subjects receiving prescribed VIMPAT
- Lacosamide dosing history (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Prior and concomitant medication(s) assessment (prior medications will only be collected for direct-enroll subjects; concomitant medications from the long-term open-label studies will be followed, as well as the recording of new concomitant medications during EP0060 for all enrolled subjects)
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- Pregnancy testing for subjects of childbearing potential will be serum testing at the Screening Visit for subjects who are prescribed VIMPAT and urine testing for subjects enrolled in long-term, open-label studies
- Withdrawal criteria
- Complete neurological examination
- Complete physical examination
- Blood sample for clinical chemistry and hematology
- Vital signs (BP and pulse rate) assessment
- 12-lead ECG
- AE reporting (AEs occurring since signature of Informed Consent form). Ongoing AEs from the long-term open-label studies will be followed, as well as recording of new AEs during EP0060.
- ILAE (International League against Epilepsy) seizure classification
- Admission to the unit
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)
- The following assessments will be carried out at Visit 1b if Screening and Baseline occur on separate days:
- Verification that the subject continues to meet the inclusion criteria
- Lacosamide dosing history (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Prior and concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings

- AE reporting (AEs occurring since signature of Informed Consent form)
- Blood sample for clinical chemistry and hematology
- Withdrawal criteria
- Vital signs (BP and pulse rate) assessment
- 12-lead ECG
- Admission to the unit
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)

Change #22

Section 8.2 Visit 2 (Day 1)

Intravenous LCM infusion treatment will begin at this visit and the following assessments will be carried out. Screening laboratory assessments may be conducted up to the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion.

- Confirmation of inclusion criteria and exclusion criteria
- Intravenous LCM infusion
- Prior and concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- Withdrawal criteria
- AE reporting
- 12-lead ECG (prior to iv LCM infusion and at 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Vital signs of BP and pulse rate (5 minutes prior to iv LCM infusion and at 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Blood sample for LCM PK (Blood draws will be performed on the arm opposite the arm where the iv LCM infusion will be administered. An indwelling cannula used for the iv LCM infusion may not be used for PK blood sampling.)
- C-SSRS (for subjects ≥6 years of age)
- Signs and symptoms of depression for subjects <6 years of age
- Intravenous LCM infusion and the following assessments will be carried out during the evening (PM) at approximately 12 hours after the start of the AM infusion:
- Intravenous LCM infusion
- Concomitant medication(s) assessment

- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- AE reporting
- 12-lead ECG (prior to iv LCM infusion and at 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Vital signs of blood pressure and pulse rate (5 minutes prior to iv LCM infusion and at 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Withdrawal criteria
- Signs and symptoms of depression for subjects <6 years of age

Has been changed to:

Section 8.2.1 Visit 2 (Day 1)

Intravenous LCM infusion treatment will begin at this visit, and iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 5 days. Screening laboratory assessments may be conducted up to and including the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion. The following assessments will be carried out:

- Intravenous LCM infusion
- Medical procedures and medical history update
- Prior and concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- Withdrawal criteria
- AE reporting
- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Blood sample for LCM PK (Blood draws will be performed on the arm opposite the arm where the iv LCM infusion will be administered at the time points described in Section 9). An indwelling cannula used for the iv LCM infusion may not be used for PK blood sampling.)
- C-SSRS (for subjects ≥6 years of age)
- The second iv LCM infusion will be administered at approximately 12 hours after the start of the first infusion, and the following assessments will be carried out:
- Intravenous LCM infusion
- AE reporting

- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Withdrawal criteria

Change #23

Section 8.3 Visit 3 (Day 2 to Day 5)

Assessments for Visit 3 (Day 2 to 5) are the same as those described for Visit 2 (Day 1) in Section 8.2.

Has been changed to:

Section 8.2.2 Visit 3 (Day 2 to Day 5)

If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed each day of iv LCM treatment in EP0060. Assessments for Visit 3 (Day 2 to 5) are the same as those described for Visit 2 (Day 1) in Section 8.2. Blood samples for LCM PK will be obtained before and after the final iv LCM infusion at the time points described in Section 9. In addition, during the course of the study, additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

Change #24

Section 8.4 Unscheduled Visit

The following assessments will be carried out during the Unscheduled Visit:

- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose) and/or VNS settings
- AE reporting
- 12-lead ECG
- Blood pressure and pulse rate
- Blood sample for LCM PK (Blood draws will be performed on the arm opposite the arm where the iv LCM infusion will be administered. An indwelling cannula used for the iv LCM infusion may not be used for PK blood sampling)
- Withdrawal criteria
- C-SSRS (for subjects ≥6 years of age). The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.
- Signs and symptoms of depression for subjects <6 years of age

Has been changed to:

Section 8.3 Unscheduled Visit

The following assessments will be carried out during the Unscheduled Visit:

- Medical procedures and medical history update
- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose) and/or VNS settings
- AE reporting
- 12-lead ECG
- BP and pulse rate
- Blood sample for LCM PK (Blood draws will be performed on the arm opposite the arm where the iv LCM infusion will be administered. An indwelling cannula used for the iv LCM infusion may not be used for PK blood sampling)
- Withdrawal criteria
- C-SSRS (for subjects ≥6 years of age). The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Change #25

Section 8.5 Final Visit (Day 2 to 6)/Termination Visit

The following assessments will be carried out the day after the last dose of iv LCM for subjects who complete the study, discontinue the study or withdraw from the study prematurely:

- Concomitant medication(s) assessment
- Pregnancy testing for subjects of childbearing potential
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose) and/or VNS settings
- AE reporting
- Complete physical examination
- Complete neurological examination
- Blood sample for clinical chemistry and hematology
- 12-lead ECG
- Blood pressure and pulse rate
- Withdrawal criteria
- Oral LCM administration

- C-SSRS (for subjects ≥6 years of age) if the Unscheduled Visit is due to an AE
- Signs and symptoms of depression for subjects <6 years of age
- Discharge from the unit

Has been changed to:

Section 8.4.1 Final Visit (Day 2 to 6)/Termination Visit

The following assessments will be carried out the day after the last dose of iv LCM for subjects who complete the study, discontinue the study, or withdraw from the study prematurely:

- Medical procedures and medical history update
- Concomitant medication(s) assessment
- Pregnancy testing for subjects of childbearing potential
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose) and/or VNS settings
- AE reporting
- Complete physical examination
- Complete neurological examination
- Blood sample for clinical chemistry and hematology
- 12-lead ECG
- BP and pulse rate
- Withdrawal criteria
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)
- Discharge from the unit

Change #26

Section 8.6 Follow-Up Period (Day 2 to Day 9)

One or 2 days after the last dose of iv LCM in the Treatment Period, a safety follow-up/telephone assessment will be conducted during the Follow-Up Period (2 to 9 days after Visit 2/Day 1). The following assessments will be collected:

Concomitant medication(s) assessment

AE reporting

Oral LCM administration

During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

Has been changed to:

Section 8.4.2 Telephone Contact (Day 2 to Day 9)

One or 2 days after the Final Visit, a safety follow-up/telephone assessment will be conducted during the End-of-Study Period (2 to 9 days after Visit 2/Day 1). The following assessments will be collected:

- Medical procedures and medical history update
- Concomitant medication(s) assessment
- AE reporting
- Oral LCM administration

During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

Change #27

Section 9 ASSESSMENT OF PHARMACOKINETICS

Blood samples for the determination of LCM and SPM12809 concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). In each case, the time the subject received the most recent dose of study medication and the time of blood sampling must be recorded.

During the Treatment Period, plasma samples will be taken for LCM determination after ECG and vital signs have been taken from the opposite arm in which the solution for infusion was administered on Day 1 and Day 5/Early Termination at the following time points:

- Predose (within 1 hour prior to iv LCM dose)
- Post dose (within 1 to 4 hours after end of iv LCM infusion)
- Final Treatment Visit (within 1 hour prior to the first iv LCM dose and 1 to 4 hours after the second iv LCM dose)

The study-related blood loss (including any losses in the maneuver), per study subject, will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90mL/kg body weight; 3% is 2.4mL of blood per kg of body weight. With today's microanalytical techniques, plasma samples for drug level determinations can be small, with less than 1mL needed.

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

Has been changed to:

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). In each case, the time the subject received the most recent dose of study medication and the time of blood sampling must be recorded.

During the Treatment Period, plasma samples will be taken for LCM and SPM 12809 determination after ECG and vital signs have been taken. Plasma samples will be obtained from the opposite arm in which the solution for infusion was administered, at the following time points:

First iv LCM infusion (Day 1):

- Predose (within 1 hour prior to iv LCM dose)
- Postdose (within 1 to 4 hours after end of iv LCM infusion)
- Final iv LCM infusion (Day 2 to 5/Early Termination):
- Predose (within 1 hour prior to iv LCM dose)
- Postdose (within 1 to 4 hours after end of iv LCM infusion)

Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

The study-related blood loss (including any losses in the maneuver), per study subject, will not exceed 3% of the total blood volume during a period of 4 weeks and will not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90mL/kg body weight; 3% is 2.4mL of blood per kg of body weight. With today's microanalytical techniques, plasma samples for drug level determinations can be small, with less than 1mL needed.

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

Change #28

Section 10.1.1.1 Signs and symptoms of depression

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

Section has been deleted

Change #29

Section 10.1.6 Pregnancy, bullets

- The subject should be withdrawn from the study.
- The subject should immediately stop the intake of iv LCM or be down-titrated as instructed at the early discontinuation visit.

- A Safety Follow-Up Visit should be scheduled 1 to 2 days after the subject has discontinued her iv LCM infusion.

Have been changed to:

- The subject may need to discontinue iv LCM. The decision to stop the intake of iv LCM will be at the discretion of the investigator.
- A Safety Follow-Up Visit should be scheduled 1 to 2 days after the subject has discontinued her iv LCM infusion.

Change #30

Section 10.7.1 Vital signs, body weight, height and BMI

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

Has been changed to:

Section 10.7.1 Vital signs, body weight, and height

Noninvasive measurements of BP (systolic and diastolic) and pulse rate will be performed after at least 3 minutes at rest, when feasible, according to the tabular schedule of study assessments (Section 5.2). Body weight will be determined without shoes and wearing light clothing, and height will be measured without shoes; body weight and height will be assessed according to the tabular schedule of study procedures (Section 5.2).

Change #31

Section 10.7.2 12-lead ECG, paragraph 2

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording, when feasible.

Has been changed to:

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest at least 5 minutes prior to each recording and should be motionless during the recording, when feasible.

Change #32

Section 10.7.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well

as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Table 5-1).

The C-SSRS is not validated and will not be used for subjects <6 years of age. Signs and symptoms of depression for subjects <6 years of age will also be assessed whenever a C-SSRS assessment is performed. 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.

Has been changed to:

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Table 5-1). All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version used at subsequent visits.

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

Change #33

Section 12 STATISTICS

Selected disposition, exposure, demographic, and Baseline summaries will be presented by cohort and all subjects overall. Descriptive statistics will be displayed to provide an overview of the Baseline characteristics, pharmacokinetic, and safety results. For categorical variables, these will consist of the number and percentage of subjects in each category. The denominator and percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous variables, display of descriptive statistics will generally include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

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

Has been changed to:

Selected disposition, exposure, demographic, and Baseline summaries will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Descriptive statistics will be displayed to provide an overview of the Baseline characteristics, PK, and safety results.

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

Change #34

Section 12.3 Planned pharmacokinetic analyses

Descriptive statistics for LCM plasma concentrations, including but not limited to geometric mean and coefficient of variation (CV%), will be computed for pre-infusion and post-infusion time points on each infusion day where LCM plasma is collected.

If an adequate number of samples are collected on Day 5, then statistical comparisons between trough plasma concentrations from Day 1 and Day 5 as well as post-infusion plasma concentrations from Day 1 and Day 5 will be performed.

Has been changed to:

Descriptive statistics for LCM and SPM 12809 plasma concentrations, including but not limited to geometric mean and CV, will be computed for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected.

Change #35

Section 12.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary efficacy, key safety, or PK/PD outcomes (if applicable) for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

Has been changed to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary safety outcomes (if applicable) for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

Change #36

Section 12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of each cohort.

Has been changed to:

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 10 subjects in each cohort.

Change #37

Section 12.7.1 Definition of stopping rules

No formal stopping rule will be applied. The DMC may give a recommendation to stop the study after reviewing the safety data for Cohort 1 or Cohort 2. A recommendation for stopping should be based on the collective experience of the DMC members. After meeting to review data from each cohort, the DMC will provide a recommendation in writing, regarding whether to continue or to stop the study. UCB will consider this recommendation and ensure the study investigators are informed of the sponsor's decision on how to continue as described below.

Has been changed to:

No formal stopping rule will be applied. The DMC may give a recommendation to stop the study after reviewing the safety data as described in 12.7.2. A recommendation for stopping should be based on the collective experience of the DMC members. After meeting to review data from each cohort, the DMC will provide a recommendation in writing regarding whether to continue or to stop the study. UCB will consider this recommendation and ensure the study investigators are informed of the sponsor's decision on how to continue as described below.

Change #38

Section 12.7.2 Data Monitoring Committee

The DMC members will be defined in the DMC charter. After completion of Cohort 1, enrollment into EP0060 will be temporarily put on hold to allow for a DMC review of the safety and tolerability data from Cohort 1. Based on the review of the Cohort 1 data, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 2.

The DMC will reconvene after the completion of Cohort 2. If the Cohort 2 target infusion duration was 30 minutes but no longer than 60 minutes, enrollment into the study will be stopped once Cohort 2 has completed. If the Cohort 2 target infusion duration was 15 minutes but no longer than 30 minutes, the DMC will make a recommendation for the target infusion duration to be evaluated in Cohort 3. After completion of Cohort 3, the DMC will reconvene to review the final data to provide their overall impression.

Has been changed to:

The DMC members will be defined in the DMC charter.

EP0060 will begin with Cohort 1, where at least 20 subjects ≥12 to <17 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 1, enrollment into Cohort 1 will be temporarily put on hold to allow for the DMC review of the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥8 to <12 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, enrollment into Cohort 2 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 2 should be stopped,
- AND whether Cohort 3 can be initiated.

For Cohort 3, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 3, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 3, enrollment into Cohort 3 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1, Cohort 2, and Cohort 3. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 3 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

Change #39

Section 12.8 Determination of sample size

No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

Has been changed to:

Approximately 75 subjects will be enrolled, which includes up to 3 cohorts of at least 20 subjects. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

Change #40

Section 17 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Clinical Project Manager

[redacted]

_____
Date/Signature

Clinical Trial Biostatistician

[redacted] **MPH**

_____
Date/Signature

Study Physician

[redacted]**, MD**

_____
Date/Signature

Clinical Program Director

[redacted]

_____
Date/Signature

Has been changed to (and became Section 18):

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.

16.2 Protocol Amendment 2

Rationale for the amendment

The primary purpose of this substantial amendment is to maximize the patient pool used in the evaluation of the safety of iv LCM in pediatric subjects. Thus, enrollment has been opened to include OLL and RxL subjects who are on a stable dose of oral LCM and elect to receive iv LCM as well as IIL subjects who are not currently taking LCM and initiate adjunctive LCM treatment using iv LCM. This amendment has also included the option for RxL and IIL subjects to continue oral LCM treatment in SP848, if clinically appropriate, after completion of iv LCM in EP0060. Given this option for RxL and IIL subjects, 2 visits were added to the study design. If required, a Transition Visit has been add for RxL and IIL subjects transitioning to SP848 and requiring up to 7 days for scheduling of additional assessments to be performed during EP0060. If not transitioning to SP848, an additional telephone contact visit has been added approximately 30 days after last infusion to collect final safety data.

In order to provide treatment continuity, a short-term oral LCM solution may be dispensed to RxL and IIL subjects eligible for SP848 enrollment in the event that additional time is needed to schedule the Transition Visit.

Enrollment from EP0012 has been removed as has enrollment from future pediatric studies.

The study design was changed to merge the previous Cohort 1 (≥12 to <17 years of age) and Cohort 2 (≥8 to <12 years of age) into 1 cohort spanning the age range of ≥8 to <17 years of age while maintaining the combined planned enrollment for this age group. The decision to combine these 2 age groups is supported by the following 3 considerations: PK modeling, growth chart information, postmarketing safety assessment of iv LCM use, and a recent publication (Arkilo, et al 2016).

- In the oral and iv LCM PK pediatric modeling CL0266, simulations of iv LCM infused over durations of 15 to 60 minutes suggest that exposure is similar to oral administration. These results are consistent with the LCM PK profile and bioequivalence of iv and oral LCM established in adults. Thus, using the weight-based dosing adaptations for LCM adjunctive therapy, it is predicted that the LCM concentration at steady-state in pediatric subjects with partial-onset seizures will be similar to that in adults for both oral and iv LCM. Based on the PK modeling, the use of iv LCM is expected to be [redacted] in the pediatric patient population down to 4 years of age.
- Based on the Centers for Disease Control and Prevention (CDC) growth charts for weight-for-age percentiles (2 years to 20 years of age), the ages at which a child reaches the 50th percentile at a weight of 50kg are 13.82 years for boys and 14.21 years for girls (http://www.cdc.gov/growthcharts, 2000). Therefore, average pediatric patients weighing 50kg are approximately 2 to 3 years younger than the currently approved lower limit for age for VIMPAT (16 years [EU] or 17 years [US]). Based on PK modeling, LCM exposure in pediatric subjects weighing 50kg or more is predicted to be the same as exposure observed in adults.
- Postmarketing data were evaluated for the period from 01 Aug 2008 to 30 Nov 2015, and 49 cases were identified for iv LCM formulation use in the pediatric population (in

patients 4 to <16 years of age). Based on review of these cases, no new safety concerns were identified.

- Arkilo and colleagues examined use of iv LCM in 47 infants and children from 4 months to <12 years of age, and this study included use in nonapproved indications (ie, status epilepticus) (Arkilo, et al 2016). Evaluation of adverse effects was not possible for the 11 subjects in status epilepticus. Five of remaining 36 subjects experienced sedation, and no new safety concerns were noted in this evaluation.

Taken together, along with our knowledge of the safety of oral LCM in children down to 4 years of age, enrollment of children ≥8 to <17 years of age within the same cohort should not present a significant safety risk and should allow earlier benefit of access to the iv LCM option of treatment for those subjects who are ≥8 to <12 years of age. Initiation of the assessment of safety in patients ≥4 to <8 year olds will remain dependent on review of safety data from Cohort 1 by the DMC.

To accommodate these changes, revisions have been made to the inclusion/exclusion criteria, schedule of assessments, LCM dosing, and statistical analyses.

Additional changes have been implemented for consistency with other protocols in the LCM pediatric program and updated language in protocol template regarding monitoring for potential drug-induced liver injury events.

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

At the time of approval of this amendment, no subjects were enrolled in EP0060.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Define the 3 subject populations that are eligible for enrollment into EP0060:
  - Open-label LCM (OLL) subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
  - Prescribed-LCM (RxL) subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
  - Initiating iv LCM (IIL) subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.
- Revise the subject population who will receive iv LCM as follows:
  - Replacement for oral LCM treatment (OLL and RxL subjects):
    - Clinical need administration: Subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral

administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.

- Elective administration: Subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

– Adjunctive iv LCM treatment initiation (IIL subjects):

- Clinical need administration: Subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
- Elective administration: Subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

- Enrollment from EP0012 has been removed.
- New published data regarding use of iv LCM in children was added to the Introduction.
- As a result of extending the eligible subject population to subjects initiating treatment, the primary study objective was modified as follows to remove stable oral LCM dose:
  – The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy.
- Safety variables were clarified as either primary or other variables.
- Text was added to clarify that IIL subjects will not receive oral LCM during the Screening/Baseline Period.
- The design of the study was changed such that the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.
- The age-staggered approach to enrollment has been modified from 3 cohorts to 2 cohorts while maintaining the overall number of planned subjects, which also modified the timing of the DMC reviews as follows:

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator, Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator, Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
- OR Cohort 2 should be stopped,
- AND whether to initiate the assessment of safety in younger pediatric subjects (≥1 month to <4 years of age).
- Modifications for the number and dose of iv LCM treatment(s) were incorporated as follows:
  - The number of required infusions was reduced from 2 to 1.
  - Text was added to clarify the starting iv LCM dose to be administered to subjects initiating adjunctive LCM therapy.
- Include the option for RxL and IIL subjects to continue oral LCM treatment after completion of iv LCM; if determined clinically appropriate; these subjects will be given the option to continue oral LCM treatment in SP848.
  - Inclusion of this option added a Transition Visit for arrangement of SP848 entry assessments.

  - Oral LCM solution will be dispensed only to those RxL and IIL subjects who are interested and eligible to enroll in SP848 in the event the additional time is required for arrangement of the Transition Visit.

- The options for RxL and IIL subjects to continue LCM treatment in SP848 resulted in changing the study periods as follows:
  - For all subjects:
    - Screening and/or Baseline Period (up to 7 days),
    - Treatment Period
      (1) Clinical need administration: up to 10 doses or up to 5 days
      (2) Elective administration: up to 2 consecutive doses over approximately 24 hours
    - End-of-Study/Final Visit (1 day),
    - End-of-Study/Telephone Contact 1 (1 to 3 days),
  - Additional visits or contacts as follows:
    - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
      -Transition Visit which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
    - - RxL and IIL subjects who do not continue LCM treatment in SP848
      -End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).
- Modifications to maximum study duration were incorporated as follows:
  - Approximately 16 days:
    - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
  - Approximately 23 days
    - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
  - Approximately 45 days:
    - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.
- Anticipated regions for the study were updated to North America and Europe with possibility for expansion into other regions.
- The following changes and clarifications were made to planned assessments:
  - All pregnancy tests will be conducted on urine samples.

- Medical history or medical history update will only occur at Screening/Baseline.
- Information regarding ILAE classification will no longer be collected.
- LCM dosing information since the Treatment Period will be collected at TC1, Transistion Visit (if applicable), and TC2 (if applicable).
- Information will be collected regarding use of ketogenic diet.
- The PK samples (predose [OLL and RxL] and postdose [all subjects]) remained required for the first LCM infusion. Collection of PK samples (both predose and postdose for all subjects) from an additional iv LCM dose was changed to optional.
- If an Unscheduled Visit is due to an AE, the C-SSRS should be performed and collection of a PK blood sample is at the discretion of the investigator.
- Admission and discharge from unit were removed as hospitalization is not required for treatment.
- Seizure history was added at Screening for RxL and IIL subjects.
- Brief physical and brief neurological examinations were added during the Treatment Period.
- Clarification was added that brief physical examination, brief neurological examination, hematology/chemistry laboratory assessments, and C-SSRS should only be collected once per day during the Treatment Period.
- Text was added to clarify that the C-SSRS assessment should be performed once if the Screening and Baseline visits occur on the same day. If the Screening/Baseline and first infusion occur on the same day, the C-SSRS should be performed twice (predose and postdose).
- A Transition Visit was added to occur within 7 days of the Final Visit for RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848
  - The Final Visit and Transition Visit can occur on the same day.
  - Transition Visit in EP0060 and Visit 1 of SP848 should occur on the same day.
- Dispensing and collection of oral LCM solution was added for RxL and IIL subjects who are eligible and elect to continue oral LCM treatment in SP848.
- An additional telephone contact was added 30 days after last dose for RxL and IIL subjects who do not continue oral LCM treatment in SP848.
- Text was added to allow use of a local laboratory except for Final Visit. Central laboratory must be used for Final Visit.
- Text was added to permit the use of local laboratory results obtained for routine diagnostic and medical care whenever possible if collected no more than 24 hours prior to Screening/Baseline Visit in order to minimize blood loss associated with the study.
- Text was added to clarify the approach for LCM taper for RxL and IIL subjects.

- Time windows were added for collection of ECG and vital signs during the 2 hours after the start of infusion.
- Corrections were made in table to align with assessments listed in Section 8 of protocol.

- The inclusion and exclusion criteria were modified as follows:
  - Inclusion Criteria were reordered for a more logical flow.
  - An Inclusion Criterion was added (#4 in Amendment 2) which describes the study population to be enrolled, ie, OLL, RxL and IIL subjects.
  - Inclusion Criterion #4 (Amendment 1) has been amended such that adequate seizure control is no longer required as enrollment can now include subjects initiating adjunctive LCM treatment. The remainder of the previous criterion is now included in Amendment 2 Inclusion Criteria 6 and 7.
  - Inclusion Criterion #5 (Amendment 1) has been removed as enrollment can now include subjects initiating adjunctive LCM treatment.
  - Inclusion Criteria # 7 and #8 have been combined with Inclusion Criteria #10 and #11. In Amendment 2, these are contained within Inclusion Criterion 5.
  - Inclusion Criterion #9 (Amendment 1) has been deleted as only 1 dose is required.
  - Inclusion Criteria #10 and #11 (Amendment 1) have been reworded to incorporate and update the wording regarding stability of LCM dose from Inclusion Criterion #11 into Inclusion Criterion #10. These criteria were then folded into Inclusion Criterion 5 in Amendment 2.
  - Inclusion Criterion #12 (Amendment 1) has been deleted to remove requirements of concomitant AEDs.
  - Inclusion Criteria #5 (Amendment 2) includes requirements for subjects initiating adjunctive LCM treatment, including stable dose of other AEDs and permitted types of epilepsy.
  - Exclusion Criterion #3 has been revised to clarify investigator's assessment of hypotension and bradycardia.
  - Exclusion Criteria #5 and #16 (Amendment 1) have been deleted as epilepsy diagnosis is addressed within inclusion criteria.
  - Exclusion Criterion #6 (now Exclusion Criterion 5 in Amendment 2) has been reworded to clarify that subjects taking monoamine oxidase A inhibitors are excluded.

    Exclusion Criterion #8 (now Exclusion Criterion 7 in Amendment 2) has been revised to include medical condition impacting absorption since short-term oral LCM will be provided to eligible subjects entering SP848.
  - Exclusion Criterion #11 was removed and replaced by Exclusion Criterion #20. This criterion updates LFT exclusion criteria in line with current UCB standards.
  - Exclusion Criterion #17 (Amendment 1) has been deleted as felbamate is permitted in the long-term open-label studies for OLL subjects who may enroll in EP0060.

  - Exclusion Criterion #17 has been added since LCM has not been evaluated in the treatment of status epilepticus.
  - Exclusion Criterion #18 has been added to clarify that subjects with only Type IIA1 or Type IIA2 should not be enrolled.
  - Exclusion Criterion #19 was added to clarify that subjects with Dravet's syndrome are excluded from this study.
  - Exclusion Criterion #21 has been added to clarify that subjects enrolling to initiate adjunctive LCM treatment should not have received LCM during the past 3 months.
- Withdrawal criteria were modified in the following 4 ways:
  - Clarification was added that treatment should not go beyond 10 doses.
  - A withdrawal criterion was added such that any subject who initiated adjunctive LCM treatment and required a dose adjustment during the study should be withdrawn.
  - Addition language was added to incorporate Sponsor language surrounding LFT results and monitoring for PDILI events.
  - Clarification was added about the ability of subjects requiring more than 10 iv doses return to or enroll in the long-term open-label study pending discussion with and agreement from the Medical Monitor.
- Language regarding IMP labeling, handling and storage requirements, and drug accountability was updated to reflect new standard Sponsor text.
- Description of the short-term oral LCM supply was added, including under what circumstances it would be dispensed to RxL and IIL subjects.
- Language was added regarding oral dosing of LCM for RxL and IIL subjects who require short-term oral LCM supply in order to arrange for SP848 enrollment.
- Prohibited medications were updated to include cannibidiols not approved or indicated for epilepsy by local health authorities.
- Numbering of subjects was clarified for RxL and IIL subjects.
- Text was added to clarify reporting requirements for any suspected transmission of an infectious agent via a medicinal product to align with updated standard Sponsor text across programs.
- Potential Hy's law was added as an AE of special interest to align with updated standard Sponsor text across programs.
- New Sponsor text was added surrounding LFT monitoring to provide further detail regarding the evaluation, investigations, and follow up of PDILI events. This text is to align with FDA guidance for PDILI monitoring; addition of this language was not initiated on the basis of any new hepatic safety signal for LCM.
- A new analysis set was added to include all subjects who receive LCM (oral or iv).

- The planned PK and safety analyses were updated to include evaluation based on whether subject was receiving replacement treatment (OLL and RxL subjects) or initiating treatment (IIL subjects).
- The use of the term "admitted" has been replaced with "treated" to accurately reflect that treatment can occur at an EMU or healthcare facility and admission to a hospital is not required.
- Other changes made in this amendment are to provide clarification, are administrative in nature, or are to correct errors.

Specific changes

Change #1

Title page

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE AS REPLACEMENT FOR ORAL LACOSAMIDE IN CHILDREN (≥4 TO <17 YEARS OF AGE) WITH EPILEPSY

Has been changed to:

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN (≥4 TO <17 YEARS OF AGE) WITH EPILEPSY

Change #2

STUDY CONTACT INFORMATION

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Sponsor Study Physician

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Change #3

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Change #4

STUDY CONTACT INFORMATION

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Change #5

SERIOUS ADVERSE EVENT REPORTING

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

Has been changed to:

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

Change #6

LIST OF ABBREVIATIONS

ICH has been revised; DS, ILAE, and RDC have been deleted; and EDC, IH, OLL, PDILI, PS, and RxL were added.

Change #7

Section 1 SUMMARY

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous (iv) lacosamide (LCM) infusions as replacement for oral LCM in pediatric subjects ≥4 to <17 years of age with epilepsy. A separate Phase 2/3 study investigating the use of iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned. EP0060 will include subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure, be admitted to an epilepsy monitoring unit (EMU) or health care facility, or other situations where iv administration is clinically appropriate. Approximately 75 subjects, who are participating in a long-term, open-label study with LCM (SP848, EP0034, EP0012, or other future study) or who are currently prescribed VIMPAT® (LCM) will be enrolled. Pediatric subjects entering into EP0060 from a long-term, open-label study will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll directly into EP0060 will temporarily switch from their prescribed VIMPAT oral treatment to the iv LCM formulation. Subjects will be enrolled from approximately 40 sites in North America, Europe, Asia Pacific, and Latin America. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy, after temporarily switching from the equivalent stable oral LCM dose. EP0060 is planned to include up to 3 age-based cohorts of at least 20 subjects per cohort: ≥12 to <17 years (Cohort 1), ≥8 to <12 years (Cohort 2), and ≥4 to <8 years (Cohort 3). A Data Monitoring Committee (DMC) will review the safety and tolerability data for each cohort to make recommendations for the progression of subsequent cohort enrollment and iv infusion durations to be evaluated.

EP0060 is comprised of the following study periods:

- Screening and/or Baseline Period (up to 7 days),

- Treatment Period (up to 5 days),
- End-of-Study/Final Visit (1 day),
- End-of-Study/Telephone Contact (1 to 2 days).

During the Screening Period (Day -7 to Day -1), oral LCM will be administered in accordance with each subject's oral LCM dosage regimen. During the Treatment Period, subjects will receive iv LCM infusions twice daily (bid) at approximately 12-hour intervals for up to 5 days. The daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and detailed safety assessments will be performed. An End-of-Study/Final Visit will be conducted the day after the last dose of iv LCM after completion of or withdrawal from the Treatment Period. A safety follow-up Telephone Contact should occur 1 to 2 days after the End-of-Study/Final Visit.

The maximum study duration for an individual subject will be approximately 15 days. After completion of or discontinuation from EP0060, only subjects who enrolled into EP0060 from a long-term, open-label study will resume their participation in that study and resume oral LCM treatment accordingly. Subjects who were prescribed VIMPAT should continue antiepileptic drug (AED) treatment at the discretion of the treating physician.

EP0060 will begin with Cohort 1, where at least 20 subjects ≥12 to <17 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 1, enrollment into Cohort 1 will be temporarily put on hold to allow for the DMC review of the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥8 to <12 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, enrollment into Cohort 2 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,

- OR Cohort 2 should be stopped,
- AND whether Cohort 3 can be initiated.

For Cohort 3, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 3, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 3, enrollment into Cohort 3 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1, Cohort 2, and Cohort 3. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 3 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations.

Has been changed to:

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous (iv) lacosamide (LCM; VIMPAT®) infusions in pediatric subjects ≥4 to <17 years of age with epilepsy. Investigation the use of iv LCM in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned.

EP0060 will include approximately 75 subjects. The following subjects will be eligible for enrollment in EP0060:

- Open-label LCM (OLL) subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- Prescribed-LCM (RxL) subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- Initiating iv LCM (IIL) subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: Subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an epilepsy monitoring unit (EMU) or health

care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.

  - Elective administration: Subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: Subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: Subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation. Subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America and Europe. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy. EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including at least 20 subjects who are ≥4 to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. A Data Monitoring Committee (DMC) will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2) or separate study for the evaluation of iv LCM in children <4 years of age (as detailed further below).

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration: up to 10 doses or up to 5 days
    (2) Elective administration: up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),

  - End-of-Study/Telephone Contact 1 (1 to 3 days),

- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, 12-lead electrocardiogram [ECG], laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration. For OLL and RxL subjects, the daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg (subjects weighing <50kg) or 50mg (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg) or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and detailed safety assessments will be performed.

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion or withdrawal from the Treatment Period and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose if the last LCM infusion was performed in the morning, and time permits completion of assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM after completion of or withdrawal from the Treatment Period. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM

solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue antiepileptic drug (AED) treatment at the discretion of the treating physician. For RxL and IIL subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen or taper at the discretion of the treating physician.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator, Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator, Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
- OR Cohort 2 should be stopped,
- AND whether to initiate the assessment of safety in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

Change #8

Section 2 INTRODUCTION, first paragraph

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy–about 1% of the world's population (Dichek, 1999). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). The Institute of Medicine of the National Academies recently provided a review of the burdens of epilepsy, global incidence and prevalence of epilepsy, classification systems for seizure types and syndromes, gaps in information about epilepsy, and general recommendations (Institute of Medicine, 2012). In the past 2 decades, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

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 (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, classification systems for seizure types and

syndromes, gaps in information about epilepsy, and general recommendations (Institute of Medicine, 2012). In the past 2 decades, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation (VNS).

Change #9

Section 2 INTRODUCTION, fifth paragraph

Intravenous formulations are particularly helpful as short-term replacement of oral formulations for patients unable to take oral products (eg, preoperative and postoperative patients, patients with acute gastrointestinal disorders). Such formulations allow patients to be maintained on the same AED on their stable dose when they are unable to take the drug orally.

Has been changed to:

Intravenous formulations are particularly helpful as short-term replacement of oral formulations for patients unable to take oral products (eg, preoperative and postoperative patients, patients with acute gastrointestinal disorders). Such formulations allow patients to be maintained on the same AED on their stable dose when they are unable to take the drug orally. Intravenous formulations may also be helpful in the initiation of treatment in certain situations when the patient is unable to take oral medications.

Change #10

Section 2 Introduction, sixth paragraph

The iv formulation of LCM is approved in the US, EU, and several countries worldwide at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects with epilepsy when oral administration is temporarily not feasible. Intravenous LCM is approved in patients ≥16 years of age and for infusion durations of 15 to 60 minutes depending on the country-specific labeling.

Has been changed to:

In the US, the iv formulation of LCM is approved in patients ≥17 years of age at a maximum dose of 400mg/day as monotherapy and adjunctive therapy in the treatment of partial onset seizures in subjects with epilepsy when oral administration is temporarily not feasible. In EU, the iv formulation is approved in patients ≥16 years at a maximum dose of 600mg/day as monotherapy (EU CHMP positive opinion received on 11 Nov 2016) and at a maximum dose of 400mg/day as adjunctive therapy in the treatment of partial onset seizures in subjects with epilepsy when oral administration is temporarily not feasible. Intravenous LCM is approved in patients ≥16 years of age and for infusion durations of 15 to 60 minutes depending on the country-specific labeling.

Change #11

Section 2 INTRODUCTION, new seventh paragraph

Recently, a retrospective evaluation was conducted to examine the use of iv LCM in 47 infants and children from 4 months to <12 years of age (Arkilo et al, 2016). The median age across the 47 children was 6.5 years, and 18 children were <3 years of age. Intravenous LCM was administered as adjunctive treatment along with ≥2 other AED. Lacosamide dose levels ranged from 1 to 11mg/kg, and the infusion was given over 30 minutes. Fifteen of the children were administered iv LCM either as replacement treatment for oral maintenance dose (n=10) or to initiate maintenance dose (n=5). For the remaining children, iv LCM was used to treat acute exacerbation of seizure frequency (n=18), status epilepticus (n=11) or epilepsia partialis continua (n=3). Children were observed for at least 48 hours after infusion. The 11 children with status epilepticus were not able to respond to inquiries about adverse effects. Of the remaining 36 subjects, 5 experienced adverse effect of sedation which resolved in all 5 within 24 hours. No other observable adverse effects were noted. No cardiac events were noted during the infusions for the 80% of children who had ECG evaluation during the infusion. This study shows an initial positive benefit-risk profile for the use of iv LCM in infants and children from 4 months to <12 years of age.

Has been added

Change #12

Section 2 INTRODUCTION, seventh paragraph (now eighth paragraph)

The results of EP0060 will provide safety, tolerability, and PK data regarding the use of the iv LCM formulation as replacement for oral LCM in pediatric subjects ≥4 to <17 years with epilepsy.

Has been changed to:

The results of EP0060 will provide safety, tolerability, and PK data regarding the use of the iv LCM formulation either as replacement for oral LCM or for adjunctive LCM treatment initiation in pediatric subjects ≥4 to <17 years with epilepsy.

Change #13

Section 3 STUDY OBJECTIVE(S)

The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy, after temporarily switching from the equivalent stable oral LCM dose. An additional objective is to evaluate the PK of iv LCM replacement in pediatric subjects with epilepsy.

Has been changed to:

The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy. An additional objective is to evaluate the PK of iv LCM in pediatric subjects with epilepsy.

Change #14

Section 4.1 Primary variable(s) (now Primary safety variables)

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

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver (including parent/legal guardian) or observed by the investigator
- Subject withdrawals due to AEs
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (blood pressure [BP] and pulse rate)

Has been changed to:

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

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

Change #15

Section 4.2 Other safety variables

Other safety variables include the following:

- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (blood pressure [BP] and pulse rate)
- Changes in physical examinations
- Changes in neurological examinations

Has been added.

This change also shifted the numbering of the Section describing the Pharmacokinetic variables from Section 4.2 to Section 4.3.

Change #16

Section 5.1 Study description

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions as replacement for oral LCM in pediatric subjects ≥4 to <17 years of age with epilepsy. EP0060 will include subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure, be admitted to an EMU or health care facility, or other situations where iv administration is clinically appropriate. Approximately 75 subjects, who are participating in long-term, open-label studies with LCM or who are currently prescribed VIMPAT, will be enrolled. Pediatric subjects entering into EP0060 from a long-term, open-label study will temporarily suspend their

participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll directly into EP0060 will temporarily switch from their prescribed oral VIMPAT treatment to the iv LCM formulation. Subjects will not be prescribed or maintained on VIMPAT for the purposes of participating in EP0060. Subjects will be enrolled from approximately 40 sites in North America, Europe, Asia Pacific, and Latin America. Additional sites or regions may be added if deemed necessary.

EP0060 is planned to include up to 3 age-based cohorts of at least 20 subjects per cohort: ≥12 to <17 years (Cohort 1), ≥8 to <12 years (Cohort 2), and ≥4 to <8 years (Cohort 3). A DMC will review the safety and tolerability data for each cohort to make recommendations for the progression of subsequent cohort enrollment and iv infusion durations to be evaluated. Details regarding the DMC are provided in Section 12.7.2.

EP0060 is comprised of the following study periods:

- Screening and/or Baseline Period (up to 7 days),
- Treatment Period (up to 5 days),
- End-of-Study/Final Visit (1 day),
- End-of-Study/Telephone Contact (1 to 2 days).

During the Screening Period (Day -7 to Day -1), oral LCM will be administered in accordance with each subject's oral LCM dosage regimen. For subjects enrolled in a long-term, open-label study, the oral LCM will be administered from the long-term, open-label study supply. For subjects prescribed VIMPAT and enrolling directly into EP0060, oral LCM will be administered from the subject's prescribed VIMPAT supply.

Subjects will be under medical care at a healthcare facility for the duration of the iv LCM infusion treatment in EP0060. If necessary, the Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion. In this case, it is required that all screening procedures are performed and the results of examinations (ie, ECG) are available to allow verification of subject eligibility. During the Treatment Period, subjects will receive iv LCM infusion bid at approximately 12-hour intervals for up to 5 days. The daily dose of iv LCM will be the same as the subject's current stable bid dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). During the Treatment Period, blood samples will be obtained for PK analysis, and safety assessments will be performed (physical and neurological exams, pulse rate, BP, 12-lead ECG, clinical hematology and chemistry, and Columbia-Suicide Severity Rating Scale [C-SSRS] when applicable). An End-of-Study/Final Visit will be conducted the day after the last dose of iv LCM after completion of or withdrawal from the Treatment Period. A safety follow-up Telephone Contact should occur 1 to 2 days after the End-of-Study/Final Visit.

The maximum study duration for an individual subject will be approximately 15 days. After completion of or discontinuation from EP0060, subjects who enrolled into EP0060 from a long-term, open-label study will resume their participation in that study and resume oral LCM treatment accordingly. Subjects who were prescribed VIMPAT should continue AED treatment at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

EP0060 will begin with Cohort 1, where at least 20 subjects ≥12 to <17 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 1, enrollment into Cohort 1 will be temporarily put on hold to allow for the DMC review of the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥8 to <12 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, enrollment into Cohort 2 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 2 should be stopped,
- AND whether Cohort 3 can be initiated.

For Cohort 3, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 3, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 3, enrollment into Cohort 3 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1, Cohort 2, and Cohort 3. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 3 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations.

Has been changed to:

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric subjects ≥4 to <17 years of age with epilepsy. EP0060 will include approximately 75 subjects. The following subjects will be eligible for enrollment in EP0060:

- OLL subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- RxL subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- IIL subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation while subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America and Europe. Additional sites or regions may be added if deemed necessary.

EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including at least 20 subjects who are ≥4 to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. A DMC will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2) or separate study for the evaluation of iv LCM in children <4 years of age. Details regarding the DMC are provided in Section 12.7.2.

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration (see above in this Section): up to 10 doses or up to 5 days
    (2) Elective administration (see above in this Section): up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration. For OLL and RxL subjects, the daily

dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg (subjects weighing <50kg) or 50mg (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg) or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for PK analysis, and safety assessments will be performed (AEs, physical and neurological exams, pulse rate, BP, 12-lead ECG, clinical hematology and chemistry, and Columbia-Suicide Severity Rating Scale [C-SSRS] when applicable).

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion or withdrawal from the Treatment Period and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose if the last LCM infusion was performed in the morning, and time permits completion of assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM after completion of or withdrawal from the Treatment Period. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue AED treatment at the discretion of the treating physician. For RxL and IIL subjects who directly enrolled and will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen or taper at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

Change #17

Section 5.1.1 Study duration per subject, first paragraph

The maximum iv LCM exposure per subject will be up to 5 days with a total study duration of up to 15 days (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, and a safety follow-up Telephone Contact 1 to 2 days after the Final Visit).

Has been changed to:

For clinical need administration, the planned maximum iv LCM exposure will be up to 10 doses (or up to 5 days). For elective administration, the planned maximum iv LCM exposure will be up to 2 consecutive doses (over approximately 24 hours).

For OLL subjects, the planned maximum total study duration assuming clinical need administration will be approximately 16 days (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, and a safety follow-up Telephone Contact 1 at 1 to 3 days after the Final Visit).

For RxL and IIL subjects who will continue LCM treatment in SP848, the planned maximum total study duration assuming clinical need administration will be approximately 23 days to allow arrangement for assessments to transition to SP848 (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, safety follow-up Telephone Contact 1 at 1 to 3 days after the Final Visit, and the Transition Visit at 1 to 7 days after the last dose). The Final Visit and the Transition Visit may occur on the same day or separate days, depending on availability and scheduling.

For RxL and IIL subjects who will not continue LCM treatment in SP848, the planned maximum total study duration (assumes clinical need administration) will be approximately 45 days to allow for further safety follow-up (up to 7 days for screening, up to 5 days of treatment, 1 day for discharge/Final Visit, safety follow-up Telephone Contact 1 at 1 to 2 days after the Final Visit, and safety follow-up Telephone Contact 2 at 30 days [±2 days] after the last dose).

For those subjects electively receiving iv LCM, the above maximum total study durations are reduced by 4 days.

Change #18

Section 5.1.2 Planned number of subjects and site(s)

Approximately 75 subjects currently participating in long-term, open-label studies with LCM or who are currently prescribed VIMPAT will be enrolled at approximately 40 sites.

The following cohorts are planned:

- Cohort 1: at least 20 subjects from ≥12 to <17 years of age
- Cohort 2: at least 20 subjects from ≥8 to <12 years of age
- Cohort 3: at least 20 subjects from ≥4 to <8 years of age

The remaining subjects may be enrolled in any of the 3 cohorts.

Has been changed to:

Approximately 75 subjects will be enrolled at approximately 40 sites.

The following cohorts are planned:

- Cohort 1: at least 40 subjects from ≥8 to <17 years of age, with at least 20 subjects from ≥12 to <17 years of age and at least 20 subjects from ≥8 to <12 years of age
- Cohort 2: at least 20 subjects from ≥4 to <8 years of age

The remaining subjects may be enrolled in either of the 2 cohorts.

Change #19

Section 5.1.3 Anticipated regions and countries

The study will be conducted at selected sites from North America, Europe, Asia Pacific, and Latin America. Additional sites may be added as deemed necessary.

Has been changed to:

The study will be conducted at selected sites from North America and Europe. Additional sites may be added as deemed necessary.

Change #20

Table 5-1 Schedule of study assessments

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[c]	End-of-Study Period	
Visit	**V1a**	**V1b[a]**	**V2**	**V3[b]**		**Final Visit[d]**	**TC[e]**
Study Day	**-7 to -1**	**-1**	**1**	**2 to 5**		**2 to 6**	**2 to 9**
Written informed consent	X						
Inclusion/exclusion criteria	X	X[f]					
Demographics	X						
Medical procedures	X	X	X	X	X	X	X
Procedure history[g]	X						
Medical history/update[g]	X	X	X	X	X	X	X
Diagnosis of epilepsy[g]	X						
Childbearing potential[g]	X						
LCM dosing history[h]	X						
Prior and concomitant medications[i]	X	X	X	X	X	X	X
Concomitant AEDs/VNS settings	X	X	X	X	X	X	
Pregnancy testing[j]	X					X	
Withdrawal criteria	X	X	X	X	X	X	
AE reporting[k]	X	X	X	X	X	X	X
ILAE seizure classification	X						
Physical examination (complete)	X					X	
Neurological examination (complete)	X					X	
Clinical chemistry and hematology[l]	X	X	X			X	
12-lead ECG	X	X[m]	X[m]	X[m]	X	X	

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[c]	End-of-Study Period	
Visit	**V1a**	**V1b[a]**	**V2**	**V3[b]**		**Final Visit[d]**	**TC[e]**
Study Day	**-7 to -1**	**-1**	**1**	**2 to 5**		**2 to 6**	**2 to 9**
Vital signs	X	X[n]	X[n]	X[n]	X	X	
Body weight and height	X						
PK blood sampling[o]			X	X	X		
Admission to the unit[p]	X	X					
Oral LCM administration[q]	X	X				X	X
Intravenous LCM infusion[r]			X	X	X		
C-SSRS[s]	X	X[t]	X	X	X[c]	X	
Discharge from the unit						X	

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ILAE=International League against Epilepsy; iv=intravenous; LCM=lacosamide; PK=pharmacokinetics; TC=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

[a] Visit 1b only applies when Screening and Baseline occur on separate days.

[b] If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed each day of iv LCM treatment in EP0060.

[c] If an Unscheduled Visit is needed, the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

[d] A Final Visit must be completed the day after the last dose of iv LCM for all subjects who complete or withdraw prematurely from EP0060. For subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and refer to the long-term, open-label studies taper regimen.

[e] The Telephone Contact assessment should be performed 1 to 2 days after the Final Visit (2 to 7 days after Visit 2/Day 1). During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

[f] Verification that the subject continues to meet inclusion/exclusion criteria if Screening and Baseline occur on separate days.

[g] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for direct-enroll subjects who were prescribed VIMPAT prior to entering the study. Medical history update will be collected for subjects from the long-term open-label studies.

[h] Lacosamide dosing history will include date, time, and dosage information during the last 3 days.

[i] Prior medications will only be collected for direct-enroll subjects. Concomitant medications from the long-term open-label studies will be followed, as well as the recording of new concomitant medications during EP0060 for all enrolled subjects.

[j] Pregnancy testing for subjects of childbearing potential will be serum testing at the Screening Visit for direct-enroll subjects who are prescribed VIMPAT and urine testing for subjects enrolled in long-term, open-label studies. Urine pregnancy testing (or serum pregnancy test if no urine sample can be

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[c]	End-of-Study Period	
Visit	V1a	V1b[a]	V2	V3[b]		Final Visit[d]	TC[e]
Study Day	-7 to -1	-1	1	2 to 5		2 to 6	2 to 9

obtained) will be conducted on all subjects of childbearing potential at the Final Visit.

[k] Ongoing AEs from the long-term open-label studies will be followed, as well as recording of new AEs during EP0060.

[l] Laboratory assessments will be performed for subjects who are directly enrolled into EP0060. Screening laboratory assessments may be conducted up to the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion.

[m] 12-lead ECG will be performed approximately 20 minutes prior to each infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of each iv administration. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest at least 5 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[n] Vital signs will be performed approximately 10 minutes prior to each infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of each iv administration. Noninvasive BP (systolic and diastolic) and pulse rate will be measured at study visits after at least 3 minutes at rest, when feasible.

[o] Samples for PK will be drawn after ECG and vital signs have been taken. Plasma samples will be obtained from the opposite arm in which the solution for infusion was administered for the first iv LCM infusion (Day 1): predose (within 1 hour prior to iv LCM infusion) and postdose (within 1 to 4 hours after end of iv LCM infusion), and for the final iv LCM infusion (Day 2 to 5/Early Termination): predose (within 1 hour prior to iv LCM infusion) and postdose (within 1 to 4 hours after end of iv LCM infusion). Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

[p] Admission to the health care facility to participate in the study should take place at least the day prior to the start of the first iv LCM infusion. However, when necessary for the wellbeing of the subject or when the investigator deems it appropriate, the admission to the health care facility and the first iv LCM infusion can start on the same day.

[q] On Day -1, oral LCM will be administered in accordance with each subject's LCM dosage regimen.

[r] LCM will be administered twice daily at approximately 12-hour intervals, once in the morning and once in the evening, for up to 5 days.

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

[t] The C-SSRS assessment (see Section 10.7.5) does not need to be completed twice if Screening/Baseline assessments are done on the same day.

Has been changed to:

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**
Written informed consent	X								
Inclusion/exclusion criteria	X	X[i]							
Demographics	X								
Medical procedures	X	X	X	X	X	X	X		X
Procedure history[j]	X								
Medical history/update[j]	X	X							
Diagnosis of epilepsy[j]	X								
Seizure history[k]	X								
Childbearing potential[j]	X								
LCM dosing history[l]	X	X							
LCM dosing information since Treatment Period							X	X	X
Prior and concomitant medications[m]	X	X	X	X	X	X	X	X	X
Concomitant AEDs/VNS settings/ ketogenic diet	X	X	X	X	X	X	X[n]		X[n]
Urine pregnancy testing (as applicable)	X	X				X			
Withdrawal criteria	X	X	X	X	X	X			

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**
AE reporting	X	X	X	X	X	X	X	X	X
Physical examination (complete)	X					X			
Physical examination (brief)		X	X[o]	X[o]	X				
Neurological examination (complete)	X					X			
Neurological examination (brief)		X	X[o]	X[o]	X				
Clinical chemistry and hematology[p]	X	X[q]				X			
12-lead ECG	X	X	X[r]	X[r]		X			
Vital signs	X	X	X[s]	X[s]	X	X			
Body weight and height	X								
PK blood sampling			X[t]	X[u]					
Intravenous LCM infusion[v]			X	X					
C-SSRS[w]	X	X[x]	X[o]	X[o]	X[d]	X			
Additional items for RxL and IIL subjects continuing into SP848									
Dispense transitional supply of oral LCM solution[g]			X[y]						
Collect transitional supply of oral LCM solution								X	
Visit 1 SP848 assessments (documented in SP848)								X	

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IIL=initiating iv LCM; iv=intravenous; LCM=lacosamide; OLL=open-label LCM; PK=pharmacokinetics; RxL=prescribed commercial LCM; TC=Telephone Contact; V=Visit; VNS=vagus nerve stimulation

[a] The Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion, if necessary. In this case, it is required that all Screening procedures are performed and the results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility.

[b] Visit 1b only applies when Screening and Baseline occur on separate days.

[c] If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed for each infusion of iv LCM treatment in EP0060, unless otherwise noted (see footnote o).

[d] If an Unscheduled Visit is needed, the assessments noted will be performed. Additional assessments can be performed at the investigator's discretion. If the Unscheduled Visit is due to an AE, the C-SSRS assessment should be completed and collection of a blood sample for LCM PK analysis is at the discretion of the investigator.

[e] A Final Visit must be completed for all subjects who complete or withdraw prematurely from EP0060. If the last iv infusion of LCM for the study occurs in the morning, the Final Visit may occur on the same day as the last infusion, time permitting. Otherwise, the Final Visit should occur on the following day (ie, last infusion in evening). For subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen or taper at the discretion of the treating physician for those subjects who enrolled directly.

[f] The Telephone Contact 1 Visit assessment should be performed 1 to 3 days after the Final Visit. During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

[g] The Transition Visit will only be conducted for RxL and IIL subjects who will continue LCM treatment in SP848. This visit can occur at the same time as the Final Visit or on another day up to and including 7 days after the Final Visit and should occur at the same time as Visit 1 for SP848.

[h] The Telephone Contact 2 Visit will only be conducted for RxL and IIL subjects who will not continue LCM treatment in SP848.

[i] Verification that the subject continues to meet inclusion/exclusion criteria if Screening and Baseline occur on separate days.

[j] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for RxL and IIL subjects at Screening. For OLL subjects, a medical history update will be performed in order to collect medical history that was not captured during the course of the prior study.

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

[l] For OLL and RxL subjects, LCM dosing history will include date, time, and dosage information during the last 3 days.

[m] Prior medications will only be collected for direct-enroll subjects.

[n] At Telephone Contact follow-up calls, only concomitant AED and ketogenic diet information will be gathered (ie, settings for VNS will not be gathered).

[o] During the Treatment Period, brief physical examination, brief neurological examination, and C-SSRS should be performed once per day and after an infusion.

[p] Screening laboratory assessments may be conducted up to and including the day of the infusion provided they are reviewed and meet inclusion/exclusion

Table 5–1: Schedule of study assessments

Assessments	Screening/ Baseline		Treatment Period		Unscheduled Visit[d]	End-of-Study Period			
Visit	**V1a[a]**	**V1b[b]**	**V2**	**V3[c]**		**Final Visit[e]**	**TC1[f]**	**Transition Visit[g]**	**TC2[h]**
Study Day	**-7 to 1**	**-1 to 1**	**1**	**2 to 5**		**1 to 6**	**2 to 9**	**1 to 13**	**29 to 37**

criteria prior to the infusion. For all subjects, local laboratory results obtained for routine diagnostic and medical care can be used whenever possible if collected no more than 24 hours prior to Screening/Baseline Visit in order to minimize blood loss associated with the study. Use of the central or local laboratory is at the discretion of the investigator for all visits except the Final Visit. The central laboratory must be used for laboratory samples collected at the Final Visit.

[q] If Screening and Baseline Visits are not performed on the same day, repetition of laboratory assessments at Baseline is at the discretion of the investigator.

[r] A 12-lead ECG will be performed approximately 20 minutes prior to each infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of each iv administration. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest (sitting or supine) at least 3 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[s] Vital signs will be performed approximately 10 minutes prior to each infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of each iv administration. Noninvasive BP (systolic and diastolic) and pulse rate will be measured at study visits after at least 3 minutes at rest, when feasible.

[t] Plasma samples will be obtained from a different region of the body from the region in which the solution for infusion was administered for the first iv LCM infusion (Day 1): predose for OLL and RxL subjects (within 1 hour prior to iv LCM infusion) and postdose for all subjects (within 1 to 4 hours after end of iv LCM infusion). If the postdose PK sample is taken at a similar time for ECG and vital signs (ie, the 2 hour time point), the PK sample will be drawn after ECG and vital signs have been taken. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

[u] If the subject has more than 1 iv LCM infusion, it is optional to also collect plasma samples for the final iv LCM infusion (Day 2 to 5/Early Termination): predose for all subjects (within 1 hour prior to iv LCM infusion) and postdose for all subjects (within 1 to 4 hours after end of iv LCM infusion). If the postdose PK sample is taken at a similar time for ECG and vital signs (ie, the 2 hour time point), the PK sample will be drawn after ECG and vital signs have been taken. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

[v] During the Treatment Period subjects will receive at least 1 dose of iv LCM. If more than 1 infusion is needed, infusions will occur bid at approximately 12-hour intervals up to either 2 doses (elective administration) or 10 doses (clinical need administration).

[w] All subjects ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the "Since Last Visit" version used at subsequent visits. If the subject is <6 years of age, assessment for signs of depression will be conducted as described in Section 10.7.5 of the protocol.

[x] The C-SSRS assessment does not need to be completed twice if Screening/Baseline assessments are done on the same day. If Screening/Baseline and Visit 2 occur on the same day, 2 assessments should be completed with 1 predose and 1 after infusion.

[y] For RxL and IIL subjects who are eligible and wish to enroll in SP848, a short-term oral LCM solution will be dispensed to allow continuity of LCM treatment while visits and assessments are scheduled for starting SP848. Subjects (or their caregivers) will administer the oral LCM solution twice a day according to the investigator's instructions until the subject returns for the Transition Visit.

Change #21

Table 5-2 Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Table 5-2: Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Approximate time points referred to iv infusion	Vital signs[a]	12-lead ECG[b]	PK blood sampling[c]
-59min to -3min			X
-20min		X	
-10min	X		
T0 (start of infusion)			
+5min	X		
+10min	X		
+15min		X	
+20min	X		
+30min		X	
+45min	X		
+60min	X	X	
+1h to +4h[d]			X
+2h	X	X	

AE=adverse event; BP=blood pressure; ECG=electrocardiogram; h=hours; iv=intravenous; LCM=lacosamide; min=minutes; PK=pharmacokinetics; T=time

[a] Noninvasive BP (systolic and diastolic) and pulse rate will be measured after at least 3 minutes at rest, when feasible, at the indicated approximate time points before and after the start of each iv LCM infusion.

[b] A 12-lead ECG will be performed at the indicated approximate time points before and after the start of each iv LCM infusion. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest at least 5 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[c] Samples for PK will be drawn after ECG and vital signs have been taken. Plasma samples will be obtained from the opposite arm in which the solution for infusion was administered for the first iv LCM infusion (Day 1) and the final iv LCM infusion (Day 2 to 5/Early Termination), predose and postdose, at the time points indicated in the table. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE. Depending on the target duration defined for the cohort and subject tolerability, end of infusion can be at 15, 30, or 60 minutes, or whenever the infusion is stopped (if prematurely terminated).

[d] Time points are in reference to T0 (start of infusion) except the postdose PK sample, which should be obtained within 1 to 4 hours after the end of the iv LCM infusion.

Has been changed to:

Table 5-2: Timing of infusion, blood sampling, and measurement of vital signs and ECG on Treatment Days (Infusion Day 1 to Day 5)

Approximate time points in relation to iv LCM infusion	Vital signs[a]	12-lead ECG[b]	PK blood sampling[c]
-59min to -3min			X[d]
-20min (±10 min)		X	
-10min (±5 min)	X		
T0 (start of infusion)			
+5min (±2 min)	X		
+10min (±2 min)	X		
+15min (±5 min)		X	
+20min (±5 min)	X		
+30min (±5 min)		X	
+45min (±5 min)	X		
+60min (±10 min)	X	X	
+1h to +4h[e]			X
+2h (±15 min)	X	X	

AE=adverse event; BP=blood pressure; ECG=electrocardiogram; h=hours; iv=intravenous; LCM=lacosamide; min=minutes; PK=pharmacokinetics; T=time

[a] Noninvasive BP (systolic and diastolic) and pulse rate will be measured after at least 3 minutes at rest, when feasible, at the indicated approximate time points before and after the start of each iv LCM infusion.

[b] A 12-lead ECG will be performed at the indicated approximate time points before and after the start of each iv LCM infusion. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should be at rest (sitting or supine) at least 3 minutes prior to each ECG recording and should be motionless during the recording, when feasible.

[c] If the postdose PK sample is taken at a similar time for ECG and vital signs (ie, the 2 hour time point), the PK sample will be drawn after ECG and vital signs have been taken. Plasma samples will be obtained a different region of the body from the region in which the solution for infusion was administered for the first iv LCM infusion (Day 1). If the subject has more than 1 iv LCM infusion, it is optional to also collect plasma samples for the final iv LCM infusion (Day 2 to 5/Early Termination), predose and postdose, at the time points indicated in the table. Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE. Depending on the target duration defined for the cohort and subject tolerability, end of infusion can be at 15, 30, or 60 minutes, or whenever the infusion is stopped (if prematurely terminated).

[d] For the first LCM infusion, the predose PK sample is required for OLL and RxL subjects and not required for IIL subjects. For optional PK sample collection of a subsequent LCM infusion, the predose sample should be collected from all subjects.

[e] Time points are in reference to T0 (start of infusion) except the postdose PK sample, which should be obtained within 1 to 4 hours after the end of the iv LCM infusion.

Change #22

Section 5.3 Rationale for study design and selection of dose, first 4 paragraphs

EP0060 is an open-label, multicenter study to investigate the safety and tolerability of iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy aged ≥4 to <17 years. A separate Phase 2/3 study investigating the use of iv LCM as replacement for oral LCM therapy in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned. The results of EP0060 will provide safety and PK data regarding the use of the iv LCM formulation in pediatric subjects (≥4 to <17 years of age). The EP0060 design is based on the study design for SP757, which evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies.

The iv LCM formulation is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥16 years of age (depending on country-specific labeling) with epilepsy when oral administration is temporarily not feasible.

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for subjects enrolling from the long-term open-label studies and for subjects currently prescribed VIMPAT and enrolling directly into EP0060.

EP0060 will initially enroll older pediatric subjects (Cohort 1), which will include at least 20 subjects ≥12 to <17 years of age. Cohort 2 (at least 20 subjects ≥8 to <12 years of age) and Cohort 3 (at least 20 subjects ≥4 to <8 years of age) will follow sequentially based on DMC recommendation. After the first 10 subjects in each cohort have received iv LCM over infusion durations of 30 to 60 minutes, the enrollment will be temporarily put on hold for the DMC to review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort (ie, 30 to 60 minutes or 15 to 30 minutes), if the study/cohort should be stopped, and if the next cohort can be initiated, and if a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age) can be initiated.

Have been changed to:

EP0060 is an open-label, multicenter study to investigate the safety and tolerability of iv LCM in pediatric subjects with epilepsy aged ≥4 to <17 years. A separate Phase 2/3 study investigating the use of iv LCM in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned. The results of EP0060 will provide safety and PK data regarding the use of the iv LCM formulation in pediatric subjects (≥4 to <17 years of age). The EP0060 design is based on components of the study design for SP757, which evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies. In an effort to maximize the patient pool used in the evaluation of the safety of iv LCM in pediatric subjects, Protocol Amendment 2 has opened enrollment to also include OLL and RxL subjects who are on a stable dose of oral LCM and elect to receive iv LCM as well as IIL subjects who

are not currently taking LCM and initiate adjunctive LCM treatment using iv LCM. This expansion of the subject population occurred prior to the start of study enrollment. Protocol Amendment 2 has also included the option for RxL and IIL subjects to continue oral LCM treatment after completion of iv LCM, if determined clinically appropriate, in SP848. If required, a short-term supply of oral LCM solution will be provided for RxL and IIL subjects transitioning to start SP848 to ensure continuity of LCM treatment while allowing flexibility to schedule a clinical visit to initiate SP848. For RxL and IIL subjects who do not continue into SP848 (either by choice or not clinically appropriate), an additional telephone contact approximately 30 days after last dose of iv LCM IMP is added in order to collect final safety data.

The iv LCM formulation is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥16 years of age (depending on country-specific labeling) with epilepsy when oral administration is temporarily not feasible, which can also include initiation of LCM treatment.

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for OLL and RxL subjects, with a maximum dose of 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, this range of doses above also includes the pediatric starting dose of 2mg/kg/day (subjects <50kg) or 100mg/day (subjects ≥50kg), which is the same as those used in the Phase 3 pediatric LCM studies. The LCM dose at initiation of treatment should remain constant for at least 7 days prior to a LCM dose increase.

EP0060 will initially enroll at least 40 older pediatric subjects (Cohort 1) and will include at least 20 subjects ≥12 to <17 years of age and at least 20 subjects ≥8 to <12 years of age. Cohort 2 (at least 20 subjects ≥4 to <8 years of age) will follow sequentially based on DMC recommendation. After the first 20 subjects (Cohort 1) or 10 subjects (Cohort 2) have received iv LCM over infusion durations of 30 to 60 minutes, the DMC will review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort (ie, 30 to 60 minutes for all remaining subjects or 15 to 30 minutes [only for subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; otherwise 30 to 60 minutes]), if the study/cohort should be stopped, and if the next cohort can be initiated, and if a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age) can be initiated (Section 12.7.2).

Change #23

Section 6.1 Inclusion criteria

To be eligible to participate in EP0060, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal

representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.

2. Subject/legal representative is considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female from ≥4 to <17 years of age.
4. Subject has, in the opinion of the investigator, adequate seizure control for participation in EP0060, and is able to comply with all study requirements including admission to the health care facility, multiple blood draws, and iv infusions. Subject (or parent[s] or legal representative) is willing to comply with all study requirements.
5. Subject is participating in a long-term, open-label study with LCM or is currently prescribed oral VIMPAT and needs to undergo a procedure, is admitted to an EMU or health care facility, or other situations where iv administration of LCM is clinically appropriate.
6. Subject is an acceptable candidate for venipuncture and iv infusion.

Subjects who are participating in a long-term, open-label study with LCM must fulfill the following additional inclusion criteria:

7. Subject is currently enrolled in a long-term, open-label study, receiving oral LCM for the treatment of epilepsy.
8. Subject has been on a stable bid dosage regimen of oral LCM for the last 3 days in their long-term, open-label study.
9. Subject is expected to benefit from participation in EP0060, in the opinion of the investigator.

Subjects who are currently prescribed oral VIMPAT and enroll directly into EP0060 must fulfill the following additional inclusion criteria:

10. Subject has been prescribed oral VIMPAT at a dose of 2mg/kg/day to 12mg/kg/day (for subjects <50kg) or 100mg/day to 600mg/day (for subjects ≥50kg).
11. Subject has been prescribed oral VIMPAT for the treatment of epilepsy for at least 1 month prior to Screening and has not been prescribed or maintained on VIMPAT for the purposes of participating in EP0060. Prescribed oral VIMPAT dose must be stable for at least 7 days, and intake of the prescribed total daily dose confirmed for at least 3 days prior to first infusion.
12. If the subject is on a concomitant AED, the daily dosage regimen of AED therapy must be kept constant for a period of at least 1 week prior to Screening. VNS is allowed, but settings must be kept constant for a period of at least 1 week prior to Screening.

Has been changed to:

To be eligible to participate in EP0060, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.

2. Subject is male or female from ≥4 to <17 years of age.
3. Subject has a diagnosis of epilepsy with partial-onset seizures or primary generalized tonic-clonic seizures.
4. Subject meets 1 of the following criteria:
   - OLL subject: Subject is currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study); OR,
   - RxL subject: Subject is currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy; OR,
   - IIL subject: Subject is not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.
5. Subject is an OLL or RxL subject and meets both of the following criteria:
   - Subject has been administered LCM for the treatment of epilepsy for at least 2 weeks prior to Screening; AND,
   - Subject has been administered (OLL) or prescribed (RxL) oral LCM at a dose of 2mg/kg/day to 12mg/kg/day (for subjects <50kg) or 100mg/day to 600mg/day (for subjects ≥50kg). Open-label study drug LCM (OLL) or prescribed oral LCM dose (RxL) must be stable for at least 3 days prior to first LCM infusion.

   -OR-

   Subject is an ILL subject and is on a stable dosage regimen of at least 1 AED. The daily dosage regimen of concomitant AED therapy must be kept constant for a period of at least 2 weeks prior to Screening.
6. Subject is an acceptable candidate for venipuncture and iv infusion.
7. Subject is, in the opinion of the investigator, able to comply with all study requirements. Subject (or parent[s] or legal representative) is willing to comply with all study requirements.

Change #24

Section 6.2 Exclusion criteria

Subjects are not permitted to enroll in EP0060 if any of the following criteria are met:

1. Subject has previously received iv LCM in this study.
2. Subject has any medical, neurological, or psychiatric condition that, in the opinion of the investigator, could jeopardize the subject's health or compromise the subject's ability to participate in EP0060.
3. Subject has clinically significant hypotension or bradycardia.
4. Subject ≥6 years of age has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as

indicated by positive responses ("Yes") to either Question 4 or Question 5 of the C-SSRS at Screening.

5. Subject does not have a diagnosis of epilepsy.
6. Subject is taking monoamine oxidase inhibitors (MAOIs).

Subjects who are participating in a long-term, open-label study with LCM are not permitted to enroll in EP0060 if any of the following additional criteria are met:

7. Subject has any ongoing AE in their long-term, open-label study that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate EP0060.

Subjects who are currently prescribed oral VIMPAT are not permitted to directly enroll in EP0060 if any of the following additional criteria are met:

8. Subject has a medical condition that could reasonably be expected to interfere with drug distribution, metabolism, or excretion.
9. Subject has a known hypersensitivity to any component of the investigational medicinal product (IMP).
10. Subject is a female of childbearing potential and does not practice an acceptable method of contraception for the duration of participation in EP0060.
    a) Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone, oxcarbazepine]) which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.
    b) The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit.
11. Subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level greater than or equal to 2 times the upper limit of normal (ULN), or creatinine clearance less than 30mL/min.
12. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a QT prolongation greater than 450ms).
13. Subject has hemodynamically significant heart disease (eg, heart failure).
14. Subject has an arrhythmic heart condition requiring medical therapy.
15. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
16. Subject has only nonepileptic events, including psychogenic seizures, which could be confused with seizures. If both epileptic and nonepileptic events are present, epileptic events must be distinguished from nonepileptic phenomena.

17. Subject has been treated with felbamate for at least 12 months prior to entering EP0060 and has experienced any toxicity issues with this treatment. Note: Any subject who is currently treated with felbamate, and has received felbamate for a period of less than 12 months, is excluded from EP0060.
18. Subject has an acute or subacutely progressive central nervous system disease. Subject has epilepsy secondary to a progressing cerebral disease or any other progressive or neurodegenerative disease (malignant brain tumor or Rasmussen syndrome).
19. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.

Has been changed to:

Subjects are not permitted to enroll in EP0060 if any of the following criteria are met:

1. Subject has previously received iv LCM in this study.
2. Subject has any medical, neurological, or psychiatric condition that, in the opinion of the investigator, could jeopardize the subject's health or compromise the subject's ability to participate in EP0060.
3. Subject has clinically significant hypotension or bradycardia in the opinion of the investigator.
4. Subject ≥6 years of age has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by positive responses ("Yes") to either Question 4 or Question 5 of the C-SSRS at Screening.
5. Subject is taking monoamine oxidase A inhibitors (MAOI-A).

For OLL subjects, enrollment in EP0060 is not permitted if any of the following additional criteria are met:

6. Subject has any ongoing AE in their long-term, open-label study that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate EP0060 or the subject meets any of the criteria for required withdrawal from the long-term open-label study.

For RxL and IIL subjects, enrollment in EP0060 is not permitted if any of the following additional criteria are met:

7. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
8. Subject has a known hypersensitivity to any component of the investigational medicinal product (IMP).
9. Subject is a female of childbearing potential and does not practice an acceptable method of contraception for the duration of participation in EP0060.
    a) Medically acceptable contraceptive method includes oral or depot contraceptive treatment with at least 30µg ethinylestradiol per intake (or 50µg if associated with carbamazepine [or other strong enzyme inducers, eg, phenobarbital, primidone,

oxcarbazepine]) which must be used in conjunction with a barrier method. Sexual abstinence is also an acceptable method of contraception.

b) The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the investigator of any potential change in status. Females of childbearing potential must have a negative pregnancy test at the Screening Visit.

10. Subject has creatinine clearance less than 30mL/min.
11. Subject has a clinically relevant ECG abnormality, in the opinion of the principal investigator (ie, second or third degree heart block at rest or a QT prolongation greater than 450ms).
12. Subject has hemodynamically significant heart disease (eg, heart failure).
13. Subject has an arrhythmic heart condition requiring medical therapy.
14. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
15. Subject has an acute or subacutely progressive central nervous system disease. Subject has epilepsy secondary to a progressing cerebral disease or any other progressive or neurodegenerative disease (malignant brain tumor or Rasmussen syndrome).
16. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.
17. Lacosamide is intended for treatment of generalized convulsive status epilepticus.
18. Subject has exclusively typical absence (Type IIA1) or atypical absence (Type IIA2) seizures (no other generalized seizure types are reported).
19. Subject has diagnosis of Dravet's syndrome.
20. Subject has >2 upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For 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 Case Report form (CRF).

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

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

For IIL subjects, enrollment in EP0060 is not permitted if the following additional criterion is met:

21. Subject has been treated with LCM within the last 3 months prior to Screening.

Change #25

Section 6.1 Withdrawal criteria

Subjects are free to withdraw from EP0060 at any time, without prejudice to their continued care.

Subjects **must** be withdrawn from EP0060 if any of the following events occur:

1. Subject experiences intolerable AEs and AEs associated with iv administration that, in the opinion of the investigator, preclude further participation in EP0060.
2. The subject requires more than 5 days of iv LCM dosing.
3. The sponsor or a regulatory agency requests withdrawal of the subject.
4. Subject has corrected QT interval (QTc) ≥500ms that is confirmed by a cardiologist over read on any ECG.
5. Subject becomes pregnant during the study, as evidenced by a positive serum or urine pregnancy test.
6. Subject develops a second- or third-degree atrioventricular (AV) block or another clinically relevant change in medical condition (or ECG) as determined by the investigator, or if the investigator feels it is in the interest of the subject to withdraw.
7. 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 "Children's Since Last Visit" version of C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from EP0060.
8. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in EP0060.
9. Investigator decides that withdrawal from further participation would be in the subject's best interest.
10. In the case of liver function test (LFT) results of transaminases (AST, ALT, or both) ≥3x ULN to <5xULN and total bilirubin ≥2xULN or transaminases (AST, ALT, or both) ≥5xULN, 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.

Participation in EP0060 **may** be discontinued for any of the following reasons:

11. Subject experiences convulsive status epilepticus.
12. Subject has any clinically relevant change in medical or psychiatric condition (if, in the opinion of the investigator, the change in condition warrants discontinuation from EP0060).
13. Subject requires a medication that is not permitted by the protocol (see Section 7.8.1).
14. Subject and/or delegated caregiver is noncompliant with EP0060 procedures or medication, in the opinion of the investigator.
15. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality

(ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

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

Investigators should also attempt to obtain information on subjects in the case of withdrawal or discontinuation. Withdrawal assessments will be recorded in EP0060. For subjects returning to a long-term, open-label study, withdrawal assessments from the long-term open-label study should be evaluated separately from the EP0060 withdrawal assessments. For subjects considered as lost to follow up, the investigator should make efforts (at least 1 phone call and 1 written message to the subject), and document his/her efforts (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The Case Report form (CRF) must document the primary reason for withdrawal or discontinuation.

Has been changed to:

Subjects are free to withdraw from EP0060 at any time, without prejudice to their continued care. The following criteria for subject withdrawal from EP0060 are outlined below. Additional discontinuation criteria for potential drug-induced liver injury are presented in Section 6.3.1.

Subjects **must** be withdrawn from EP0060 if any of the following events occur:

1. Subject experiences intolerable AEs and AEs associated with iv administration that, in the opinion of the investigator, preclude further participation in EP0060.
2. The subject requires more than 10 iv LCM doses.
3. The sponsor or a regulatory agency requests withdrawal of the subject.
4. Subject has corrected QT interval (QTc) ≥500ms that is confirmed by a cardiologist over read on any ECG.
5. Subject becomes pregnant during the study, as evidenced by a positive urine pregnancy test.
6. Subject develops a second- or third-degree atrioventricular (AV) block or another clinically relevant change in medical condition (or ECG) as determined by the investigator, or if the investigator feels it is in the interest of the subject to withdraw.
7. 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 “Children’s Since Last Visit” version of C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from EP0060.
8. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in EP0060.
9. Investigator decides that withdrawal from further participation would be in the subject’s best interest.

Participation in EP0060 **may** be withdrawn for any of the following reasons:

10. Subject experiences generalized convulsive status epilepticus.
11. Subject has any clinically relevant change in medical or psychiatric condition (if, in the opinion of the investigator, the change in condition warrants discontinuation from EP0060).
12. Subject requires a medication that is not permitted by the protocol (see Section 7.8.1).
13. Subject and/or delegated caregiver is noncompliant with EP0060 procedures or medication, in the opinion of the investigator.
14. Subject who initiated adjunctive LCM treatment in EP0060 and requires a change in LCM dose during the Treatment Period.
15. Subject electively administering LCM requires more than 2 iv doses. If, in the opinion of the Investigator, there is a clinical need to administer more than 2 iv doses, the subject may remain in the study. The Investigator should document the clinical need in the medical record/source documents.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance. Investigators should also attempt to obtain information on subjects in the case of withdrawal. Withdrawal assessments, which are the same as those for Final Visit, will be recorded in EP0060. For subjects considered as lost to follow up, the investigator should make efforts (at least 1 phone call and 1 written message to the subject/subject's parent or legal guardian), and document his/her efforts (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The Case Report form (CRF) must document the primary reason for withdrawal.

For subjects returning to a long-term, open-label study, withdrawal assessments from the long-term open-label study should be evaluated separately from the EP0060 withdrawal assessments. The Medical Monitor may provide guidance on whether the subject should return to continued treatment within the long-term open-label study (OLL subject), be allowed to enroll in SP848 (RxL and IIL subjects), or withdraw completely. For the particular withdrawal criterion of requiring more than 10 iv doses or if the route of LCM administration (iv) is the sole reason for withdrawal of consent, subjects may be allowed to return to their long-term open-label study (OLL subjects) or enroll in SP848 (RxL and IIL subjects) after discussion with and agreement from the Medical Monitor. If an OLL subject is advised to withdraw from the long-term open-label study (EP0034 or SP848), the subject will be required to return to the long-term open-label study to complete the required withdrawal and safety follow-up assessments.

Change #26

Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Has been added:

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

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

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

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and 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 10.6.2. 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 CRF must document the primary reason for IMP discontinuation.

Change #27

Section 7.1 Description of investigational medicinal product

Investigational medicinal product will be provided as LCM solution in glass iv vials (10mg/mL in a 20mL vial; each vial contains LCM 200mg). Both the iv vials and the carton containing the vials will be labeled for the study.

Has been changed to:

7.1.1 Lacosamide solution for infusion

Investigational medicinal product for infusion will be provided as LCM solution for infusion in glass iv vials (10mg/mL in a 20mL vial; each vial contains LCM 200mg). Both the iv vials and the carton containing the vials will be labeled for the study.

Further details regarding dilution and storage of LCM solution for infusion are provided in the IMP Handling Manual.

7.1.2 Lacosamide oral solution for RxL and IIL subjects transitioning to SP848

Lacosamide syrup/oral solution will be provided in a polyethylene terephthalate bottle (10mg/mL in 200mL bottle). The bottle will be labeled for the study. Study medication will be measured and administered via a dosing syringe.

Lacosamide oral solution will only be distributed to those RxL and IIL subjects who are eligible and choose to participate in SP848. This supply, if required, will be dispensed at Visit 2 in the event that additional time is needed to coordinate scheduling of Visit 1 of SP848, and any remaining oral LCM solution will be returned to the site at the Transition Visit.

Change #28

Section 7.2 Treatment(s) to be administered

Treatment Period (up to 5 days)

During the Treatment Period, iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 5 days. The iv LCM dose will be equivalent (mg-for-mg) to the subject's current stable oral LCM dose or prescribed oral VIMPAT dose (always in bid regimen) of 2 to 12mg/kg/day or 100 to 600mg/day. The first iv LCM dose will be given on Day 1.

A calibrated infusion pump should be used for delivering the iv LCM dose at a constant rate over the target duration defined for the cohort. A previously unused vial must be administered for each dose. Dilution is not required prior to administration of iv LCM. If needed to obtain a total volume compatible with the specified infusion duration, the iv LCM solution can be diluted; iv LCM is compatible with the following diluents: dextrose 5%, lactated ringers, and normal saline (NaCl 0.9%). The total volume of diluent should be calculated not to exceed a total volume of fluid intake/day based on the Holliday-Segar equation as follows:

- For children weighing ≤10kg: 100mL/kg body weight
- For children weighing >10 to ≤20kg: 1000mL + 50mL/kg for each kg body weight ≥10kg
- For children weighing ≥20kg: 1500mL + 20mL/kg for each kg body weight ≥20kg

Intravenous LCM administration should be completed within 4 hours after dilution.

For the first 10 subjects ≥12 to <17 years of age enrolled into Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

The duration of infusion for the remaining subjects in Cohort 1 and subsequent cohort(s) will be based on DMC recommendation:

- 30 minutes but no longer than 60 minutes whenever possible,
- OR 15 minutes but no longer than 30 minutes whenever possible.

Further details on the timing of DMC recommendations regarding infusion duration are provided in Section 12.7.2.

When necessary for the safety of the subject or when the investigator deems it appropriate, the iv LCM dose can be modified after the first infusion, once the Day 1 PK samples have been taken.

A subject cannot receive iv LCM for more than 5 days in EP0060. If a subject requires iv LCM treatment for more than 5 days, the subject may continue on iv VIMPAT, but he/she will need to discontinue EP0060. Subjects who were enrolled in a long-term, open-label study may be eligible to resume participation in that study, according to the protocol requirements. If subjects need to discontinue LCM, the subjects should be tapered off LCM gradually as specified in their long-term, open-label study. This taper should occur as a part of the long-term, open-label study.

Subjects who were prescribed oral VIMPAT should continue AED treatment at the discretion of the treating physician.

Has been changed to:

7.2.1 Treatment Period

During the Treatment Period, subjects will receive at least 1 dose of iv LCM at the dose levels noted below. The first iv LCM dose will be given on Day 1. If more than 1 infusion is given, iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration.

Specific dosing regimens for subjects who will receive iv LCM replacement therapy for oral treatment (OLL and RxL subjects) or for subjects who will initiate adjunctive LCM treatment (IIL subjects) are as follows:

- **Replacement for oral treatment:** For OLL and RxL subjects, the iv LCM daily dose will be equivalent (mg-for-mg) to the subject's current oral LCM dose or prescribed oral LCM (ie, VIMPAT) dose (always in bid regimen) of 2 to 12mg/kg/day or 100 to 600mg/day. The first infusion must be equivalent to the subject's stable oral LCM dose.
- **Adjunctive LCM treatment initiation:** For IIL subjects, the iv LCM daily dose will be 2mg/kg/day for subjects <50kg or 100mg/day for subjects ≥50kg. As LCM is given bid, the actual dose for the first infusion will be LCM 1mg/kg (subjects weighing <50kg) or 50mg (subjects weighing ≥50kg). For these subjects, the LCM dose should remain unchanged for the duration of the iv Treatment Period (see Section 6.3).

A calibrated infusion pump should be used for delivering the iv LCM dose at a constant rate over the target duration defined for the cohort. A previously unused vial must be administered for each dose. Dilution is not required prior to administration of iv LCM. If needed to obtain a total volume compatible with the specified infusion duration, the iv LCM solution can be diluted; iv LCM is compatible with the following diluents: dextrose 5%, lactated ringers, and normal saline (NaCl 0.9%). The total volume of diluent should be calculated not to exceed a total volume of fluid intake/day based on the Holliday-Segar equation as follows:

- For children weighing ≤10kg: 100mL/kg body weight
- For children weighing >10 to ≤20kg: 1000mL + 50mL/kg for each kg body weight ≥10kg
- For children weighing ≥20kg: 1500mL + 20mL/kg for each kg body weight ≥20kg

Intravenous LCM administration should be completed within 4 hours after dilution.

For the first 20 subjects ≥8 to <17 years of age enrolled into Cohort 1 and the first 10 subjects ≥4 to <8 years in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

The duration of infusion for the remaining subjects in each cohort will be based on DMC recommendation:

- EITHER target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR all remaining subjects will have a target infusion duration of 30 minutes but no longer than 60 minutes

Further details on the timing of DMC recommendations regarding infusion duration are provided in Section 12.7.2.

For OLL and RxL subjects, the iv LCM dose can be modified after the first infusion when necessary for the safety of the subject or when the investigator deems it appropriate; however, modification should not occur until after the Day 1 PK samples have been taken. Modification of iv LCM dose is not permitted for IIL subjects.

A subject cannot receive iv LCM for more than 10 doses (up to 5 days) within the Treatment Period of EP0060 (or more than 2 consecutive doses [over approximately 24 hours] for elective administration. If a subject requires iv LCM treatment for more than 5 days, the subject may continue on iv VIMPAT, but he/she will need to discontinue EP0060. Upon completion/discontinuation of EP0060, OLL subjects are eligible to resume participation in their respective open-label study, according to the protocol requirements. If a subject is withdrawn from EP0060 due to requirement of more than 10 iv LCM doses, the subject may be allowed to return to their long term open-label study (OLL subjects) or enroll in SP848 (RxL and IIL subjects) after discussion with and agreement from the Medical Monitor. If an OLL subject meets any other "must withdrawal" criteria for the respective open-label study, the subject will return to the open-label study to complete the appropriate withdrawal assessments and safety follow-up.

For RxL and IIL subjects, AED treatment will continue at the discretion of the treating physician, upon completion/discontinuation of EP0060. If determined clinically appropriate, these subjects will be given the option to continue oral LCM treatment for up to 2 years in SP848. If LCM treatment is not continued in SP848 (either by choice or not clinically appropriate), RxL and IIL subjects will be followed for approximately 30 days after the Final Visit in order to collect safety data. All concomitant medications taken during this 30-day period, including prescribed AEDs, will be collected at TC2.

If subjects need to discontinue LCM, the subjects should be tapered off LCM either as specified in their long-term, open-label study or at the discretion of the treating physician for RxL and IIL subjects. For OLL subjects this taper should occur as a part of the long-term, open-label study and not as a part of EP0060.

Change #29

Section 7.2.2 Transition oral lacosamide

Oral LCM solution will only be distributed to those RxL and IIL subjects who are eligible and choose to participate in SP848.

For OLL and RxL subjects, the oral LCM daily dose will be equivalent (mg-for-mg) to the subject's current oral LCM dose or prescribed oral LCM (ie, VIMPAT) dose (always in bid regimen) of 2 to 12mg/kg/day.

For IIL subjects, the oral LCM solution daily dose (always in bid) will be 2mg/kg/day for subjects <50kg or 100mg/day for subjects ≥50kg if the subject has been taking LCM for less than 7 days. If the subject has reached 7 days of LCM exposure, an increase in dose titration can be initiated.

Has been added

Change #30

Section 7.5 Handling and storage requirements

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

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

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

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

Has been changed to:

The investigator (or designee) is responsible for the safe and proper storage of LCM at the site. Lacosamide stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured by controlling the temperature and 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 reported as per instructions contained in the IMP Handling Manual.

In the case of dispensing oral LCM solution, the investigator (or designee) will instruct the subject's parent or guardian to store the IMP following the instructions on the label.

Changes #31 and #32

Section 7.6 Drug accountability, first and last paragraphs

First paragraph:

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

Last paragraph:

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

Have been changed to:

First paragraph:

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

Last paragraph:

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

Change #33

Section 7.8.1 Permitted and prohibited concomitant treatments (medications and therapies), first and second paragraphs

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

Use of MAOIs is prohibited during EP0060.

Have been changed to:

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

Use of the following concomitant treatments (medications and therapies) is prohibited during EP0060:

- MAOI-A inhibitors
- Cannabidiols not approved or indicated for epilepsy by local health authority

Change #34

Section 7.10 Randomization and numbering of subjects

Subjects will not be randomized in EP0060. For a subject enrolled in a long-term, open-label study, the unique identification number assigned to them in that study will be used to identify them and maintain subject confidentiality throughout EP0060. Direct-enroll subjects prescribed VIMPAT will be assigned a unique identification number in EP0060.

Has been changed to:

Subjects will not be randomized in EP0060. For an OLL subject, the unique identification number assigned to them in that study will be used to identify them and maintain subject confidentiality throughout EP0060. A unique identification number in EP0060 will be assigned for RxL and IIL subjects.

Change #35

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline, first 2 paragraphs

8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent form. When possible, or as required by the local IRB/IEC, an IRB/IEC-approved written Assent form will also be properly executed and documented. During the Screening Period, subjects will be evaluated for their suitability for enrollment. The Screening Period assessments may be conducted on more than 1 day and begin up to 7 days prior to Day 1 (Visit 1a). When necessary for the well-being of the subject or when the investigator deems it appropriate, the Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion (Day 1) provided all test results are available and reviewed to assess inclusion and exclusion criteria prior to enrollment/treatment in the study. Oral LCM will be administered in accordance with each subject's current stable LCM dosage regimen of 2 to 12mg/kg/day or 100 to 600mg/day. For subjects enrolled in a long-term open-label study, the oral LCM will be taken from the long-term open-label study supply. For subjects who have been prescribed VIMPAT, oral LCM will be taken from the subject's prescribed VIMPAT supply.

Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria at Visit 1a and/or Visit 1b. The following pretreatment assessments will be carried out at Visit 1a:

Have been changed to:

8.1.1 Visit 1a and Visit 1b (Day -7 to Day 1) Screening and/or Baseline

Prior to the conduct of any study-related procedures, a complete explanation (both verbally and written) of the nature and purpose of the study will be given to the subject (when possible or as required according to local IRBs/IECs) and the subject's parent/legal guardian by the investigator (or designee). The subject's parent/legal guardian will be requested to sign and date the IRB/IEC-approved Informed Consent form. When possible, or as required by the local IRB/IEC, an IRB/IEC-approved written Assent form will also be properly executed and documented. During the Screening Period, subjects will be evaluated for their suitability for enrollment. The Screening Period assessments may be conducted on more than 1 day and begin up to 7 days prior to Day 1 (Visit 2).

The Screening and/or Baseline Visit can occur on the same day as the first iv LCM infusion (Day 1), if necessary, provided all test results (ie, 12-lead ECG and laboratory results) are available and reviewed to assess inclusion and exclusion criteria prior to enrollment/treatment in the study. For all subjects, laboratory results obtained for routine diagnostic and medical care can be used whenever possible if collected no more than 24 hours prior to Screening/Baseline Visit in order to minimize blood loss associated with the study. At the Screening/Baseline Visit, the use of a central or local laboratory is at the discretion of the investigator.

If Screening/Baseline do not occur on the same day as the first infusion, oral LCM will be administered for OLL and RxL subjects during the Screening/Baseline Period from their open-label study or prescribed LCM supply in accordance with each subject's current stable LCM dosage regimen of 2 to 12mg/kg/day or 100 to 600mg/day. For IIL subjects, no LCM will be administered during the Screening Period.

Each subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria at Visit 1a and/or Visit 1b. Demographic data will be collected at Visit 1a. The following pretreatment assessments will be carried out at Visit 1a:

Change #36

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline, bullets 6, 7, 8, 9, 10, 15, 16, 20, and 21

- Medical history update for subjects from long-term open-label studies, or complete medical history for subjects receiving prescribed VIMPAT
- Lacosamide dosing history (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Prior and concomitant medication(s) assessment (prior medications will only be collected for direct-enroll subjects; concomitant medications from the long-term open-label studies will be followed, as well as the recording of new concomitant medications during EP0060 for all enrolled subjects)
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings

- Pregnancy testing for subjects of childbearing potential will be serum testing at the Screening Visit for subjects who are prescribed VIMPAT and urine testing for subjects enrolled in long-term, open-label studies
- Vital signs (BP and pulse rate) assessment
- 12-lead ECG
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)

Have been changed to:

- Medical history update for OLL subjects from long-term open-label studies, or complete medical history for RxL and IIL subjects
- For OLL and RxL subjects, LCM dosing history (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Prior and concomitant medication(s) assessment (prior medications will only be collected for direct-enroll subjects)
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or use of ketogenic diet
- Urine pregnancy testing for subjects of childbearing potential
- Vital signs (BP and pulse rate) assessment (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- 12-lead ECG (conducted on subjects who have rested [sitting or supine] at least 3 minutes prior to each ECG recording, when feasible)
- C-SSRS (for subjects ≥6 years of age). For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.

If Screening/Baseline and the first infusion do not occur on the same day, oral LCM administration for OLL and RxL subjects will continue in accordance with each subject's LCM dosage regimen and using the subject's open-label study or prescribed oral LCM supply, respectively.

And

- Seizure history for RxL and IIL subjects

Has been added

Change #37

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline, bullets 18 and 19

- ILAE (International League against Epilepsy) seizure classification

- Admission to the unit

Have been deleted

Change #38

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day 1) Screening and/or Baseline, Visit 1b bullets 2, 4, 6, 8, 9, 11, and 12

- Lacosamide dosing history (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- Blood sample for clinical chemistry and hematology
- Vital signs (BP and pulse rate) assessment
- 12-lead ECG
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)

Have been changed to:

- For OLL and RxL subjects, the LCM dosing history will be collected (including formulation, date, and time of use, and dose and unit during the last 3 days)
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or ketogenic diet
- Blood sample for clinical chemistry and hematology (Repetition of laboratory assessments is at the discretion of the investigator if Visit 1b is on a separate day from Visit 1a.)
- Vital signs (BP and pulse rate) assessment (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- 12-lead ECG (conducted on subjects who have rested [sitting or supine] at least 3 minutes prior to each ECG recording, when feasible)
- C-SSRS (for subjects ≥6 years of age). For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.

If Screening/Baseline and the first infusion do not occur on the same day, oral LCM administration for OLL and RxL subjects will continue in accordance with each subject's LCM dosage regimen and using the subject's open-label study or prescribed oral LCM supply, respectively.

Change #39

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline, Visit 1b bullet 10

- Admission to the unit

Has been deleted

Change #40

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day -1) Screening and/or Baseline, Visit 1b, new bullets (currently numbering) 11, 12, 13, 14, and 15

- Medical procedures
- Medical history update for OLL subjects, or complete medical history for RxL and IIL subjects
- Urine pregnancy testing for subjects of childbearing potential
- Brief physical examination
- Brief neurological examination

Have been added

Change #41

Section 8.2.1 Visit 2 (Day1), first paragraph

Intravenous LCM infusion treatment will begin at this visit, and iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 5 days. Screening laboratory assessments may be conducted up to and including the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion. The following assessments will be carried out:

Has been changed to:

Intravenous LCM infusion treatment will begin at this visit. Subjects will receive at least 1 dose of iv LCM. If more than 1 infusion is given, iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration.

Screening laboratory assessments may be conducted up to and including the day of the infusion provided they are reviewed and meet inclusion/exclusion criteria prior to the infusion. Section 8.1.1 details under what conditions laboratory results within 24 hours of signing the Informed Consent form can be used.

The following assessments will be carried out:

Change #42

Section 8.2.1 Visit 2 (Day 1), bullets 2, 4, 7, 8, 9 and 10 for first infusion

- Medical procedures and medical history update
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or VNS settings
- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Blood sample for LCM PK (Blood draws will be performed on the arm opposite the arm where the iv LCM infusion will be administered at the time points described in Section 9). An indwelling cannula used for the iv LCM infusion may not be used for PK blood sampling.)
- C-SSRS (for subjects ≥6 years of age)

Have been changed to:

- Medical procedures
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or use of ketogenic diet
- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion) (conducted on subjects who have rested [sitting or supine] for at least 3 minutes prior to each ECG recording, when feasible)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion) (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- Blood sample for LCM PK (Blood draws will be performed from a region of the body that is different from the region where the iv LCM infusion will be administered at the time points described in Section 9. An indwelling peripheral cannula used for the iv LCM infusion may not be used for PK blood sampling.)
- C-SSRS (for subjects ≥6 years of age) after infusion. For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.

Change #43

Section 8.2.1 Visit 2 (Day 1), bullets 11, 12, and 13

- Brief physical examination
- Brief neurological examination

- For RxL and IIL subjects who are eligible and choose to participate in the long-term open label oral LCM study SP848 after completion of EP0060, a short-term oral LCM solution will be dispensed at Visit 2. This supply is to allow continuity of LCM treatment after the last iv LCM infusion and the scheduled Transition Visit.

Have been added

Change #44

Section 8.2.1 Visit 2 (Day 1), second paragraph

The second iv LCM infusion will be administered at approximately 12 hours after the start of the first infusion, and the following assessments will be carried out:

Has been changed to:

If a second iv LCM infusion is given, it will be administered at approximately 12 hours after the start of the first infusion, and the following assessments will be carried out:

Change #45

Section 8.2.1 Visit 2 (Day 1), bullets 3 and 4 for second infusion

- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion)

Have been changed to:

- 12-lead ECG (approximately 20 minutes prior to iv LCM infusion and at approximately 15, 30, 60 minutes, and 2 hours from the start of iv LCM infusion) (conducted on subjects who have rested [sitting or supine] for at least 3 minutes prior to each ECG recording, when feasible)
- Vital signs of BP and pulse rate (approximately 10 minutes prior to iv LCM infusion and at approximately 5, 10, 20, 45, 60 minutes, and 2 hours from the start of iv LCM infusion) (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)

Change #46

Section 8.2.1 Visit 2 (Day 1), bullets 6 and 7 for second infusion

- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose), VNS settings, and/or use of ketogenic diet

Have been added

Change #47

Section 8.2.1 Visit 2 (Day 1), last paragraph

If the subject has more than 1 iv LCM infusion, it is optional to also collect blood samples for LCM PK before and after the final iv LCM infusion at the time points described in Section 9. In addition, during the course of the study, additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

Has been added

Change #48

Section 8.2.2 Visit 3 (Day 2 to Day 5)

If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed each day of iv LCM treatment in EP0060. Assessments for Visit 3 (Day 2 to 5) are the same as those described for Visit 2 (Day 1) in Section 8.2. Blood samples for LCM PK will be obtained before and after the final iv LCM infusion at the time points described in Section 9. In addition, during the course of the study, additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

Has been changed to:

If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed each day of iv LCM treatment in EP0060. Assessments for Visit 3 (Day 2 to 5) are the same as those described for Visit 2 (Day 1) in Section 8.2. If the subject has more than 1 iv LCM infusion, it is optional to also collect blood samples for LCM PK before and after the final iv LCM infusion at the time points described in Section 9. In addition, during the course of the study, additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

Change #49

Section 8.3 Unscheduled Visit, bullets 1, 3, 6, and 9

- Medical procedures and medical history update
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose) and/or VNS settings
- BP and pulse rate
- C-SSRS (for subjects ≥6 years of age). The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE.

Has been changed to:

- Medical procedures
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose), VNS settings, and/or use of ketogenic diet
- BP and pulse rate (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- C-SSRS (for subjects ≥6 years of age). The C-SSRS assessment should be completed if the Unscheduled Visit is due to an AE. For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.

Change #50

Section 8.3 Unscheduled Visit, bullets 5 and 7

- 12-lead ECG
- Blood sample for LCM PK (Blood draws will be performed on the arm opposite the arm where the iv LCM infusion will be administered. An indwelling cannula used for the iv LCM infusion may not be used for PK blood sampling)

Has been deleted

Change #51

Section 8.3 Unscheduled Visit, bullets 10 and 11

- Brief physical examination
- Brief neurological examination

Have been added

Change #52

Section 8.3 Unscheduled Visit, final paragraph

Additional assessments can be performed at the investigator's discretion, including collection of a blood sample for LCM PK if the reason for the unscheduled visit is an AE.

Has been added

Change #53

Section 8.4.1 Final Visit (Day 2 to 6 [now Day 1 to 6])/Termination Visit, first paragraph

The following assessments will be carried out the day after the last dose of iv LCM for subjects who complete the study, discontinue the study, or withdraw from the study prematurely:

Has been changed to:

If the last iv infusion of LCM for the study occurs in the morning, the Final Visit may occur on the same day as the last infusion, time permitting. Otherwise, the Final Visit should occur on the following day (ie, last infusion in evening).

The following assessments will be carried out after the last dose of iv LCM for subjects who complete the study, discontinue the study, or withdraw from the study prematurely:

Change #54

Section 8.4.1 Final Visit (Day 2 to 6 [now Day 1 to Day 6])/Termination Visit, bullets 1, 3, 4, 8, 9, 10, 12, and 13

- Medical procedures and medical history update
- Pregnancy testing for subjects of childbearing potential
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose) and/or VNS settings
- Blood sample for clinical chemistry and hematology
- 12-lead ECG
- BP and pulse rate
- Oral LCM administration
- C-SSRS (for subjects ≥6 years of age)

Have been changed to:

- Medical procedures
- Urine pregnancy testing for subjects of childbearing potential
- Concomitant AED(s) assessment (identification of drugs, amount and time of last dose), VNS settings, and/or use of ketogenic diet
- Blood sample for clinical chemistry and hematology which must be analyzed at the central laboratory
- 12-lead ECG (conducted on subjects who have rested [sitting or supine] for at least 3 minutes prior to each ECG recording, when feasible)
- BP and pulse rate (measured on subjects who have rested [sitting or supine] for at least 3 minutes, when feasible)
- Oral LCM administration, if applicable:
  - For OLL subjects, oral LCM administration will continue in accordance with each subject's LCM dosage regimen using the subject's open-label study LCM supply

  - For RxL subjects who are not eligible or do not wish to continue LCM treatment in SP848, oral LCM administration may continue from the subject's prescribed LCM supply at the physician's recommended dosage regimen.
  - For RxL and IIL subjects who are eligible and wish to enroll in SP848, oral LCM administration may continue from the short-term oral LCM solution that was dispensed at Visit 2. Additional assessments will be conducted at the Transition Visit, as outlined in Section 8.4.3.
- C-SSRS (for subjects ≥6 years of age) For subjects <6 years, signs and symptoms of depression will be evaluated as described in Section 10.7.5.

Change #55

Section 8.4.1 Final Visit (Day 2 to 6)/Termination Visit, last bullet

- Discharge from the unit

Has been deleted

Change #56

Section 8.4.2 Telephone Contact (Day 2 to Day 9), section title

Has been changed to:

Section 8.4.2 Telephone Contact 1 (Day 2 to Day 9)

Change #57

Section 8.4.2 Telephone Contact (Day 2 to Day 9), first paragraph

One or 2 days after the Final Visit, a safety follow-up/telephone assessment will be conducted during the End-of-Study Period (2 to 9 days after Visit 2/Day 1). The following assessments will be collected:

Has been changed to:

One to 3 days after the Final Visit, a safety follow-up/telephone assessment will be conducted during the End-of-Study Period. The following assessments will be collected:

Change #58

Section 8.4.2 Telephone Contact (Day 2 to Day 9), first and last bullets

- Medical procedures and medical history update
- Oral LCM administration

Have been changed to:

- Medical procedures
- Information regarding LCM dosing since Final Visit

Change #59

Section 8.4.2 Telephone Contact (Day 2 to Day 9), new bullet

- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose)

Has been added

Change #60

Section 8.4.3 Transition Visit (Day 1 to Day 13)

For RxL and IIL subjects who are eligible and wish to enroll in SP848, the Final Visit and Transition Visit may occur on the same day or may occur up to 7 days after the Final Visit. The Transition Visit for EP0060 should occur on the same day as Visit 1 in SP848.

The following assessments will be conducted at the Transition Visit if the visit is not conducted on the same day as the Final Visit:

- Collection of the short-term oral LCM solution, if dispensed at Visit 2
- Information regarding LCM dosing since Final Visit
- Concomitant medication(s) assessment
- AE reporting

Additional assessments for enrollment in SP848 (Visit 1) are detailed within the SP848 protocol.

Has been added

Change #61

Section 8.4.4 Telephone Contact 2 (Day 29 to Day 37)

Thirty days (±2 days) after the Final Visit, a safety follow-up/telephone assessment will be conducted during the End-of-Study Period (29 to 37 days after Visit 2/Day 1). This assessment will only occur for those subjects who directly enrolled in EP0060 and will not be continuing LCM therapy in SP848.

The following assessments will be collected:

- Concomitant medication(s) assessment
- Concomitant AED(s) assessment (identification of drugs, amount, and time of last dose) and/or use of ketogenic diet
- AE reporting

- Information regarding LCM dosing since Telephone Contact 1
- Medical procedures

During the contact, the site should inquire as to whether the subject noted any change at the site of the infusion.

Has been added

Change #62

Section 9 ASSESSMENT OF PHARMACOKINETICS, first, second, third, and fourth paragraphs and first bullet point

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). In each case, the time the subject received the most recent dose of study medication and the time of blood sampling must be recorded.

During the Treatment Period, plasma samples will be taken for LCM and SPM 12809 determination after ECG and vital signs have been taken. Plasma samples will be obtained from the opposite arm in which the solution for infusion was administered, at the following time points:

First iv LCM infusion (Day 1):

- Predose (within 1 hour prior to iv LCM dose)

Final iv LCM infusion (Day 2 to 5/Early Termination):

Have been changed to:

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). In each case, the time the subject received the most recent dose of IMP and the time of blood sampling must be recorded.

During the Treatment Period, plasma samples will be taken for LCM and SPM 12809 determination after ECG and vital signs have been taken. Plasma samples will be obtained from a different region of the body from the region in which the solution for infusion was administered, at the following time points:

First iv LCM infusion (Day 1) – required samples:

- Predose (within 1 hour prior to iv LCM dose) for OLL and RxL subjects

Final iv LCM infusion (Day 2 to 5/Early Termination) – optional samples:

Change #63

Section 10.1.6 Pregnancy, second bullet

- A Safety Follow Up Visit should be scheduled 1 to 2 days after the subject has discontinued her iv LCM infusion.

Has been changed to:

- A Safety Follow-Up Visit should be scheduled 1 to 3 days after the subject has discontinued her iv LCM infusion.

Change #64

Section 10.1.7 Suspected transmission of an infectious agent via a medicinal product

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

Has been added

Change #65

Section 10.1.8 (previously Section 10.1.7) Overdose of investigational medicinal product

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

Has been changed to:

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

Change #66

Numbering for Section 10.1.8 (Safety signal detection) is now Section 10.1.9

Change #67

Section 10.2.1 Definition of serious adverse event, Bullet 5

- 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 #68

Section 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.

Has been changed to:

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. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDIDI events are provided in Section 10.6.2.

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

Change #69

Section 10.3 Adverse events of special interest, last bullet point

- 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.

Has been added

Change #70

Section 10.5 Anticipated serious adverse events, first paragraph

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

Has been changed to:

The following list of anticipated SAEs is anticipated to occur in the epilepsy population at some frequency that is independent of drug exposure.

Change #71

Section 10.6 Laboratory measurements, first paragraph

Blood specimens for routine assay of hematology and clinical chemistry testing will be collected according to the tabular schedule of study assessments (Section 5.2). Samples will be prepared and evaluated by the local laboratory as described in the laboratory manual.

Has been changed to:

Blood specimens for routine assay of hematology and clinical chemistry testing will be collected according to the tabular schedule of study assessments (Section 5.2). To minimize risk from blood loss associated with this study, local laboratory results obtained for routine diagnostic and medical care can be used whenever possible if collected no more than 24 hours prior to Screening/Baseline Visit. Use of the central or local laboratory is at the discretion of the investigator for all visits except the Final Visit. The central laboratory must be used for laboratory samples collected at the Final Visit. Samples will be prepared and evaluated by a central laboratory as described in the laboratory manual.

Change #72

Section 10.6.1 Liver function tests (now Section 10.6.2)

Transaminases (AST, ALT, or both) ≥3xULN but <5xULN, in the presence of total bilirubin ≥2xULN, or transaminases (AST, ALT, or both) ≥5xULN will result in immediate discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case 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 deleted (see Change #73).

Change #73

Numbering for Section 10.6.2 (Pregnancy testing) is now Section 10.6.1.

Change #74

Section 10.6.2 Liver function tests and evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 10.6.2.2 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 10.2.1).

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 10.6.2.1). 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 10.6.2.4).

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

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

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

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings.

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

The table below summarizes the approach to investigate PDILI.

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.6.2.3); 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, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 10.6.2.2).	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 10.6.2.3).	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 10.6.2.1. 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.

10.6.2.1 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 10.6.2.3) and SAE report (if applicable).

10.6.2.2 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.

10.6.2.3 Testing: identification/exclusion of alternative etiology

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

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

The following measurements are to be assessed:

Table 10-4: PDILI laboratory measurements

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

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

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

The following additional information is to be collected:

Table 10-5: PDILI information to be collected

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

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

10.6.2.4 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.

Has been added

Change #75

Section 10.7.2 12-lead ECG, second paragraph

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest at least 5 minutes prior to each recording and should be motionless during the recording, when feasible.

Has been changed to:

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest at least 3 minutes prior to each recording and should be motionless during the recording, when feasible.

Change #76

Section 10.7.4 Complete physical examination (now Physical examination)

The complete physical examination will include cardiac and respiratory function via auscultation, and review of all body systems. Clinically significant physical examination findings are to be reported as AEs.

Has been changed to:

10.7.4.1 Complete physical examination

The complete physical examination will include cardiac and respiratory function via auscultation, and review of all body systems. Clinically significant physical examination findings are to be reported as AEs.

10.7.4.2 Brief physical examination

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

Change #77

Section 10.7.5 Assessment of suicidality, first paragraph

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Table 5-1). All subjects who are ≥6 years of age will complete the “Baseline/Screening” version of the C-SSRS at Visit 1 and will complete the “Since Last Visit” version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and the “Since Last Visit” version used at subsequent visits.

Has been changed to:

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Table 5–1). If the Screening and Baseline visit is on the same day, the C-SSRS does not need to be completed twice. The C-SSRS should be performed once per day during the Treatment Period. If Screening/Baseline and Visit 2 occur on the same day, 2 assessments should be completed with 1 predose and 1 after infusion.

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

Change #78

Section 10.7.6 Complete neurological examination (now 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. Clinically significant neurological examination findings are to be reported as AEs.

Has been changed to:

10.7.6.1 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. Clinically significant neurological examination findings are to be reported as AEs.

10.7.6.2 Brief neurological examination

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

Changes #79 to #80

Section 11.3.1 Case Report form completion, first and third paragraphs

First paragraph:

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

Third paragraph:

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

Have been changed to:

First paragraph:

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

Third paragraph:

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

Change #81

Section 11.3.2 Database entry and reconciliation, first paragraph

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. As the study is performed using RDC, the data are entered into the electronic CRFs once and are subsequently verified.

Has been changed to:

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. As the study is performed using EDC, the data are entered into the electronic CRFs once and are subsequently verified.

Change #82

Section 12 STATISTICS, first paragraph

Selected disposition, exposure, demographic, and Baseline summaries will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Descriptive statistics will be displayed to provide an overview of the Baseline characteristics, PK, and safety results.

Has been changed to:

Selected disposition, exposure, demographic, and Baseline summaries will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Within cohort and infusion duration, presentation will include the IIL subject group and the OLL and RXL subject group.

Change #83

Section 12.1 Definition of analysis sets, first paragraph

The Safety Set (SS) will include subjects who received at least 1 dose of iv LCM. The SS will be the primary analysis set for the analysis of safety data.

Has been changed to:

The Safety Set iv (SS-iv) will include subjects who received at least 1 dose of iv LCM. The SS will be the primary analysis set for the analysis of safety data.

The Safety Set (SS) will include subjects who received at least 1 dose of LCM (oral or iv). Selected safety summaries will be presented for the SS.

Change #84

Section 12.3 Planned pharmacokinetic analyses

Descriptive statistics for LCM and SPM 12809 plasma concentrations, including but not limited to geometric mean and CV, will be computed for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected.

Has been changed to:

Descriptive statistics for LCM and SPM 12809 plasma concentrations, including but not limited to geometric mean and CV, will be computed for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected. Data will be presented by cohort and infusion duration, and the IIL and OLL and RXL groups of subjects in EP0060 will also be presented.

Change #85

Section 12.4 Planned safety and other analyses (now titled Planned safety analyses), first paragraph

Safety analyses will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Within cohort and infusion duration, the OLL and RxL groups of subjects and the IIL subject group will also be presented.

Has been added

Change #86

Section 12.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary safety outcomes (if applicable) for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

Has been changed to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary safety outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

Change #87

Section 12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 10 subjects in each cohort.

Has been changed to:

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 subjects in Cohort 1 and after completion of the first 10 subjects in Cohort 2.

Change #88

Section 12.7.2 Data Monitoring Committee. Paragraph 2 through end of section

EP0060 will begin with Cohort 1, where at least 20 subjects ≥12 to <17 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 1, enrollment into Cohort 1 will be temporarily put on hold to allow for the DMC review of the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥8 to <12 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, enrollment into Cohort 2 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 2 should be stopped,
- AND whether Cohort 3 can be initiated.

For Cohort 3, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 3, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 3, enrollment into Cohort 3 will be temporarily put on hold for the DMC to review the available safety and tolerability data from Cohort 1, Cohort 2, and Cohort 3. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 15 minutes but no longer than 30 minutes whenever possible,
- OR approximately 15 additional subjects will be enrolled in Cohort 3 with a target infusion duration of 30 minutes but no longer than 60 minutes whenever possible,
- OR Cohort 3 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

Has been changed to:

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion durations as follows:
  - 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,
  - 30 minutes but no longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the Investigator
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion durations as follows:
  - 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,
  - 30 minutes but no longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the Investigator
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

Change #89

Section 12.8 Determination of sample size

Approximately 75 subjects will be enrolled, which includes up to 3 cohorts of at least 20 subjects. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

Has been changed to:

Approximately 75 subjects will be enrolled, which includes up to 2 cohorts of at least 40 subjects for Cohort 1 and at least 20 subjects for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

Changes #90 and #91

Section 15 References

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

Has been deleted and

Arkilo D, Gustafson M, Ritter FJ. Clinical experience of intravenous lacosamide in infants and young children. Eur J Paediatr Neurol. 2016;20(2):212-7.

CDC growth curves. Girls: http://www.cdc.gov/growthcharts/data/set1clinical/cj41c022.pdf. Boys: http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf. 2000.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

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

Have been added

16.3 Protocol Amendment 3

Rationale for the amendment

The primary purpose of this substantial amendment is to lower the age of subjects from ≥4 years to ≥1 month in an effort to maximize the subject pool in the evaluation of iv LCM, to include age stratification within Cohort 2 to be most informative with regard to safety and PK, and to increase study enrollment from 75 to 100 subjects to reflect the inclusion of subjects down to 1 month of age. Since initial conception of the study, substantial new safety and efficacy information on the lowest age group (≥1 month to <4 years of age) has been accumulated, reported, and published. The available safety information consists of postmarketing data (n=27 patient cases), data from internal studies (n=15 patient cases), as well as from two published reports (n=15 and n=22 patient cases) (Arkilo et al, 2016; Welsh et al, 2017). These reports cover the age range from ≥1 month to <4 years of age and also cover the clinical spectrum from an open-label extension study with oral treatment to critically care patients receiving iv treatment. This data points to no specific risks in the age group after administration of Vimpat® and UCB, therefore, believes it is justified to open Cohort 2 to the lowest age group in agreement with the DMC outcome on safety of Cohort 1.

Additional changes include the following:

- Study contact information has been updated as applicable.
- Additional region to maximize enrollment has been included.
- Number of subjects included in the DMC process in Cohort 2 has been modified.
- The timing of the End-of-Study/Final Visit has been clarified.
- Wording regarding the taper of LCM for ILL subjects who discontinue use has been removed.
- US and EU regulatory authority approvals of LCM have been updated.
- Pharmacokinetic variables have been further defined as “Other”.
- Bicarbonate testing is optional for subjects weighing less than 8kg.
- New inclusion criterion has been added for all subjects.
- New exclusion criterion has been added for RxL and ILL subjects.
- Oral LCM should be administered approximately 12 hours after the final iv LCM infusion has been clarified.
- PDILI language has been updated to most current UCB template.
- List of hematology PDILI laboratory measurements have been updated.
- List of chemistry PDILI laboratory measurements have been updated.
- Clarification has been added regarding the reading of 12-lead ECGs.
- Definitions of analysis sets have been modified.
- Data presentations for planned pharmacokinetic and safety analyses have been revised.

- Minor typographical errors and clarifications have been made and are not listed in the summary of changes.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- Text has been modified to lower the age of subject enrollment to ≥1 month of age.
- Approximately 100 subjects will be included in EP0060.
- Asia with the possibility of other regions has been added to study regions.
- Age stratification has been included within Cohort 2. Every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.
- Number of subjects in the DMC process in Cohort 2 has been revised.
  - For Cohort 2, approximately 44 subjects ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.
  - After completion of the first 20 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:
    - EITHER approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
    - OR approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
    - OR Cohort 2 should be stopped.
- The Final Visit can be conducted on the same day as the last dose of iv LCM if time permits to complete all assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM.
- Text has been amended to include US and EU regulatory authority approvals of LCM for pediatric patients down to 4 years of age.
  - In the US, oral tablets and oral solution (syrup) of LCM are indicated for the treatment of partial-onset seizures in patients 4 years of age and older. As the safety of LCM injection for iv use has not been established in pediatric patients, LCM injection for iv use at infusion durations of 15 to 60 minutes is indicated for the treatment of partial-onset

seizures only in patients 17 years of age and older as an alternative when oral administration is temporarily not feasible.

  - Additionally, LCM has been approved in the EU (oral tablets, oral solution [syrup], and solution for iv infusion), as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 4 years of age and older. The iv formulation at infusion durations of 15 to 60 minutes is approved as an alternative for patients when oral administration is temporarily not feasible.

- The Inclusion Criterion 8 has been added to enroll patients who weigh ≥4kg.
- The Exclusion Criterion 20a has been added to clarify RxL and IIL subject must not be currently participating in another study of IMP.
- PDILI language has been modified with current UCB language to clarify which laboratory values IMP must be immediately and permanently discontinued.
- Text has been amended to clarify OLL subjects will not have a medical history performed in EP0060.
- The following changes were made to PDILI laboratory measurements:
  - Hematocrit, hemoglobin, platelet count, RBC count, WBC count, and WBC differential count have replaced eosinophil count as hematology measurements.
  - ALT, AST, ALP, GGT, and albumin have been added to chemistry measurements.
- 12-lead ECG will be read by a central reader in addition to the initial review.
- Analyis sets have been defined as follows:
  - The Safety Set (SS) will include subjects who received at least 1 dose of EP0060 study drug LCM (oral and/or iv). Selected safety summaries will be presented for the SS.
  - The Safety Set iv (SS-iv) will include subjects in the SS who received at least 1 dose of EP0060 study drug iv LCM. The SS-iv will be the primary analysis set for the analysis of safety data.
  - The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all subjects in the SS-iv having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 study day with documented iv LCM intake times and without important protocol deviations impacting the interpretability of the PK analysis.

Specific changes

Change #1

Title page

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN (≥4 TO <17 YEARS OF AGE) WITH EPILEPSY

Has been changed to:

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN (≥**1 MONTH** TO <17 YEARS OF AGE) WITH EPILEPSY

Change #2

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted] **MD**
Address:	**UCB BIOSCIENCES, GmbH.** **Alfred-Nobel-Straβe 10** **40789 Monheim am Rhein** **Germany**
Phone:	[redacted]
Mobile:	[redacted]

Change #3

STUDY CONTACT INFORMATION

Clinical Project Manager

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc.

	8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Project Manager

Name:	[redacted]
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
Fax:	**Not Applicable**

Change #4

STUDY CONTACT INFORMATION

Clinical Trial Biostatistician

Name:	[redacted] MPH
Address:	UCB BIOSCIENCES, Inc. 8010 Arco Corporate Drive, Suite 100 (courier) Raleigh, NC 27617, USA PO Box 110167 (mail) Research Triangle Park, NC 27709, USA
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted]
Address:	**UCB BIOSCIENCES, GmbH.**

	Alfred-Nobel-Straβe 10 **40789 Monheim am Rhein** **Germany**
Phone:	[redacted]
Fax:	**Not Applicable**

Change #5

Section 1 SUMMARY

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous (iv) lacosamide (LCM; VIMPAT®) infusions in pediatric subjects ≥4 to <17 years of age with epilepsy. Investigation the use of iv LCM in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned.

EP0060 will include approximately 75 subjects. The following subjects will be eligible for enrollment in EP0060:

- Open-label LCM (OLL) subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- Prescribed-LCM (RxL) subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- Initiating iv LCM (IIL) subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: Subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an epilepsy monitoring unit (EMU) or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: Subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: Subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv

administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.

– Elective administration: Subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation. Subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America and Europe. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy. EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including at least 20 subjects who are ≥4 to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. A Data Monitoring Committee (DMC) will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2) or separate study for the evaluation of iv LCM in children <4 years of age (as detailed further below).

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration: up to 10 doses or up to 5 days
    (2) Elective administration: up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, 12-lead electrocardiogram [ECG], laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration. For OLL and RxL subjects, the daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg (subjects weighing <50kg) or 50mg (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg) or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and detailed safety assessments will be performed.

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion or withdrawal from the Treatment Period and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose if the last LCM infusion was performed in the morning, and time permits completion of assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM after completion of or withdrawal from the Treatment Period. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.

- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue antiepileptic drug (AED) treatment at the discretion of the treating physician. For RxL and IIL subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen or taper at the discretion of the treating physician.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator, Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator, Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.

- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
- OR Cohort 2 should be stopped,
- AND whether to initiate the assessment of safety in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

Has been changed to:

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous (iv) lacosamide (LCM; VIMPAT®) infusions in pediatric subjects ≥**1 month** to <17 years of age with epilepsy. ~~Investigation the use of iv LCM in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned.~~

EP0060 will include approximately **100** subjects. The following subjects will be eligible for enrollment in EP0060:

- Open-label LCM (OLL) subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- Prescribed-LCM (RxL) subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- Initiating iv LCM (IIL) subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: Subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an epilepsy monitoring unit (EMU) or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: Subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: Subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv

administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.

– Elective administration: Subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation. Subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America, Europe, and **Asia**. Additional sites or regions may be added if deemed necessary.

The primary objective of EP0060 is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥**1 month** to <17 years with epilepsy. EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including **approximately 44** subjects who are ≥**1 month** to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age**. Within Cohort 2, every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.**

A Data Monitoring Committee (DMC) will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2) ~~or separate study for the evaluation of iv LCM in children <4 years of age (as detailed further below)~~.

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration: up to 10 doses or up to 5 days
    (2) Elective administration: up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848

- End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, 12-lead electrocardiogram [ECG], laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days for clinical need administration or up to 2 consecutive doses **[**over approximately 24 hours**]**) for elective administration. For OLL and RxL subjects, the daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg **bid** (subjects weighing <50kg) or 50mg **bid** (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg)**,** or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for pharmacokinetic (PK) analysis, and detailed safety assessments will be performed.

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion ~~or withdrawal from the Treatment Period~~ and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose **of iv LCM** if ~~the last LCM infusion was performed in the morning, and~~ time permits **to complete all** assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM ~~after completion of or withdrawal from the Treatment Period~~. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:

  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.

- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue antiepileptic drug (AED) treatment at the discretion of the treating physician. For RxL ~~and IIL~~ subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and ~~either refer to the long-term, open-label studies taper regimen or~~ taper at the discretion of the treating physician.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, **approximately 44** subjects ≥**1 month** to <8 years of age will be enrolled to receive iv LCM. For the first **20** subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first **20** subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would

directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.

- OR approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
- OR Cohort 2 should be stopped.
- ~~AND whether to initiate the assessment of safety in younger pediatric subjects (≥1 month to <4 years of age).~~

This design will result in a total exposure of approximately **100** pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

Change #6

Section 2 INTRODUCTION, sixth paragraph

In the US, the iv formulation of LCM is approved in patients ≥17 years of age at a maximum dose of 400mg/day as monotherapy and adjunctive therapy in the treatment of partial onset seizures in subjects with epilepsy when oral administration is temporarily not feasible. In EU, the iv formulation is approved in patients ≥16 years at a maximum dose of 600mg/day as monotherapy (EU CHMP positive opinion received on 11 Nov 2016) and at a maximum dose of 400mg/day as adjunctive therapy in the treatment of partial onset seizures in subjects with epilepsy when oral administration is temporarily not feasible. Intravenous LCM is approved in patients ≥16 years of age and for infusion durations of 15 to 60 minutes depending on the country-specific labeling.

Has been changed to:

In the US, **oral tablets and oral solution (syrup) of LCM are indicated for the treatment of partial-onset seizures in patients 4 years of age and older. As the safety of LCM injection for iv use has not been established in pediatric patients, LCM injection for iv use at infusion durations of 15 to 60 minutes is indicated for the treatment of partial-onset seizures only** in patients 17 years of age **and older as an alternative** when oral administration is temporarily not feasible.

Additionally, LCM has been approved in the EU (oral tablets, oral solution [syrup], and solution for iv infusion), as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 4 years of age and older. The iv formulation at infusion durations of 15 to 60 minutes is approved **as an alternative** for patients when oral administration is temporarily not feasible**.**

Change #7

Section 2 INTRODUCTION, ninth paragraph

The results of EP0060 will provide safety, tolerability, and PK data regarding the use of the iv LCM formulation either as replacement for oral LCM or for adjunctive LCM treatment initiation in pediatric subjects ≥4 to <17 years with epilepsy.

Has been changed to:

The results of EP0060 will provide safety, tolerability, and PK data regarding the use of the iv LCM formulation either as replacement for oral LCM or for adjunctive LCM treatment initiation in pediatric subjects ≥**1 month** to <17 years with epilepsy.

Change #8

Section 3 STUDY OBJECTIVE(S)

The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy. An additional objective is to evaluate the PK of iv LCM in pediatric subjects with epilepsy.

Has been changed to:

The primary objective of this study is to evaluate the safety and tolerability of iv LCM infusion(s) in pediatric subjects ≥**1 month** to <17 years with epilepsy. An additional objective is to evaluate the PK of iv LCM in pediatric subjects with epilepsy.

Change #9

Section 4.3 Pharmacokinetic variable(s)

4.3 Pharmacokinetic variable(s)

The PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

Has be changed to:

4.3 Other pharmacokinetic variable(s)

The **other** PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

Change #10

Section 5.1 Study description

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric subjects ≥4 to <17 years of age with epilepsy. EP0060 will include approximately 75 subjects. The following subjects will be eligible for enrollment in EP0060:

- OLL subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- RxL subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- IIL subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation while subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America and Europe. Additional sites or regions may be added if deemed necessary.

EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including at least 20 subjects who are ≥4 to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. A DMC will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next

cohort (Cohort 2) or separate study for the evaluation of iv LCM in children <4 years of age. Details regarding the DMC are provided in Section 12.7.2.

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration (see above in this Section): up to 10 doses or up to 5 days
    (2) Elective administration (see above in this Section): up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration. For OLL and RxL subjects, the daily dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg (subjects weighing <50kg) or 50mg (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg) or 100mg/day

(subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for PK analysis, and safety assessments will be performed (AEs, physical and neurological exams, pulse rate, BP, 12-lead ECG, clinical hematology and chemistry, and Columbia-Suicide Severity Rating Scale [C-SSRS] when applicable).

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM infusion or withdrawal from the Treatment Period and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose if the last LCM infusion was performed in the morning, and time permits completion of assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM after completion of or withdrawal from the Treatment Period. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days:
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue AED treatment at the discretion of the treating physician. For RxL and IIL subjects who directly enrolled and will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen or taper at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv

LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

Has been changed to:

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric subjects ≥**1 month** to <17 years of age with epilepsy. EP0060 will

include approximately **100** subjects. The following subjects will be eligible for enrollment in EP0060:

- OLL subjects: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- RxL subjects: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy.
- IIL subjects: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL subjects.

Subjects can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL subjects):
  - Clinical need administration: subjects currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) and elect to receive iv LCM administration at an EMU or healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL subjects):
  - Clinical need administration: subjects not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these subjects, the maximum number of iv doses of LCM is 10.
  - Elective administration: subjects not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these subjects, the maximum number of iv doses of LCM is 2.

Pediatric subjects entering into EP0060 from the OLL group will temporarily suspend their participation in that study to receive iv LCM treatment in EP0060. Subjects who enroll into EP0060 from the RxL group will temporarily switch from their prescribed oral LCM treatment to the iv LCM formulation while subjects in the IIL group will initiate adjunctive treatment with iv LCM. After completion of this study, eligible subjects from the RxL and IIL groups will have the option to continue LCM treatment in SP848. Subjects will be enrolled from approximately 40 sites in North America, Europe, and **Asia**. Additional sites or regions may be added if deemed necessary.

EP0060 is planned to include up to 2 age-based cohorts with Cohort 1 including at least 40 subjects who are ≥8 to <17 years and Cohort 2 including **approximately 44** subjects who are ≥**1 month** to <8 years. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age**. Within Cohort 2, every attempt will be**

made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.

A DMC will review the safety and tolerability data for each cohort to make the following recommendations: the progression of the current cohort, including iv infusion durations to be evaluated, and progression to initiate enrollment in the next cohort (Cohort 2) ~~or separate study for the evaluation of iv LCM in children <4 years of age.~~ Details regarding the DMC are provided in Section 12.7.2.

EP0060 is comprised of the following study periods:

- For all subjects:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration (see above in this Section): up to 10 doses or up to 5 days
    (2) Elective administration (see above in this Section): up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),
  - End-of-Study/Telephone Contact 1 (1 to 3 days),
- Additional visits or contacts as follows:
  - RxL and IIL subjects who are eligible and choose to continue oral LCM treatment for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL subjects who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

For all subjects, the Screening, Baseline, Treatment Period, and Final Visit may occur in 1 day, provided the subject only requires 1 iv infusion, results of examinations (ie, ECG, laboratory measurements) are available to allow verification of subject eligibility prior to infusion, and time permits for completion of Final Visit assessments.

If further time is required for Screening assessments or to obtain results, the Screening Period can last up to 7 days. For OLL and RxL subjects, oral LCM will be administered during this time from their open-label study or prescribed LCM supply in accordance with each subject's oral LCM dosage regimen. For IIL subjects, no LCM will be administered during the Screening Period.

During the Treatment Period, at least 1 dose of iv LCM will be administered. If more than 1 infusion is given, infusions will occur twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days) for clinical need administration or up to 2 consecutive doses (over approximately 24 hours) for elective administration. For OLL and RxL subjects, the daily

dose of iv LCM will be the same as the subject's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL subjects is 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, the iv LCM dose will be 1mg/kg **bid** (subjects weighing <50kg) or 50mg **bid** (subjects weighing ≥50kg). The total LCM daily dose for IIL subjects should be 2mg/kg/day (subjects weighing <50kg)**,** or 100mg/day (subjects weighing ≥50kg) and should remain constant for at least 7 days prior to a LCM dose increase.

During the Treatment Period, blood samples will be obtained for PK analysis, and safety assessments will be performed (AEs, physical and neurological exams, pulse rate, BP, 12-lead ECG, clinical hematology and chemistry, and Columbia-Suicide Severity Rating Scale [C-SSRS] when applicable).

The timing of the End-of-Study/Final Visit will depend on the timing of the last LCM ~~infusion or withdrawal from the Treatment Period~~ and available time to complete all assessments. The Final Visit can be conducted on the same day as the last dose **of iv LCM** if ~~the last LCM infusion was performed in the morning, and~~ time permits **to complete all** assessments. Otherwise, the Final Visit should be conducted the day following the last dose of iv LCM ~~after completion of or withdrawal from the Treatment Period~~. The safety follow-up Telephone Contact 1 should occur 1 to 3 days after the Final Visit for all subjects.

For RxL and IIL subjects who are eligible and choose to continue LCM treatment in SP848, a Transition Visit will be conducted either concurrent with the Final Visit or separately. Oral LCM solution will be provided for these subjects to allow continuity of LCM therapy after the final LCM infusion and the subject's Transition Visit in EP0060 and Visit 1 for SP848.

For RxL and IIL subjects who will not continue LCM treatment in SP848, an additional safety follow-up Telephone Contact 2 should occur 30 days (±2 days) after the last iv dose of study LCM treatment.

The maximum study durations are as follows:

- Approximately 16 days:
  - Subjects in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days
  - Subjects in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Subjects in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

Subjects should continue AED treatment at the discretion of the treating physician. For ~~RxL and IIL~~ subjects who directly enrolled and will discontinue use of LCM, the subject should complete the EP0060 Final Visit and ~~either refer to the long-term, open-label studies taper regimen or~~ taper at the discretion of the treating physician.

The schedule of study assessments is provided in Section 5.2.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, **approximately 44** subjects ≥**1 month** to <8 years of age will be enrolled to receive iv LCM. For the first **20** subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first **20** subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped.
- ~~AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).~~

This design will result in a total exposure of approximately **100** pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a subject who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).

Change #11

Section 5.1.2 Planned number of subjects and site(s)

Approximately 75 subjects will be enrolled at approximately 40 sites.

The following cohorts are planned:

- Cohort 1: at least 40 subjects from ≥8 to <17 years of age, with at least 20 subjects from ≥12 to <17 years of age and at least 20 subjects from ≥8 to <12 years of age
- Cohort 2: at least 20 subjects from ≥4 to <8 years of age

The remaining subjects may be enrolled in either of the 2 cohorts.

Has been changed to:

Approximately **100** subjects will be enrolled at approximately 40 sites.

The following cohorts are planned:

- Cohort 1: at least 40 subjects from ≥8 to <17 years of age, with at least 20 subjects from ≥12 to <17 years of age and at least 20 subjects from ≥8 to <12 years of age
- Cohort 2: **every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.**

The remaining subjects may be enrolled in either of the 2 cohorts.

Change #12

Section 5.1.3 Anticipated regions and countries

The study will be conducted at selected sites from North America and Europe. Additional sites may be added as deemed necessary.

Has been changed to:

The study will be conducted at selected sites from North America, Europe, and **Asia**. Additional sites **or regions** may be added as deemed necessary.

Change #13

Table 5–1 Schedule of study assessments, Clinical chemistry and hematology, Unscheduled Visit column

Clinical chemistry and hematology[p]	X	X[q]				X			

Has been changed to:

Clinical chemistry and hematology[p,q]	X	X[r]				X			

Change #14

Table 5–1 Schedule of study assessments, footnote c

[c] If iv LCM treatment is continued after Day 1, assessments for Visit 3 must be completed for each infusion of iv LCM treatment in EP0060, unless otherwise noted (see footnote o).

Has been changed to:

[c] If iv LCM treatment is continued after Day 1, assessments for Visit 3 **(excluding PK blood sampling [see footnote u])** must be completed for each infusion of iv LCM treatment in EP0060, unless otherwise noted (see footnote o).

Change #15

Table 5-1 Schedule of study assessments, footnote e

[e] A Final Visit must be completed for all subjects who complete or withdraw prematurely from EP0060. If the last iv infusion of LCM for the study occurs in the morning, the Final Visit may occur on the same day as the last infusion, time permitting. Otherwise, the Final Visit should occur on the following day (ie, last infusion in evening). For subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen or taper at the discretion of the treating physician for those subjects who enrolled directly.

Has been changed to:

[e] A Final Visit must be completed for all subjects who complete or withdraw prematurely from EP0060. ~~If the last iv infusion of LCM for the study occurs in the morning,~~ **T**he Final Visit may occur on the same day as the last **dose of iv LCM**, time permitting. Otherwise, the Final Visit should occur on the following day ~~(ie, last infusion in evening)~~. For subjects who will discontinue use of LCM, the subject should complete the EP0060 Final Visit and either refer to the long-term, open-label studies taper regimen **for OLL subjects** or taper at the discretion of the treating physician for **RxL subjects** ~~those subjects who enrolled directly~~.

Change #16

Table 5-1 Schedule of study assessments, footnote j

[j] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for RxL and IIL subjects at Screening. For OLL subjects, a medical history update will be performed in order to collect medical history that was not captured during the course of the prior study.

Has been changed to:

[j] Procedure history, medical history, diagnosis of epilepsy, and childbearing potential will be collected for RxL and IIL subjects at Screening. For OLL subjects, a medical history update will be **captured in the previous long-term open-label study and not in EP0060.**

Change #17

Table 5-1 Schedule of study assessments, new footnote q

[q] Bicarbonate testing is optional for subjects weighing less than 8kg. Consider testing for bicarbonate in subjects weighing less than 8kg in cases of suspected metabolic disturbances such as metabolic acidosis.

Has been added and subsequent footnotes have been renumbered.

Change #18

Table 5-1 Schedule of study assessments, footnote z

[z] For RxL and IIL subjects who are eligible and wish to enroll in SP848, a short-term oral LCM solution will be dispensed to allow continuity of LCM treatment while visits and assessments are scheduled for starting SP848. Subjects (or their caregivers) will administer the oral LCM solution twice a day according to the investigator's instructions until the subject returns for the Transition Visit.

Has been changed to:

[z] For RxL and IIL subjects who are eligible and wish to enroll in SP848, a short-term oral LCM solution will be dispensed to allow continuity of LCM treatment while visits and assessments are scheduled for starting SP848. Subjects (or their caregivers) will administer the oral LCM solution twice a day, **starting approximately 12 hours after the final iv LCM infusion**, according to the investigator's instructions until the subject returns for the Transition Visit.

Change #19

Section 5.3 Rationale for study design and selection of dose

EP0060 is an open-label, multicenter study to investigate the safety and tolerability of iv LCM in pediatric subjects with epilepsy aged ≥4 to <17 years. A separate Phase 2/3 study investigating the use of iv LCM in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned. The results of EP0060 will provide safety and PK data regarding the use of the iv LCM formulation in pediatric subjects (≥4 to <17 years of age). The EP0060 design is based on components of the study design for SP757, which evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies. In an effort to maximize the patient pool used in the evaluation of the safety of iv LCM in pediatric subjects, Protocol Amendment 2 opened enrollment to also include OLL and RxL subjects who are on a stable dose of oral LCM and elect to receive iv LCM as well as IIL subjects who are not currently taking LCM and initiate adjunctive LCM treatment using iv LCM. This expansion of the subject population occurred prior to the start of study enrollment. Protocol Amendment 2 also included the option for RxL and IIL subjects to continue oral LCM treatment after completion of iv LCM, if determined clinically appropriate, in SP848. If required, a short-term supply of oral LCM solution will be provided for RxL and IIL subjects transitioning to start

SP848 to ensure continuity of LCM treatment while allowing flexibility to schedule a clinical visit to initiate SP848. For RxL and IIL subjects who do not continue into SP848 (either by choice or not clinically appropriate), an additional telephone contact approximately 30 days after last dose of iv LCM IMP is added in order to collect final safety data.

The iv LCM formulation is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥16 years of age (depending on country-specific labeling) with epilepsy when oral administration is temporarily not feasible, which can also include initiation of LCM treatment.

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for OLL and RxL subjects, with a maximum dose of 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, this range of doses above also includes the pediatric starting dose of 2mg/kg/day (subjects <50kg) or 100mg/day (subjects ≥50kg), which is the same as those used in the Phase 3 pediatric LCM studies. The LCM dose at initiation of treatment should remain constant for at least 7 days prior to a LCM dose increase.

EP0060 will initially enroll at least 40 older pediatric subjects (Cohort 1) and will include at least 20 subjects ≥12 to <17 years of age and at least 20 subjects ≥8 to <12 years of age. Cohort 2 (at least 20 subjects ≥4 to <8 years of age) will follow sequentially based on DMC recommendation. After the first 20 subjects (Cohort 1) or 10 subjects (Cohort 2) have received iv LCM over infusion durations of 30 to 60 minutes, the DMC will review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort (ie, 30 to 60 minutes for all remaining subjects or 15 to 30 minutes [only for subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator; otherwise 30 to 60 minutes]), if the study/cohort should be stopped, and if the next cohort can be initiated, and if a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age) can be initiated (Section 12.7.2).

This design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM in subjects ≥4 to <17 years of age over a range of infusion durations.

Taken together, the iv LCM dosing scheme and planned target infusion durations being evaluated in EP0060 (2 to 12mg/kg/day or 100 to 600mg/day; 15 to 60 minutes) allow for administration of a range of pediatric doses, and include infusion durations that are the same as those approved for adults and adolescents.

Has been changed to:

EP0060 is an open-label, multicenter study to investigate the safety and tolerability of iv LCM in pediatric subjects with epilepsy aged ≥**1 month** to <17 years. ~~A separate Phase 2/3 study investigating the use of iv LCM in pediatric subjects with epilepsy ≥1 month to <4 years of age is planned.~~ The results of EP0060 will provide safety and PK data regarding the use of the iv

LCM formulation in pediatric subjects (≥**1 month** to <17 years of age). The EP0060 design is based on components of the study design for SP757, which evaluated iv LCM replacement in adults with partial-onset seizures, as well as based on design elements of other pediatric iv AED studies. In an effort to maximize the patient pool used in the evaluation of the safety of iv LCM in pediatric subjects**, EP0060** has opened enrollment to include ~~also~~ OLL and RxL subjects who are on a stable dose of oral LCM and elect to receive iv LCM as well as IIL subjects who are not currently taking LCM and initiate adjunctive LCM treatment using iv LCM. The expansion of the subject population occurred prior to the start of study enrollment**. EP0060** also includes the option for RxL and IIL subjects to continue oral LCM treatment after completion of iv LCM, if determined clinically appropriate, in SP848. If required, a short-term supply of oral LCM solution will be provided for RxL and IIL subjects transitioning to start SP848 to ensure continuity of LCM treatment while allowing flexibility to schedule a clinical visit to initiate SP848. For RxL and IIL subjects who do not continue into SP848 (either by choice or not clinically appropriate), an additional telephone contact approximately 30 days after last dose of iv LCM IMP is added in order to collect final safety data.

The iv LCM formulation **at infusion durations of 15 to 60 minutes** is approved at doses of 200 to 400mg/day as adjunctive therapy in the treatment of partial-onset seizures in subjects ≥1**7** years of age ~~(depending on country-specific labeling)~~ with epilepsy when oral administration is temporarily not feasible, which can also include initiation of LCM treatment, **for infusion durations of 15 to 60 minutes. Additionally in the EU, the iv formulation is also approved in pediatric subjects down to 4 years of age at maximum weight-based doses depending on weight band and whether LCM is administered as monotherapy or adjunctive therapy, for infusion durations of 15 to 60 minutes. An infusion duration of at least 30 minutes for administration >200mg per infusion (ie, >400mg/day) is preferred.**

A weight-based LCM dosing scheme for pediatric subjects is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100 to 600mg/day). Thus, the iv LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for OLL and RxL subjects, with a maximum dose of 12mg/kg/day or 600mg/day, whichever is lower. For IIL subjects, this range of doses above also includes the pediatric starting dose of 2mg/kg/day (subjects <50kg) or 100mg/day (subjects ≥50kg), which is the same as those used in the Phase 3 pediatric LCM studies. The LCM dose at initiation of treatment should remain constant for at least 7 days prior to a LCM dose increase.

EP0060 will initially enroll at least 40 older pediatric subjects (Cohort 1) and will include at least 20 subjects ≥12 to <17 years of age and at least 20 subjects ≥8 to <12 years of age. Cohort 2 **will enroll approximately 44 subjects** (**with every attempt to enroll** 20 subjects ≥4 to <8 years of age**, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age**) **and** will follow sequentially based on DMC recommendation. After **completion of** the first 20 subjects (Cohort 1) **and after completion of 20** subjects (Cohort 2) have received iv LCM over infusion durations of 30 to 60 minutes, the DMC will review the available safety and tolerability data. Based on their review, the DMC will recommend the target infusion duration for the remaining subjects in the cohort (ie, 30 to 60 minutes for all remaining subjects or 15 to 30 minutes [only

for subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator; otherwise 30 to 60 minutes]), if the study/cohort should be stopped, and if the next cohort can be initiated~~, and if a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age) can be initiated~~ (Section 12.7.2).

This design will result in a total exposure of approximately **100** pediatric subjects to assess the safety and tolerability of iv LCM in subjects ≥**1 month** to <17 years of age over a range of infusion durations.

Taken together, the iv LCM dosing scheme and planned target infusion durations being evaluated in EP0060 (2 to 12mg/kg/day or 100 to 600mg/day; 15 to 60 minutes) allow for administration of a range of pediatric doses, and include infusion durations that are the same as those approved for adults and adolescents.

Change #20

Section 6.1 Inclusion criteria, second criterion

2. Subject is male or female from ≥4 to <17 years of age.

Has been changed to:

2. Subject is male or female from ≥**1 month** to <17 years of age.

Change #21

Section 6.1 Inclusion criteria

8. Subject weighs ≥4kg.

Has been added.

Change #22

Section 6.2 Exclusion criteria

20a. Subject is currently participating in another study of an IMP.

Has been added.

Change #23

Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria, first paragraph and bullets

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

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

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

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and 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).

Has been changed to:

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be **immediately and permanently** discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

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

- 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, and right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below **requires discussion with Medical Monitor to decide whether subject is allowed** 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).

Change #24

Section 7.2.1 Treatment Period, fifth paragraph

For the first 20 subjects ≥8 to <17 years of age enrolled into Cohort 1 and the first 10 subjects ≥4 to <8 years in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

Has been changed to:

For the first 20 subjects ≥8 to <17 years of age enrolled into Cohort 1 and the first **20** subjects ≥**1 month** to <8 years in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

Change #25

Section 7.2.1 Treatment Period, final paragraph

If subjects need to discontinue LCM, the subjects should be tapered off LCM either as specified in their long-term, open-label study or at the discretion of the treating physician for RxL and IIL subjects. For OLL subjects this taper should occur as a part of the long-term, open-label study and not as a part of EP0060.

Has been changed to:

If subjects need to discontinue LCM, **OLL** subjects should be tapered off LCM ~~either~~ as specified in their long-term, open-label study or at the discretion of the treating physician for RxL ~~and IIL~~ subjects**,** this taper should occur as a part of the long-term, open-label study and not as a part of EP0060.

Change #26

Section 8.1.1 Visit 1a and Visit 1b (Day -7 to Day 1) Screening and/or Baseline, fourth paragraph, sixth bullet

- Medical history update for OLL subjects from long-term open-label studies, or complete medical history for RxL and IIL subjects

Has been changed to:

- ~~Medical history update for OLL subjects from long-term open-label studies, or~~ **C**omplete medical history for RxL and IIL subjects **(a medical history update will be captured in the previous long-term open-label study for OLL subjects)**

Change #27

Section 8.2.1 Visit 2 (Day 1), third paragraph, final bullet

For RxL and IIL subjects who are eligible and choose to participate in the long-term open-label oral LCM study SP848 after completion of EP0060, a short-term oral LCM solution will be dispensed at Visit 2. This supply is to allow continuity of LCM treatment after the last iv LCM infusion and the scheduled Transition Visit.

Has been changed to:

For RxL and IIL subjects who are eligible and choose to participate in the long-term open-label oral LCM study SP848 after completion of EP0060, a short-term oral LCM solution will be dispensed at Visit 2. This supply is to allow continuity of LCM treatment after the last iv LCM

infusion and the scheduled Transition Visit. **Oral LCM solution administration should begin approximately 12 hours after the final iv LCM infusion.**

Change #28

Section 8.4.1 Final Visit (Day 1 to 6)/Termination Visit, first paragraph

If the last iv infusion of LCM for the study occurs in the morning, the Final Visit may occur on the same day as the last infusion, time permitting. Otherwise, the Final Visit should occur on the following day (ie, last infusion in evening).

Has been Changed to:

~~If the last iv infusion of LCM for the study occurs in the morning,~~ **T**he Final Visit may occur on the same day as the last infusion, time permitting. Otherwise, the Final Visit should occur on the following day ~~(ie, last infusion in evening)~~.

Change #29

Section 8.4.1 Final Visit (Day 1 to 6)/Termination Visit, second paragraph, Oral LCM administration, if applicable bullet, third dash

For RxL and IIL subjects who are eligible and wish to enroll in SP848, oral LCM administration may continue from the short-term oral LCM solution that was dispensed at Visit 2. Additional assessments will be conducted at the Transition Visit, as outlined in Section 8.4.3.

Has been changed to:

For RxL and IIL subjects who are eligible and wish to enroll in SP848, oral LCM administration ~~may continue~~ from the short-term oral LCM solution that was dispensed at Visit 2, **should begin approximately 12 hours after the final iv LCM infusion regardless of when the Final Visit occurs**. Additional assessments will be conducted at the Transition Visit, as outlined in Section 8.4.3.

Change #30

Section 10.6.2 Liver function tests and evaluation of PDILI, seventh paragraph

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.

Has been changed to:

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~~.

Change #31

Table 10-2 Laboratory tests, Clinical chemistry column, bicarbonate

[a] Bicarbonate testing is optional for subjects weighing less than 8kg. Consider testing for bicarbonate in subjects weighing less than 8kg in cases of suspected metabolic disturbances such as metabolic acidosis.

Has been added.

Change #32

Table 10-3 Required investigations and follow up for PDILI, Immediate Actions column for ≥3xULN for ALT or AST

Immediate, temporary or permanent, IMP discontinuation.

Has been changed to:

Immediate, ~~temporary or~~ permanent~~,~~ IMP discontinuation.

Change #33

Table 10-4 PDILI laboratory measurements, hematology measurements

Hematology	Eosinophil count

Has been changed to:

Hematology	**Hematocrit**
	Hemoglobin
	Platelet count
	RBC count
	WBC count
	WBC differential count

Change #34

Table 10-4 PDILI laboratory measurements, chemistry measurements

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

Has been changed to:

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
	ALT
	AST
	ALP
	GGT
	Albumin

Change #35

Section 10.7.3 Overall ECG interpretation

An immediate initial review of the ECGs will be conducted locally by the investigator, subinvestigator, or qualified designated reader. If this reading identifies abnormal ECG findings that are assessed by the investigator or subinvestigator to be clinically significant, then the ECG should be repeated in 1 hour, unless circumstances require a more rapid assessment. If the clinically significant abnormality is confirmed by the repeat ECG or if the investigator feels it is medically necessary, the subject must be withdrawn from EP0060 (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 EP0060.

Has been changed to:

An immediate initial review of the ECGs will be conducted locally by the investigator, subinvestigator, or qualified designated reader. If this reading identifies abnormal ECG findings that are assessed by the investigator or subinvestigator to be clinically significant, then the ECG should be repeated in 1 hour, unless circumstances require a more rapid assessment. If the clinically significant abnormality is confirmed by the repeat ECG or if the investigator feels it is medically necessary, the subject must be withdrawn from EP0060 (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 EP0060. **Additionally, the ECGs will be sent to a central reader for review.**

Change #36

Section 12.1 Definition of analysis sets

The Safety Set iv (SS-iv) will include subjects who received at least 1 dose of iv LCM. The SS will be the primary analysis set for the analysis of safety data.

The Safety Set (SS) will include subjects who received at least 1 dose of LCM (oral or iv). Selected safety summaries will be presented for the SS.

The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all subjects in the SS having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 study day with documented LCM intake times.

Has been changed to:

The Safety Set (SS) will include subjects who received at least 1 dose of **EP0060** study drug LCM (oral **and/**or iv). Selected safety summaries will be presented for the SS.

The Safety Set iv (SS-iv) will include subjects **in the SS** who received at least 1 dose of **EP0060 study drug** iv LCM. The SS-iv will be the primary analysis set for the analysis of safety data.

The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all subjects in the SS**-iv** having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 study day with documented **iv** LCM intake times **and without important protocol deviations impacting the interpretability of the PK analysis**.

Change #37

Section 12.3 Planned pharmacokinetic analyses

Descriptive statistics for LCM and SPM 12809 plasma concentrations, including but not limited to geometric mean and CV, will be computed for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected. Data will be presented by cohort and infusion duration, and the IIL and OLL and RxL groups of subjects in EP0060 will also be presented.

Has been changed to:

Descriptive statistics for LCM and SPM 12809 plasma concentrations, including but not limited to geometric mean and CV, will be computed for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected. ~~Data will be presented by cohort and infusion duration, and the IIL and OLL and RxL groups of subjects in EP0060 will also be presented.~~

Change #38

Section 12.4 Planned safety analyses, first paragraph

Safety analyses will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Within cohort and infusion duration, the OLL and RxL groups of subjects and the IIL subject group will also be presented.

Has been changed to:

Safety analyses will be presented by **age** cohort ~~and infusion duration, cohorts overall, and all subjects overall. Within cohort and infusion duration, the OLL and RxL groups of subjects and the IIL subject group will also be presented~~**.**

Change #39

Section 12.5 Handling of protocol deviations, first sentence

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary safety outcomes for an individual subject.

Has been changed to:

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary ~~safety~~ outcomes for an individual subject.

Change #40

Section 12.6 Handling of dropouts or missing data

In Protocol Amendment 2, Section 12.6 Handling of dropouts or missing data was erroneously moved to become Section 17.1. This section has been restored to its original position and subsequent sections have been renumbered.

Change #41

Section 12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 subjects in Cohort 1 and after completion of the first 10 subjects in Cohort 2.

Has been changed to:

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 subjects in Cohort 1 and after completion of the first **20** subjects in Cohort 2.

Change #42

Section 12.7.2 Data Monitoring Committee, fourth paragraph through end of section

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion durations as follows:
  - 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator; OR,
  - 30 minutes but no longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the investigator
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped,
- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

Has been changed to:

For Cohort 2, **approximately 44** subjects ≥ **1 month** to <8 years of age will be enrolled to receive iv LCM. For the first **20** subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first **20** subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion durations as follows:
  - 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the investigator; OR,
  - 30 minutes but no longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the investigator
- OR approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped**.**
- ~~AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).~~

Change #43

Section 12.8 Determination of sample size

Approximately 75 subjects will be enrolled, which includes up to 2 cohorts of at least 40 subjects for Cohort 1 and at least 20 subjects for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

Has been changed to:

Approximately **100** subjects will be enrolled, which includes up to 2 cohorts of at least 40 subjects for Cohort 1 and **approximately 44** subjects for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

Change #44

Section 15 REFERENCES

Welsh SS, Lin N, Topjian AA, Abend NS. Safety of intravenous lacosamide in critically ill children. Seizure. 2017;52:76-80.

Has been added.

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: EP0060-protocol-amend-3

Version: 2.0

Document Number: CLIN-000115394

Title: EP0060 Protocol Amendment 3

Approved Date: 07 May 2018

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 04-May-2018 08:42:15 GMT+0000
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